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FIGHTING THE RISING TIDE OF DEMENTIAS

THE IN-SILICO MEDICINE APPROACH TOWARDS EARLY DIFFERENTIAL DIAGNOSIS AND TREATMENT

Tom DeBaggio's Alzheimer's Journey

Tom DeBaggio is less sure of himself these days. He fears a recurrence of an incident over a year ago in which he got lost while driving to the family-run nursery outside Washington, D.C. "I didn't really know where I was," he says. And "I still talk. I still stand up on both feet. I still look the same. And maybe [customers] go out of here and say, 'You know, doesn't look like there's anything wrong with him.' And, of course, you don't see it." And when he was asked "Is that distressing?" he responded: "Actually, no. It relieves me of a whole lot of things. You know, when you don't remember what you did yesterday, you can't feel bad about it or good about it, you know? It's just not there. And you're really living in the moment" (NPR 2005).

Recently, in the New York Times, Roger Cohen noted that while attending services at a Reform synagogue during the High Holy Days in London "I heard sermons of great worthiness from British rabbis. One was about Alzheimer's and dementia among the elderly and the need to honour the 'fragment of the divine in everyone.'" (Cohen 2014)

Dementia has arrived in the middle of our societies.

What is Dementia? The Medical and Economic Dementia Tsunami

Dementia is a syndrome in which there is deterioration in memory, thinking, behaviour and the ability to perform everyday activities. It is a broad category of brain diseases that is nowadays used to describe a syndrome that results, firstly, in cognitive function impairment and in many cases, since effective treatment remains elusive, eventually in death.

The most common form of dementia is Alzheimer's disease (60% - 75%). (WHO 2012). Other forms include vascular dementia (20-30%), frontotemporal dementia (5-10%), Lewy body dementia (<5%), as well as other rare forms of dementia.

Dementia is not a normal part of ageing, but it is more common with age. While only 3% of people between the ages of 65-74 have dementia, 47% of people over the age of 85 have some form of dementia (Wikipedia 2012). As more people are living longer, dementia is becoming more common. Worldwide, by now probably almost 40 million people have dementia, and there are some 8 million new cases every year. The prevalence is expected to nearly double to 66 million by 2030 (Wikipedia 2012) and 115 million people by 2050 (ePractice 2013).

This disease is one of the major causes of disability and dependency among older people worldwide. And it has a huge cost burden: "The total monetary cost of dementia [in the USA] in 2010 was between \$157 billion (€124 billion) and \$215 billion (€170 billion)" (Hurd 2013). The global cost was estimated at about US\$ 600 billion (€474 billion) for the same year – about 1% of the world gross domestic product (ePractice 2013).

European Support for Brain Research and the Virtual Physiological Human (VPH) Initiative

Ten years ago 11 German researchers published a Manifesto on "Brain Research in the 21st Century" (Elger et al 2004) – forecasting that within 10 years they will understand and therefore be able to better predict, perhaps avoid, or at least much better treat diseases like Alzheimer's and Parkinson's.

Unfortunately this has not happened, but the European Union continues to support a very significant number of research and innovation projects related to neurological disorders, mental illnesses, brain injuries and related conditions. The seventh EU framework programme for research, FP7 (2007-2013), provided more than €1.9 billion for 1,268 projects for brain research with 1,515 participants from the EU and beyond (European Commission 2013). Within the collaborative research programme, brain research was mainly supported by the 'Health' programme and the 'Information Communication Technology' (ICT) programme. The projects supported by the ICT programme have some common theoretical grounding and objectives:

- Provide specialists with a functional framework to work on;
- Exploit intelligent tools and objects that facilitate health and especially eHealth delivery;
- Promote better diagnosis and treatment;
- Facilitate patients' everyday life.

The "Virtual Physiological Human: Dementia Research Enabled by IT" (VPH-DARE@IT 2013) project is one of them. It has a budget of €18 million, and receives EC support of €13.5 million. It runs for 48 months, from 2013 to 2017.

It has been funded in the context of the European Virtual Physiological Human (VPH) Initiative, a European response to and support for the Global Physiome Project (Fenner et al 2008). These activities are also known as "in silico" medicine, complementing "in vitro" and "in vivo" medicine. In silico is by now a core part of the wider field of integrative systems biology, which pays tribute to the fact that "at each level of the organism, its various components are imbedded in an integrated

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network or system. Each such system has its own logic. It is not possible to understand that logic merely by investigating the properties of the system's components" (Noble 2006). Whereas the genome, proteome, and morphome all concern structure, which is necessary but not sufficient for explaining function, we also need to know about the dynamics, kinetics, and functioning of those structures and how they interact. In other words, we need more than statistical descriptions of associations among physiological variables; "we need models that include mechanisms and distinguish mere association from cause and effect." This type of mathematical modelling and simulation research responds to the macro-ethical imperative to minimise risk for people/patients while at the same time fundamentally advancing biology and medical science: prediction, prevention, personalisation, diagnosis and therapy (Bassingthwaight 2002).

The European Union research support "Framework Programme 7 (FP7)" running from 2007 to 2013, allowed Europe to gain global leadership in this field and closely cooperate with similar research communities in the USA, Japan, New Zealand and elsewhere. Support continues in the new so-called "Horizon 2020 Programme" (2014-2020). Initially, this work concerned predominantly the development of ICT technologies supporting multi-scale modelling and simulation of human organs or systems, thereby aggregating information from multiple biological levels. Building on this fundament, recently a particular focus has been put on the clinical and personal use of VPH or in silico technologies, aiming also at the clinical proof of concept of person-specific computer-based models. The clinical objectives in using person-specific computer based models are to allow for early diagnosis, prediction of disease behaviour and evolution and treatment outcomes.

Meeting the Challenge – The DARE@IT Project

The scientific and medical vision of this endeavour is based on the fact that an early and unambiguous diagnosis of

dementias will have dramatic benefits for the individual, but also for healthcare systems as a whole: delaying the onset of dementias by *a mere one year leads to a 10% reduction* in symptomatic cases – (VPH-DARE@IT 2013) with dramatic consequences on the quality of life for the subjects, but also with very

responds to the brief to provide early and differential diagnosis and management of the onset and progression of dementias, by integrating, in a truly multidisciplinary manner, heterogeneous data from individuals and populations, genetic, biochemical and metabolic pathway models, mechanistic and phenomenological mul-

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“dementia has arrived in the middle of our societies”

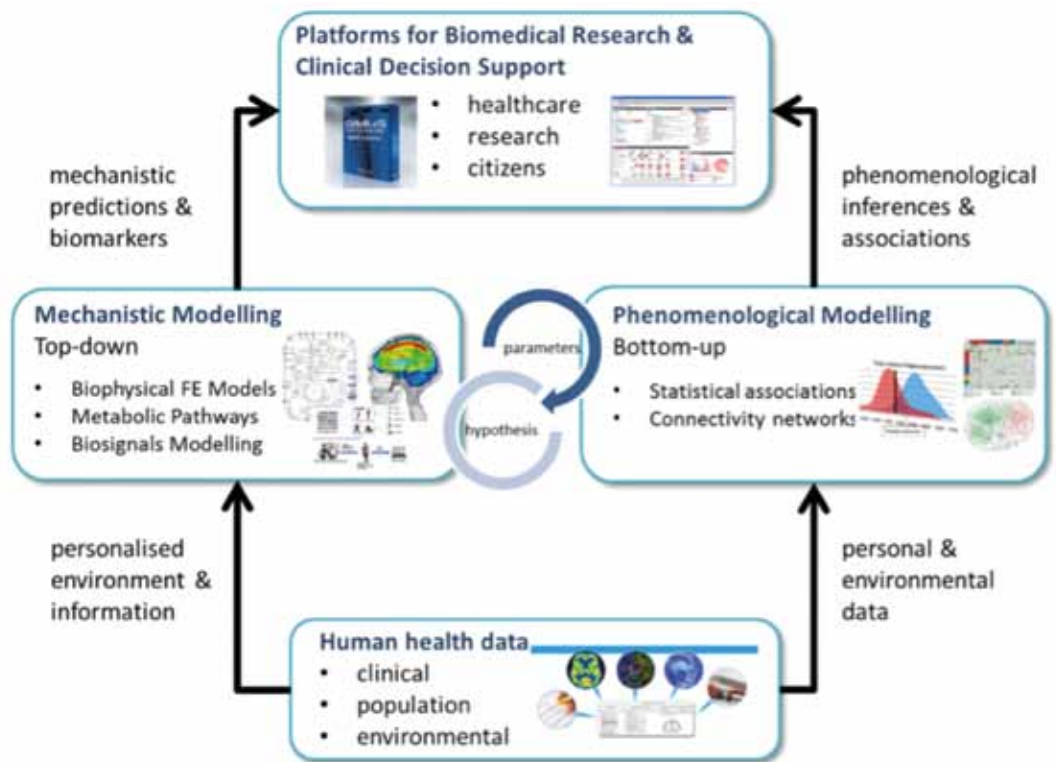
significant savings for the healthcare system. Unfortunately, both early and differential diagnoses, but also robust methods to predict the evolution of these diseases in a patient-specific manner, and thus decisions on suitable care and hopefully treatment, still elude the medical profession.

It is exactly these challenges that the VPH DARE@IT project addresses. It tackles the most pressing unmet clinical needs in this syndrome and

tiscale imaging/modelling paradigms and sophisticated information processing tools to deliver highly innovative clinical decision support systems.

By bringing together new knowledge and innovative methods in these fields, it will deliver the first ever model that can account simultaneously for the patient-specific multiscale biophysical, biochemical and biomechanical brain context, as well for a number of heterogeneous genetic, clinical, demographic, lifestyle

Multiscale Multifactoral Multiparadigm Modeling



Graph 1: The VPH-DARE@IT concept in a nutshell: combining the appropriate modelling paradigms

and other environmental factors. According to a new World Alzheimer Report 2014, the “strongest evidence for possible causal associations with dementia (plausible, consistent, strong associations, relatively free of bias and confounding) are those of low educa-

Expected Results and Impact

VPH-DARE@IT’s aim is to support researchers and enable clinicians to arrive at earlier, predictive and individualised diagnoses and prognoses of dementias to cope with the challenge of

“citizens should be empowered and supported to screen and assess their own health and risk for certain diseases”

tion in early life, hypertension in midlife, and smoking and diabetes across the life course”. VPH DARE@IT will help shed light upon such causal relations by investigating a number of observed and speculated links, including the effect of metabolic syndrome, diabetes, dietary habits, exercise, pulmonary conditions, and how the effect these conditions have on the ageing brain influences onset and evolution of dementias.

This distinctive conceptual approach and the integration of innovative data analysis and modelling methods are illustrated in the following graph, which depicts the VPH-DARE@IT concept of combining the appropriate modelling paradigms in a nutshell: (see Graph 1)

The final objective is to 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.

The resulting integrated clinical decision support platform will be validated/ tested by access to patient data contained in a dozen databases of international cross-sectional and longitudinal studies, including exclusive access to a population study that has tracked brain ageing in more than 10,000 individuals for over 20 years (Rotterdam Study [14]). The project will also quantify the benefits and costs of using the VPH-DARE@IT platform by both clinicians and industry, and contribute to the competitiveness of European industry active in the silico domain.

an ageing European society. Amongst others, this requires to identify and/ or develop:

- Novel biomedical dementia biomarkers;
- Personalised, multi-factorial brain models, taking into account genetics, metabolism, biophysics, physiology and environmental influences;
- Advanced brain image analysis tools;
- An integrative and personalised modelling platform to support clinical research in dementia;
- A validated clinical platform for the personalised diagnosis of dementia and assessment of treatment efficacy;
- A framework and infrastructure for gathering, semantically coding, sharing and integrating patient and other data from large, often heterogeneous databases.

The impact of VPH-DARE@IT achievements will range across the scientific, clinical and industrial communities of Europe and globally, and uppermost improve prevention and care of dementia patients. Its results will

- Provide for an earlier personalised prognosis, diagnosis and treatment onset, meaning reduced suffering for the individual and their relatives;
- Integrate lifestyle and other environmental factors and data with clinical, biological, and physiological factors and determine their impact on disease progression

and prevention;

- Facilitate the earlier risk assessment before a patient’s memory is already severely affected, i.e. before it tends to be too late for starting some of the presently available treatment options;
- Provide cost-efficient approaches for detecting high-risk patients and channelling them to detailed diagnostics studies at an early phase;
- Ensure greater equality between citizens through systematic and objective diagnoses (quality of healthcare currently depends on where someone is living and the capacities of their local hospital);
- Provide also for estimates of anticipated healthcare cost reductions based on state-of-the-art impact assessment models. Substantial cost reductions will require, in addition to earlier diagnosis, a delay in the progress of dementia achievable with new prevention and treatment options;
- Foster industrial progress, resulting from the availability of the ICT tools and systems, and the expertise to apply them in the context of clinical applications. For example, the pharmaceutical industry will be able to develop new products as a result of a more accurate understanding of disease progression and clinical interventions. Picture archiving and communication, radiology, electronic health records, and general clinical information, as well as decision support systems (PACS, RIS, EHR, etc.) are also likely to benefit from these products and impact on European eHealth industry leadership;
- Enable biomedical researchers to investigate the influence of environmental factors on dementias through specialised modelling software frameworks, which will be made available to the general community as Open Source platforms.

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Technology Solution – The VPH-DARE@IT Platforms

The final outcome of VPH-DARE@IT - including its decision support platform - will integrate the tools, models and workflows developed during the life time of the project as well as relevant other open source tools and sub-models that focus on dementia research. This will enable a single framework which not only provides for dementia-related decision support, but also permits to create a new generation of research and development workflows focusing on further as well as totally new multiscale patient specific treatment options for dementia. The specific results expected are to:

- Develop a workflow-oriented and extensible framework for clinical dementia research;
- Implement and make globally available a workflow-oriented and extensible framework for in silico modelling researchers in dementia;
- Specify interoperability mechanisms for leveraging functionality from other open source frameworks in dementia research;
- Define and implement integrative pipelines for data acquisition, curating and processing in the VPH-DARE@IT environment;
- Support the interaction and integration of such frameworks with the in silico and clinical data sharing infrastructure under development in related European projects ;
- Support data-provision centres of VPH-DARE@IT partners to federate their databases through this European infrastructure. (see Graph 2)

The VPH-Dare@IT project will deliver the first integrative and validated multiscale modelling platform for biomedical brain research and clinical decision support.

Outlook and Benefits

A functional, clinically validated decision-support system for prediction, diagnosis, and treatment of dementias is not yet available, in spite of

predictions made at the start of our century. There is a strong need for an in silico modelling platform that is able to assemble and integrate the biological and medical knowledge on dementia as well as the heterogeneous information and data measured from individual patients and patient populations. It must be able to generate information (e.g. from biomarkers & other clinical and environmental measures) relevant for diagnostics and monitoring of disease progression.

VPH-DARE@IT develops a modelling and analysis system that will be used for supporting early differential diagnostics of dementias. A prime application target is to estimate reliably a predictive risk score for individual patients to become dement. The lack of such clinical support has been identified as a major challenge. Considering the enormous social and economic costs for individuals and society expected for the coming decades, such a solution will have a very high impact –both for individual patients and our health systems. A better selection and stratification of individual persons with respect to their respective risk will, as a next step, permit the much better targeting of preventive interventions and, where and when possible, treatment options.

In order to enter clinical practice, the tool will be easy to use and



Graph 2:
Analysing brain images

provide information that is immediately relevant for making diagnostic decisions in routine clinical practice. In other words, clinical user requirements are equally central to the tool's design and implementation.

In addition to expensive dementia screening programmes financed from national health systems or public insurance funds, citizens should be empowered and supported to screen and assess their own health and risk for certain diseases. This project will also demonstrate the use of a portal designed for citizens to evaluate their risk for dementia and ways to integrate such a portal into research as well as clinical platforms. ■

Project Information

VPH-DARE@IT
Virtual Physiological Human:
DementiA Research Enabled by IT
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Co-ordinator: Alejandro Frangi - The University of Sheffield

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Key Points

- As more people live longer, dementia is becoming more common. The prevalence is expected to double to 66 million by 2030 and 115 million people by 2050.
- The global cost was estimated at US\$ 600 billion (€475 billion) for 2010 – about 1% of the world gross domestic product.
- An early and unambiguous diagnosis of dementias will have dramatic benefits for the individual, but also for healthcare systems as a whole: delaying the onset of dementia by a mere one year may lead to a 10% reduction in symptomatic cases.
- The European Virtual Physiological Human (VPH) Initiative supports the mathematical modelling of human organs and diseases. Also known as “in silico” medicine, it complements “in vitro” and “in vivo” medicine. In silico is by now a core part of the wider field of integrative systems biology.
- The VPH DARE@IT project develops an in silico modelling platform that enables the assembly and integration of biological and medical knowledge on dementia as well as heterogeneous data from individual patients and patient populations. It will help shed light upon causal relations by investigating a number of observed and speculated links.
- VPH-DARE@IT supports researchers and enables clinicians to arrive at earlier, predictive and individualised diagnoses and prognoses of dementias to cope with the challenge of an ageing European society.
- A better selection and stratification of persons with respect to their individual risk will permit a much better targeting of preventive interventions and, where and when possible, treatment options.