Towards the Human Motion Project - HUMO

From an International MS Trials, Research and Resource Centre to an open international collaborative research platform to study human motion

Management Summary
Achievements in 2001 – 2007 and Research Plan 2008 - 2013

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21.07.2008

Human gait is remarkable. It is the basis of human motion, gait and movement disorders are the hallmark of many disabling diseases and it is a blockbuster drug on its own: 30-45 minutes brisk walking every day has shown strong beneficial long-term effects on many significant diseases even when based on hard outcomes such as mortality.

The Human Motion Project is an analogue to the Human Genome Project: the vision is to improve human health by evidence-based decision support tools for diagnosis and treatment through a better understanding of the alphabet and the language of human motion and its consequences for mind and body.

At the centre of the project is the development of an open collaborative human motion and medical monitoring technology platform and biomedical data warehouse for collecting, archiving, analysing and disseminating human motion data.

Key medical areas are: neurologic (degenerative) diseases (MS, Parkinson's disease, Alzheimer, dementia, pain) and other disabling diseases (Chronic obstructive pulmonary disease, osteoporosis, cardiovascular diseases including stroke) as "surrogates" for the multitude of disorders which affect people in an aging society. Drivers for innovation are sports & space, which extend the limits of human physiology and motion.

Key underlying scientific areas are: mathematics, physics, biostatistics, biomedical engineering, computer science and imaging.

The Human Motion Project is expected to have a long-term impact on the development of novel interdisciplinary academic fields as well as being a stimulus and marketplace for the development of critical path tool kits [1] (see potential HUMO stakeholders in figure 1).

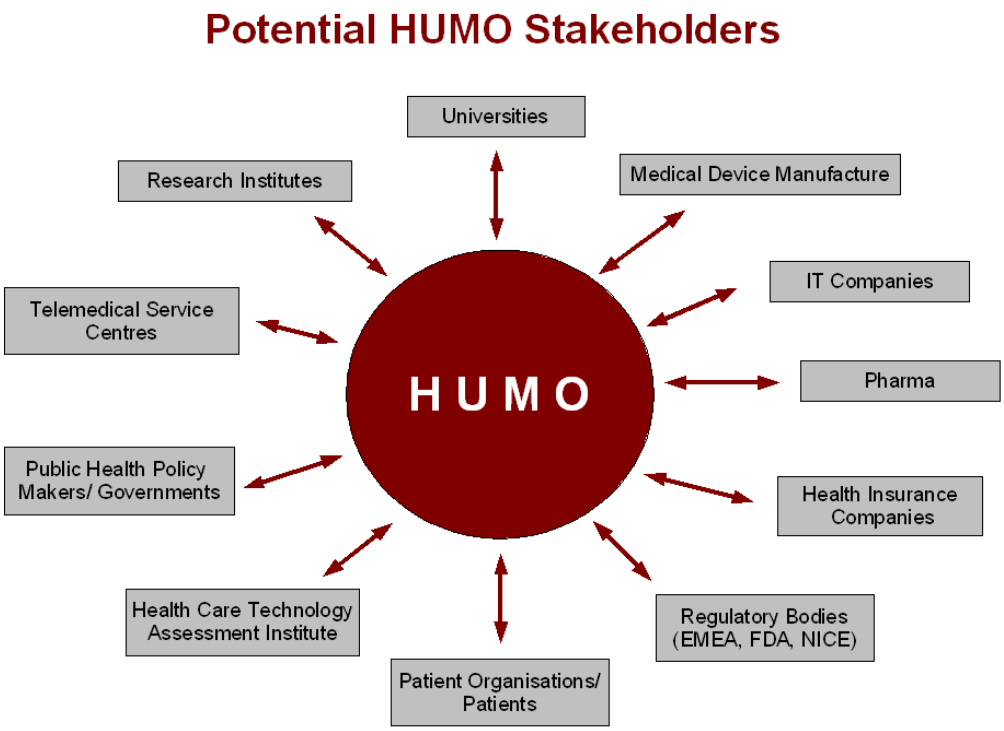

Figure 1: Potential stakeholders for the Human Motion Project

The Sylvia Lawry Centre (SLC) is in a unique position to be the crystallising point for such a development: it bundles all core competencies from mathematics/physics, IT/biomedical engineering to clinical trial expertise in a cluster in Munich, with excellent international key partners from academia, industry and regulators (FDA, EMEA) [1]. Methodologically this is captured by "Clinical Applications of Computational medicine" a novel direction of interdisciplinary biomedical research supported by the local Universities. The SLC has an excellent track record of successful implementations of public private partnerships, to serve as a productive host for international collaborative research, to develop evidence based decision support tools and to deal with the complexities of maintaining scientific independence while encouraging their entrepreneurial development [2-30].

Moreover, the human motion project is a natural development and extension based on the results of systematic patient-based meta-analyses of the SLC database in the field of MS. Here insufficient outcome measures and invalid surrogates are typical, and there is a specific need for objective tools to measure long-term disability. In addition, a recent Cochrane analysis shows that physical activity in the right dose is a low-cost and potentially powerful treatment option [31].

Essentially all planned and ongoing projects at the SLC fit into this overall program. Figure 2 summarises recent and future activities *towards the HUMO project.*

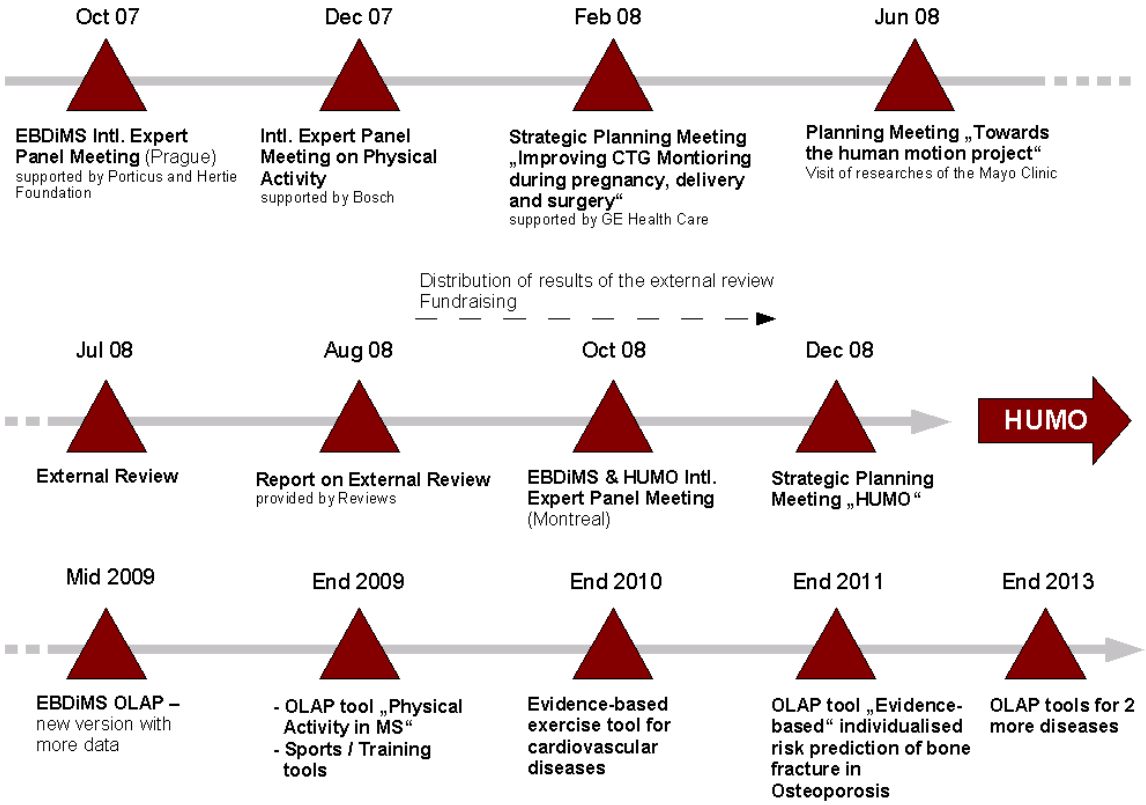

Figure 2: Recent and future activities towards the Human Motion Project.

As a follow-up of an external review of the SLC to be conducted in July 2008 there will be a strategic planning meeting with core partners of HUMO (Trium Analysis Online, TUM, Mayo Clinic and other to be selected from the stakeholders) later in December 2008. This will be a follow-up of an international expert panel meeting on physical activity that was organised by SLC and Trium with the support of Bosch in December 2007 in Munich. In order to find the right structures and partnerships that will attract the necessary funding to boost collaborative productivity by promoting long-term collaborations the following items need to be discussed: legal framework and the key questions (adapted from Nature 2008 “The collaborators’ prenup” [32]) *What do we expect to get out of this? Who is doing what and when? Who will have access to our data? How will we assign authorship? Who owns the intellectual property? How do we manage conflicts of interest?* and *What happens if one of us leaves the group?*

Milestones:

- Next version of the EBDiMS OLAP tool including more long-term follow-up data — Mid 2009
- OLAP tool “Physical activity in MS” as add-on to EBDiMS OLAP — End 2009
- Sports – Training tools — End 2009
- Evidence-based exercise tool for cardiovascular diseases — End 2010
- OLAP tool “Evidence-based individualised risk prediction of bone fracture in Osteoporosis” — End 2011
- OLAP tools for 2 more diseases (e.g. Parkinson’s disease, Obstetrics, Chronic Obstructive Pulmonary Disease (COPD), Depression / Schizophrenia) — 2013

Deliverables:

- Yearly international conferences, e.g. in cooperation with ICAMPAM (International Conference on Ambulatory Monitoring of Physical Activity and Movement) and PhysioNet on topics arising from the Human Motion Project
- Yearly peer-reviewed publications on evidence based decision support tools and topics (expected numbers are 2 (2009), 4 (2010), 8 (2011), 10 (2012), 12 (2013))
- Generation of ~ 45.000 patient hours of activity data
- Submission of grant proposal for HUMO core funding (2009)
- Yearly submission of 3 grant proposals in cooperation with stakeholders for HUMO project activities
- First impact of HUMO in commercial application (Small and Medium Enterprises (SME) and large companies) (2010)

Trium, TUM, SLC: where is the link between MS and mobile medical monitoring?

10 years ago the Technical University of Munich (TUM) spin-off company “Trium Analysis Online” followed the vision to improve human health by developing web-based online tools to collect, manage, analyse and disseminate clinical and biomedical data. Two main areas developed: the “clinical trials engine”, a platform for the electronic data management of clinical trials and from the concept for an internet-based database for supporting projects in the area of biosignal analysis “CTG Online”, a platform for evidence based online decision support in obstetrics with patented algorithms to detect drifts, shifts and outliers in biosignals [33]. In 2000 Trium joined forces with the Institute for Medical Statistics and Epidemiology of the Technical University of Munich (at that time headed by Prof. Neiß) to respond to a request for proposal to build and maintain an “International MS Trials, Research and Resource Centre - IMSTRaRC” [Advertisement in Nature May 2000]. The proposal from Munich was successful and a 5a contract with a total volume of 5m Euros was awarded from the Multiple Sclerosis International Federation (MSIF) to Trium and the TUM. The original aim was twofold: a) improving the prediction of the disease by advanced mathematical modelling – maybe leading to virtual control groups, and b) evaluating the use of MRI measures as potential surrogates for the disease course.

The Sylvia Lawry Centre for MS research (SLC) was founded by representatives of MSIF, TUM and Trium in 2001 as independent legal entity with long-term prospects for research and development. Since then, the SLC has built the world’s largest collection of MS data sets coming from placebo arms of clinical trials and natural history studies. All major pharmaceutical companies and academic centres have contributed data free of charge to the Centre, in total (as of July 2008) data from roughly 26,100 patients summing up to almost 100,600 patient years.

This resource together with a strictly enforced validation policy made the following key achievements possible:
a) The development of a freely accessible evidence based decision support tool for estimating the future course of the disease (“Individual risk profile”) that is continuously updated and refined by inclusion of new high quality data sets, by improved and validated algorithms and web-based tools [11]. Neither MRI measures nor genetic/genomic information survived variable selection in multivariate modelling.

b) MRI T2 lesion volume is not a surrogate for disability – in contrast to widespread expectations (see the plateauing effect described in [22])
c) Gadolinium enhancing lesions seen on MRI are not a surrogate for relapses – in contrast to widespread expectations [40, 41]
d) There is no strong link between relapses and subsequent disability – in contrast to widespread expectations [30]
e) The outcome measure "sustained progression" based on EDSS measurements – the gold standard in phase III clinical trials - cannot be validated for typical patient populations [15].

Also in 2000 Trium Analysis Online and TUM were successful to obtain a 3-year grant from the German Ministry for Science and Education to develop a universal platform for "Mobile Medical Monitoring" with a multi-purpose biomedical measurement tool called "medshirt". The medshirt and the corresponding platform was developed and a wearable prototype was shown to be able to record, transmit and analyse high resolution ECG data as well as other biosignals together with GPS information. In the following years multiple efforts were made to exploit potential synergies between these two fields of MS and mobile medical monitoring.

It turned out to be more and more clear that the deficiencies in the widely used outcome measures that became apparent during the analysis of the SLC database cannot be reasonably dealt with by more advanced statistical modelling. At that point a more radical change seemed to be necessary and the idea was born to use the essence of the medshirt technology to develop a universal platform for the mobile monitoring of disability: the "actibelt", essentially a medshirt compressed into a belt buckle, all sensors but the most essential one removed: the 3D acceleration sensors, that would give meaningful information about the motion of the body's centre of mass, certainly the most basic starting point when one attempts to quantify human motion, at least from a physicist's point of view.

Trium Analysis Online and subsequently the SLC became partners of one of the major post human genome projects: "bloodomics" (www.bloodomics.org) and "cardiogenics" (www.cardiogenics.org), both multi-million euro integrated projects with the focus on genome-wide cardiovascular diseases funded by the European Union [34-37]. Trium's responsibility was the development of an IT platform to pool the clinical data and link this Patient Information Management System "PIMS" to the "LIMS", the Laboratory Information Management System that is hosted at the Wellcome Trust Sanger Institute in Cambridge, UK.

The SLC had been stimulated by the Porticus Foundation to broaden its basis by trying to apply the concepts that had proved to be useful in MS research to other fields. Obviously, cardiovascular disease was a natural choice. The overarching "tetrahedron concept" that was developed is built in the "International School for Clinical Bioinformatics and Technical Medicine", a grant for fellowships and summer/winter schools that was awarded by the Porticus Foundation to the SLC and Cambridge University.

The tetrahedron concept in a nutshell:
Advances in imaging technology, genetic / genomics and biosignal analysis carry all the potential to improve clinical decision making (figure 3). Our concept is to evaluate the additional value of these areas to multivariate statistical models based on

classical clinical variables that describe the phenotype of a specific disease – “phenomics”.

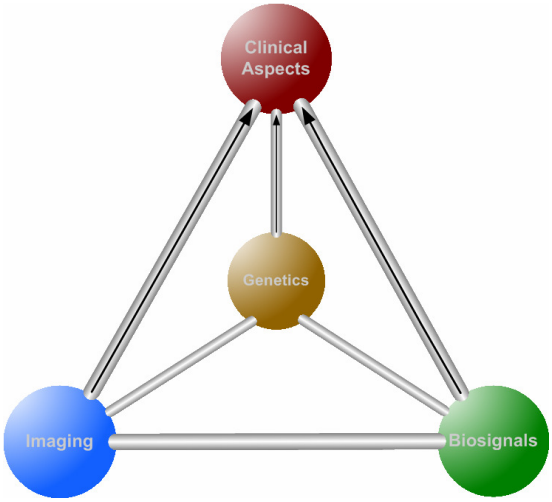

Figure 3: The tetrahedron concept.

Typically it is difficult to validate an improvement of classical prediction models. The most promising candidates with a broader spectrum of possible applications seem to be those biosignals that are related to human motion (3D accelerometry). In contrast to the Human Genome Project and its successors, where even basic concepts such as “genes” are becoming more and more vague and are still far away from the original stretch goal to develop individualised therapies, the Human Motion Projects deals with entities that are inherently meaningful for human health: human motion *always* matters, whereas specific genes and MRI images don’t necessarily [38,39].

In many diseases physical activity plays a dual role as a meaningful outcome measure and treatment option. The tetrahedron concept can be transferred to a number of diseases (see figure 4).

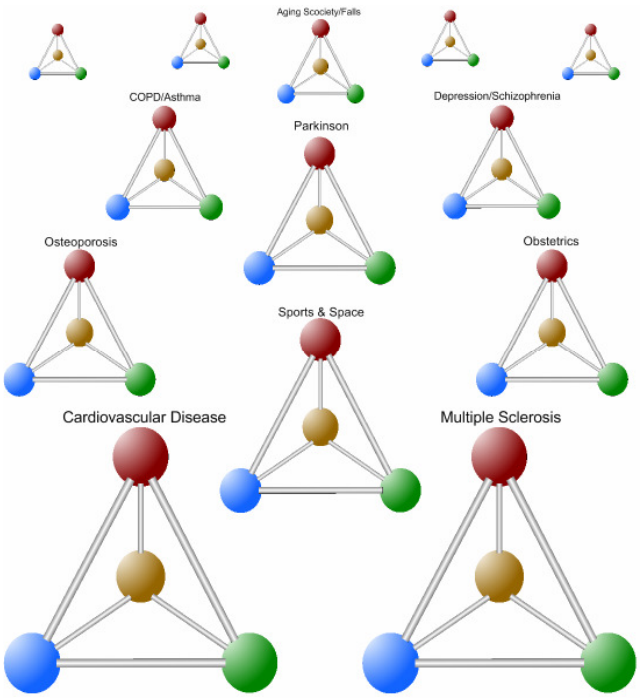

Figure 4: Transfer of the tetrahedron concept.

“Killing me softly” and “Entrepreneurial Research”

In 2005 the MSIF conducted an external review of the SLC’s achievement and future plans that led to the widely distributed recommendation to immediately close the Centre and move the database out of Germany. The Scientific Director of the SLC received full support of the SLC’s Supervisory board – after some changes within the board in the direction to continue the research in Munich - to manage this somewhat difficult phase in the development of the Centre.

The strategic options were to either give up the focus on MS or the scientific independence of the Centre. After MSIF realised that the database could not be moved outside Germany they expressed willingness to support the Centre’s activities if the Centre gave up the scientific independence: the Centre was asked to prepare a grant proposal that would need to be approved by members of the Scientific Advisory Committees of both SLC and MSIF which would have placed them in a conflict of interest situation. The SLC decided not to give up its independence and moved into a phase of what one should call “entrepreneurial research”, the attempt to do high quality independent research in other disease areas and new fields without any core funding, knowing that the resources for this development needed to be found “on the fly”. One of the consequences of the SLC’s refusals to give up its independence was that the chairman of the SLC scientific advisory committee and several members stepped down. A major proposal “EBDiMS – Evidence based decision support in MS” was not recommended for funding by the SLC’s former Scientific Advisory Committee, although the very same proposal had successfully passed the rigorous review process of the Hertie Foundation.

A major structural change was then the subsequent establishment of a new scientific advisory committee that is covering the main scientific areas and a MS expert panel. Similar expert panels can be implemented for other diseases, when necessary.

The Human Motion Project – outline of selected activities of the SLC

We are rapidly broadening our capability to pursue our new mission in MS and an increasing number of other diseases: “evidence-based decision support tools for better clinical choices”. A key element is the actibelt – a technological platform and a research tool that allows us to be involved in a large number of diseases and to be eligible for more sources of funds.

Physical activity will be considered in a number of chronic and widespread diseases. The user acceptance and feasibility of the actibelt which is used to measure physical activity will be assessed in numerous patients with MS, cardiovascular disorders, Parkinson’s disease, Depression and Schizophrenia as well as in healthy subjects. Associations between physical activity and disease specific outcomes such as evolution of disability or risk for heart attack or stroke will be evaluated and related to therapies.
Environments to collect activity data from patients with MS, Osteoporosis and Chronic Obstructive Pulmonary Disease will be set up and used to develop or improve tests and scores applied in diagnosis and therapy.
In MS the project “Evidence-Based Decision Support in MS” (EBDiMS) aims to develop an evidence-based decision support tool for treating physicians and their patients. The tool will be web-based, freely accessible for non-commercial purposes,

interactive and will continuously be updated to ensure the timely integration of new high-quality datasets into the world's largest MS data repository and the use of the most advanced, validated mathematical models.

We were successful with each of our recent grant proposals and are currently negotiating contracts in these areas:

a) The Hertie Foundation and the Porticus Foundation are now both supporting the "Evidence-based decision support in MS" project (2 years, project costs per year 385kE, contribution from Hertie Foundation **75kE per year**, Porticus Foundation **75kE per year**. 235kE per year still to be obtained). The Porticus Foundation is still additionally supporting the "International School for Clinical Bioinformatics with **75kE per year.**

b) The European Union will be funding "NETSIM", a large 4-year project in collaboration with the University of Cambridge, that will fund 1 Postdoc and one PhD student at the SLC, one PhD student at Trium and one PhD student at the Technical University of Munich (TUM). The project aims to study the contribution of physical activity (actibelt) and genetics to the risk of cardiovascular disease. Funding will amount to **110kE per year** for 4 years, but can only be used for add-on staff.

c) The European Union will be funding "VPHOP", a large 4 year integrated project in the context of the "virtual physiological human". The aim is to develop evidence-based risk prediction models for the risk of bone fracture in patients with osteoporosis. Funding for the SLC will be **50kE per year** over two years for activities related to the actibelt.

d) The German Ministry for Economic Affairs is supporting the SLC as an independent research organisation (usually only institutions like Max-Planck and Fraunhofer are eligible) with a 2-year project "Advanced Body Motion Analysis (ABMA)". Funding is **55kE per year** for research and development of the actibelt for analysing outdoor sports.

These key projects will be bundled with related activities of our national, European and international partners to form a coherent program of "The Human Motion Project". It will stimulate the early development of standards and will help to avoid the introduction of widespread unvalidated surrogate markers for physical activity, not uncommon in other medical areas [41, 42]. Patients and other stakeholders can expect from HUMO a stream of meaningful and evidence based results and tools that help to improve human health in the short and long-term.

We have the right partners, the experience and it's the right time to start to seek funding for HUMO - to move human health.

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