

MD-PAEDIGREE

N E W S L E T T E R

MD-Paedigree | Issue 3

WWW.MD-PAEDIGREE.EU

BIG DATA FELLOWSHIP



EDITORIAL

W

elcome to the third newsletter of MD-Paedigree. The project has now been running for almost two years and as such is approaching its mid-life. Since the successful first year review in Brussels the frequent interaction between the clinical and technical partners have never stopped and the multidisciplinary teams continue systematically working towards the project objectives. One of the main focuses of the second year has been the implementation of the protocols and specifications defined during the first year.

Of particular importance in MD-Paedigree is the use of anatomical and physiological models. Indeed, in paediatric disease, predicting response to treatment, and selecting and timing the appropriate treatment for a specific patient can be challenging due to small patient numbers and limited outcome data. Computational models of physiology may provide some of those parameters that belong to the patterns of risk factors. These models are particularly useful because they give access to parameters that cannot be directly measured or only invasively. Our expectation is that such parameters would be abnormal well before the development of hard intermediate outcomes, and as such we could increase the predictive value

Since the successful first year review in Brussels the frequent interaction between the clinical and technical partners have never stopped and the multidisciplinary teams continue systematically working towards the project objectives.

of measurements already available today in the clinical environment. However, to make these models useful in a clinical environment, there are two major needs:

The first need is model personalisation, i.e. the process of tuning the parameters of the model to make it patient-specific. Once personalised, a model will mimic the patient's conditions and can be used to give some answers to the issues raised



Olivier Ecabert
Modelling and Simulation
Action Leader

above. The requirements are that these personalisation methods need to work with data that is routinely available and necessitate only little manual interaction. The processing time should also be such that it fits a routine clinical workflow.

The second need deals with the presentation of the model outcome to physicians. Biophysical models can provide additional clinically useful information, however, all outcome parameters may not be understood by physicians and the quantity of information may become too much.

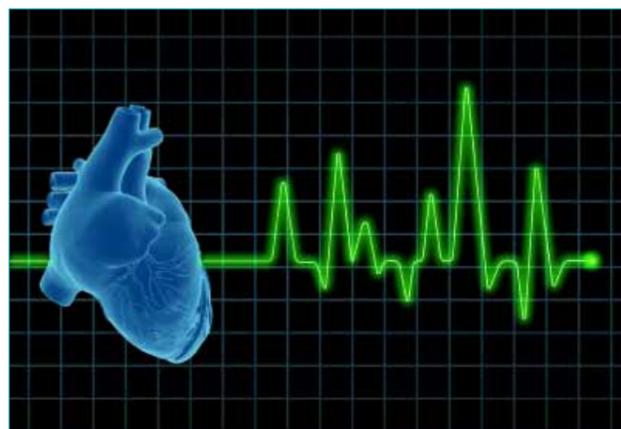
During the first half of the project much work has been done to address the first needs and I would like to review some of the recent highlights from our Modelling Action.

In the **cardiomyopathy** disease area, an efficient personalisation pipeline was set up to derive patient-specific models using information from magnetic resonance imaging (MRI), ultrasound and the electrocardiogram (ECG). Of particular interest is the level of interoperability that could be achieved. Indeed, two partners (Siemens and INRIA) have been iteratively contributing to the different steps of the personalisation pipeline, each focusing on its strengths.

In the **obesity** disease area, computational experiments



► **Cardiomyopathies**



► **Cardiovascular disease risk in obese children and adolescents**

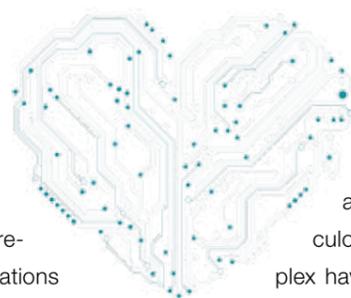


► **Juvenile idiopathic arthritis (jia)**



► **Neurological and neuromuscular diseases (nnd)**

showed that many effects due to obesity can be mimicked by a computation heart model for the electrophysiology, biomechanics and hemodynamic. In particular, the simulated effect of obesity (such as shape of torso, position of the heart, amount of fat in the torso and myocardial stiffness) yielded results in concordance with real clinical observations in the areas of electrophysiology (characterized by variations of the computed electrical axis and changes in computed ECG traces), biomechanics (left ventricular volume curves and stroke volume) and hemodynamic (pressure-volume loops). In the **neurological and neuro muscular** disease area, a three dimensional anatomical model of a pair of human legs, comprising 54 individual muscles, 12 bones, fore, middle and back feet, the skin as well as 30 landmarks was created. This complex atlas was delineated using a reference MR image which can then be matched to new unseen images using an advanced, piecewise, registration approach. The first results look



promising and there are prospects of extending the usability of this model to the **juvenile idiopathic arthritis** disease area. It is just another demonstration of the synergies of the MD-Paedigree project. In this clinical application area, patient-specific dynamic musculoskeletal models of the lower limb and foot complex have been constructed by merging gait analysis and MRI data. A dedicated acceleration technique for the finite element analysis of the trabecular bone tissue was developed to reduce the computational time using state-of-the-art graphic processing units (GPU). From a modelling perspective, the future interactions between clinical partners will focus on the validation of the models at larger scale (using several hundreds of patients) and on addressing the second need mentioned above, i.e. how to usefully convey the modelling outcomes to physicians in a way that may support them in their daily routine.

INDEX

MD-PAEDIGREE

MD-Paedigree | Issue 3

WWW.MD-PAEDIGREE.EU

EDITORIAL

p. 1

EVENTS & NEWS

p. 6

- 6 | Md-Paedigree Meeting in Utrecht
- 6 | International conference on Biomedical and Health Informatics - IEEE BHI'14
- 7 | MD-PaedigreeE at Esmac-Siamoc
- 8 | Internal Review in Amsterdam
- 8 | Opinions from our Internal Reviewers
- 9 | Avicenna 5th Event
- 10 | Clinical innovation catalyst program

MODELLING

p. 11

- 12 | Modelling and Simulation for Cardiomyopathies
- 12 | Initial Modelling Results in Juvenile idiopathic Arthritis
- 13 | Automatic Method for Segmentation

INFOSTRUCTURE

p. 14

- 14 | DCV Curation Tools
- 15 | Graphical User Interface

MD-PAEDIGREE: ALFA-PROTOTYPE

p. 14/15

- / MD-PAEDIGREE CLOUD INTEGRATION
- / FEDEHR: PATIENT CENTRIC DATA
- / SCRUM AGILE PROCESS
- / BIG DATA FEDERATION SERVICE
- / ECRF

DATA SHARING FOCUS

p. 17

- 18 | Big Data, Information Technology and Personalised Medicine
- 20 | MD-Paedigree & VPH-Share: Sharing Tools, Data and Models for the Virtual Physiological Human
- 21 | VPH Workshop On Clinical Data Management And Sustainability
- 22 | Healthy Data?
- 25 | Md-Paedigree vs. Watson

OBITUARY: ALEXEY TSYMBAL

p. 26

SCIENTIFIC PUBLICATIONS

p. 26

UPCOMING EVENTS

p. 27

NEWSLETTER INFO

p. 29

EVENTS & NEWS

MD-PAEDIGREE MEETING IN UTRECHT

MD-PAEDIGREE's 1st Exploitation Seminar and Training Workshop

► The MD-Paedigree Consortium held its 2nd Biannual Meeting in Utrecht, where both the First Exploitation Seminar and the First Training Workshop were held. The meeting has been hosted by UMCU (thanks to Prof. Berent Prakken!), in the beautiful venue of the UMCU Faculty Club. The Welcome Address has been made by Professor Edward Nieuwenhuis, director of the Children's Hospital and chair of the Child Health program.



International conference on Biomedical and Health Informatics - IEEE BHI'14

A GROUP OF MD-PAEDIGREE RESEARCHERS PARTICIPATED WITHIN BHI 2014 TO THE "STUDENT BEST PAPER RAPID FIRE COMPETITION" BEING AWARDED FIRST AND SECOND PLACE.

► In 2012, IEEE Engineering in Medicine and Biology Society (IEEE-EMBS) launched a Special Topic Conference "IEEE-EMBS International Conferences on Biomedical and Health Informatics (BHI)" with more than 330 registered attendees. The overall theme of the conference was "Translating key health challenges with advances in biomedical informatics", covering diverse topics from cutting-edge biomedical and healthcare technology re-

search and development, clinical applications, to biomedical education. MD-Paedigree actively attended the International conference on Biomedical and Health Informatics (IEEE BHI'14) in Valencia, after having got the possibility of holding within it a special session on Big Data in Healthcare. Some members of the Consortium participated in the BHI 2014 Student Best Paper Rapid Fire competition, and were successfully awarded with the first and second

prize. The presented papers have been:

- **Oscar A. Jiménez del Toro, Henning Müller,** Multi Atlas-Based Segmentation with an Intensity Feature Refinement - Awarded with the first place.
- **Lucian Itu, Costantin Suci:** A method for modeling surrounding tissue support and its global effects on arterial hemodynamics - (Awarded with the second place in the special session dedicated to Big Data in Healthcare within the Best Student Paper competition).

MD-PAEDIGREE AT ESMAC-SIAMOC

MD-Paedigree attended with a booth at the First Clinical Movement Analysis World Conference

► MD-Paedigree hosted a booth at the First Clinical Movement Analysis World Conference, held in Rome on October 1st-4th 2014, at the Angelicum Pontifical University of St. Thomas Aquinas. The partners of the NND (Neurological and Neuro-muscular disorder) area, and of the Infostructure, organised a demonstration of the use of the MD-Paedigree platform applied to NND data-sets. The team at the MD-Paedigree Booth also distributed some

copies of the Consensus Clinical Gait Analysis Protocol, asking for the support of Gait Labs across Europe to validate it. Jaap Harlaar, Marjolein van der Krogt, Marije Goudriaan, Kaat Desloovere, Gessica Vasco, Maurizio Petrarca and Enrico Castelli presented the whole project and the clinical gait analysis protocol, which is available for free at: <http://www.md-paedigree.eu/clinical-scenario-nnd/gait-analysis-protocol>.



MD-Paedigree's booth at Esmac-Siamoc



Lucian Itu being awarded the second place



Rainer Thiel presenting the paper



Internal Review in Amsterdam

► This year Md-Paedigree held its Second Internal Review in Amsterdam. Kindly hosted by the VU Medical Center University. The welcome address was given by the Dean of Vumc Professor Johannes Brug. The meeting provided the partners with the opportunity to get an overview of the work carried out in the second year of work, the status of the project and discuss issues and variations with regard to the original workplan in presence of the independent project reviewers for each specific disease area. The meeting also carried out the second training workshop and a scenario analysis session, in order to pre-empt unforeseen technical uptake problems and establish a smooth and proactive dialogue between technology developers and end-users, based on Md-Paedigree's Agile Process. Finally, an outlook on the 1st Exploitation Plan was given and a separate session dedicated to Clinical and Technical User Requirements Review, Workflow Analysis and Clinical Validation took place.



Opinions from our Internal Reviewers

► **Cardiomyopathies:**

“the modality of Co-operative competition the two Partners use in other tasks (such as in electrophysiological mechanics) appears of extreme interest for European science and for attaining qualified results in the present project. Under this modality, the two Partners develop and implement algorithms based on different assumptions, targeting the simulation of the same physiological processes, then compare the results and either accept concordance as an indication of plausibility, or investigate the causes of divergence. In a domain plagued by the difficulty of subjecting modelling results to critical analysis in the face of objective, gold-standard data, this approach is very convincing and should be showcased in future dissemination activities”.



Andrea de Gaetano
M.D., Ph.D. (Math), J.D.

Cardiovascular Risk in Obese Children: “the models developed within the project may be usefully employed to help determine clinical outcome after weight loss. The pilot dataset collected in the project will allow the correct design of clinical studies targeted at detecting the effects of weight loss interventions (pharmacological or life-style) over 12-18 months. [...] The variety of measurements, which will be combined on each experimental subject, is indeed exceptional, and the information content of the eventual database can easily be highlighted to advantage”.



AVICENNA 5TH EVENT

The Avicenna project's 5th meeting will be held in Barcelona on 4th – 5th June 2015

► THIS MEETING WILL PRESENT THE PROPOSED ROADMAP TO A LARGE GROUP OF STAKEHOLDERS AND EXPERTS AND IDENTIFY ANY REMAINING AREAS OF WORK TO BE PROGRESSED. A STRATEGY FOR THE CONTINUATION OF THE AVICENNA WORK WILL BE AGREED, INCLUDING SETTING UP WORKING GROUPS AND SPECIFYING STANDARDS TARGETS.

Day 1: Thursday 4th June, 2015

- in silico Clinical Trials: the research and technological development challenges
- Breakout sessions – RTD challenges
- Cocktail lecture – The impact of Avicenna's “Canon of Medicine” on modern clinical research

Day 2: Friday 5th June, 2015

- in silico drug discovery
- From data to knowledge: big data analytics in healthcare
- How do we see the role of in silico technologies in healthcare
- ISCT: socioeconomic challenges
- in silico models replaced animal experimentation in the FDA regulatory process for artificial pancreas technologies
- Proxy measures: the low hanging fruit of in silico medicine
- The Avicenna research roadmap: the challenges ahead
- Towards the Avicenna pre-competitive Alliance
- Pro tempore board meeting

Event 5 will be hosted and sponsored by Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS) – Agency for Health Quality and Assessment of Catalonia

Financial Support

Experts working for not-for profit organisations can apply for partial support of their travel and accommodation expenses. Reimbursements range from €200, if you travel a distance of less than 500Km, to €2000 if you travel a distance of more than 10,000 Km.

Considering that the resources available are limited, and most likely insufficient to support all requests, we recommend you apply only if there is a real need, and consider requesting only a partial reimbursement of the costs.

To request financial support please write to events@avicenna-isct.org specifying where you will travel from, and the maximum reimbursement that you would be willing to claim.

If you are interested in joining or contributing to our final event, please visit our Eventbrite Page or contact us at:

events@avicenna-isct.org

CLINICAL INNOVATION CATALYST PROGRAM

Transforming Healthcare for Babies and Children
Collaboration. Education. Research. Technology.



EMPOWERING TEAMS OF NURSES AND ALLIED HEALTH PROFESSIONALS TO CREATE INNOVATIONS THAT SOLVE CRUCIAL PATIENT CARE NEEDS

► A catalyst is defined as a person that precipitates an event or change. In the hospital setting, clinicians serve as catalysts that not only effect change among the countless patients they treat, but also improve the healthcare services we consistently utilize. These clinicians will play a significant role in a new strategy to address the systemic challenges within pediatric healthcare, such as inadequate pediatric devices and technology.

IPI's new program - called the Clinical Innovation Catalyst Program - focuses on training healthcare professionals in effective practices for developing new technologies that can impact pediatric care. These clinicians will serve as innovation catalysts in their pediatric healthcare center. Teams of clinicians will work together to develop solutions to a hospital-acquired condition selected by leaders in their hospital, and will gain experience in

identifying and developing product solution for an important performance improvement issue. Integrated with each hospital's existing infrastructure for performance improvement, the program will align with the mission and goals of the hosting institution.

This new strategy to address the significant gaps in pediatric healthcare builds upon the knowledge and skills of the clinicians that are in direct contact with pediatric patients. The program also leverages existing resources within the hospital to provide solutions to critical problems.

IPI aims to pilot the program with six pediatric hospitals across the nation, as well as develop a plan to expand the program nationally through various networks, such as the Children's Hospital Association and Solutions for Patient Safety.



pediatricinnovation.org

SAVE THE DATE

Healthcare Innovation Summit

June 15-17, 2015
InterContinental Chicago
IPI, Network for Excellence in Healthcare Innovation (NEHI), and the International Society for Pediatric Innovation (iSPI) are collaborating to improve innovation within pediatric healthcare.

IPI & iSPI Annual Meeting

June 15
For more information and sponsorship opportunities contact: [Suzanne Grillo](#).

National Healthcare Innovation Summit

June 16-17
Healthcare leaders and innovators share new and successful innovation approaches that help reduce costs and improve quality of care.

Sponsored by NEHI, HIMSS, and AVIA. [View agenda and registration information!](#)

IPI Discount Registration Codes
One day (\$495) - IPINON2015
Full conference (\$695) - HCIS100DISC

MODELLING

Modelling and Simulation for Cardiomyopathies

A joint effort towards a deeper understanding of cardiac modelling



Maxime Sermesant
Asclepios, INRIA, Sophia Antipolis, France



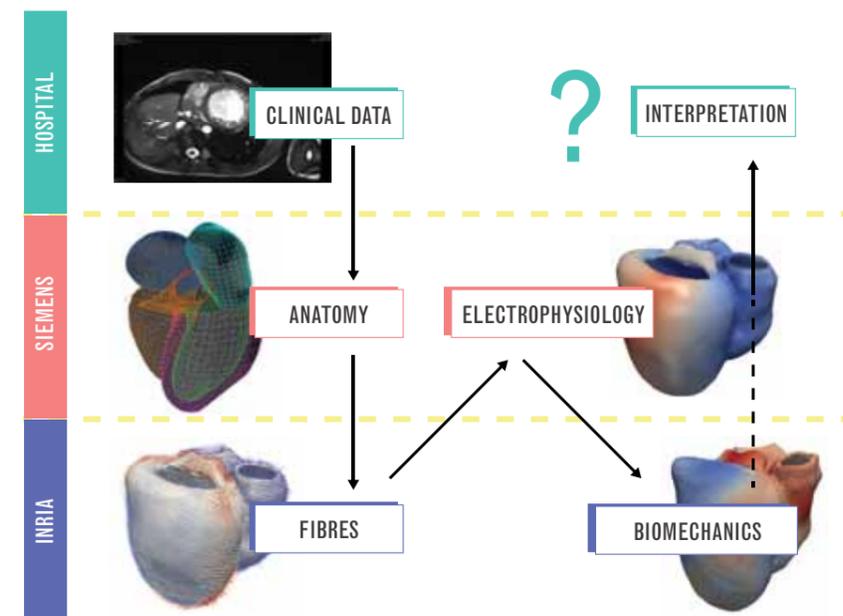
Tobias Heimann
Imaging and Computer Vision, Siemens Corporate Technology, Erlangen, Germany

One of the big challenges in cardiac modelling is the correct personalisation of the computational model, i.e. its adaption to a specific patient case. Only if this personalisation is successful, the model can be used to predict e.g. the outcome of a therapy or the evolution of a disease. In practice, however, some measurements required for an accurate personalisation are not available. One example is the fibre structure of the heart, which can currently only be determined by histologic examinations or DTI imaging of a non-moving heart – both impossible for a living patient. In order to analyse the impact of using estimated fibres, the teams of Siemens and INRIA set up a seminal experiment. Patient data from various clinical partners is analysed by

Siemens to extract the heart anatomy, which is passed on to INRIA. INRIA then generates multiple possible fibre architectures for this anatomy and passes them back to Siemens, where they are used in the computation of electrophysiology, i.e. the electrical wave propagation within the heart. These results are again sent to INRIA for a subsequent biomechanics simulation, which computes the dynamic heart motion. Analysing the results of these last two steps reveals how much impact the fibres have on the final result, an insight which can be used to estimate confidence intervals for simulation outcomes. This experiment with the multiple exchanges of data and results is made possible by the highly modular simulation frameworks of MD-Paedigree, which have been developed in close collaboration with all partners. A manuscript for a well-known scientific symposium in which the findings are presented in detail is currently in preparation (more on this in the next issue).



And all partners from WP3 and WP8 for the actual content.



experiment with the multiple exchanges of data and results is made possible by the highly modular simulation frameworks of MD-Paedigree, which have been developed in close collaboration with all partners. A manuscript for a well-known scientific symposium in which the findings are presented in detail is currently in preparation (more on this in the next issue).

Pipeline for Personalised Cardiac Electromechanical Models

Initial Modelling Results in Juvenile Idiopathic Arthritis

New biomechanical biomarkers to predict JIA progression

The JIA team has successfully developed the entire clinical study plan, including ad hoc protocols for imaging and gait analysis. These protocols have been applied to a patient zero in each centre, sent to the data repository, and analysed by the technical partners to confirm the data are of the quality necessary for patient-specific modelling. The groups in Sheffield and Fraunhofer have then started the processing of the data from the next four patients and transformed them into four patient-specific dynamic musculoskeletal models of the lower limb and foot complex by merging gait analysis and MRI data. The open source NMSBuilder and Opensimm softwares have been used to this purpose. The models have been constructed based on the Month 0 MRI ankle data, as well as the Month 6 MRI lower limb data. Initial model results have yielded

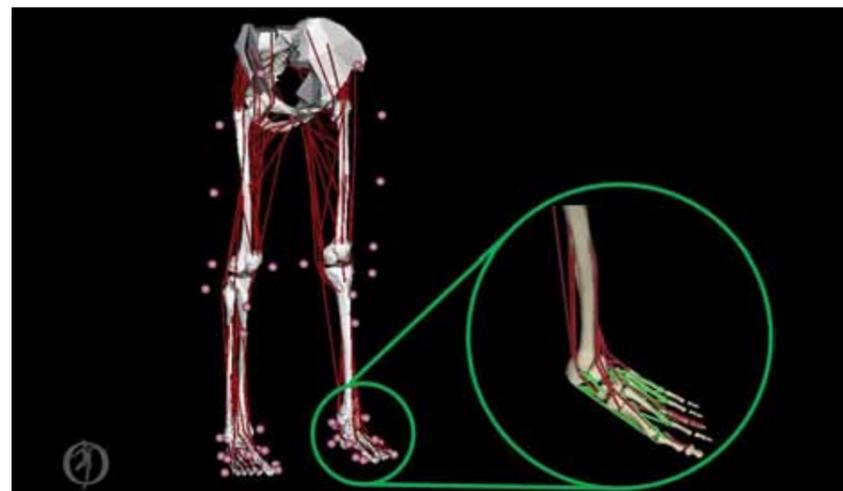
data on ankle joint loading as well as muscle activation patterns. These results will be coupled with a finite element model of the tibio-tarsal joint, which we are currently developing. Both models will provide a number of biomechanical biomarkers that will be used to quantify and predict the mechanisms that underly the JIA progression.



Claudia Mazzà
Phd, Department of Mechanical Engineering, University of Sheffield



And all partners from WP5 and WP10 for the actual content



Generic lower limb model implemented in OpenSim. Inset shows the increased detail in the foot muscles compared to the Arnold et al. (2010) model.

An Automatic Method for Segmentation

A personalised model of treatment from medical imaging

Musculoskeletal disorders can cause severe long-term pain and physical disabilities. For their diagnosis, surgical planning, post-operative assessment and overall decision support, the patient-specific modelling of the musculoskeletal system is an important challenge that can greatly contribute to or hinder the final result. MD-Paedigree aims to explore the use of complex multiscale biomechanical models of the musculoskeletal system for two of its selected disease areas (Juvenile idiopathic arthritis and Neurological and neuromuscular diseases), in order to deliver personalised models

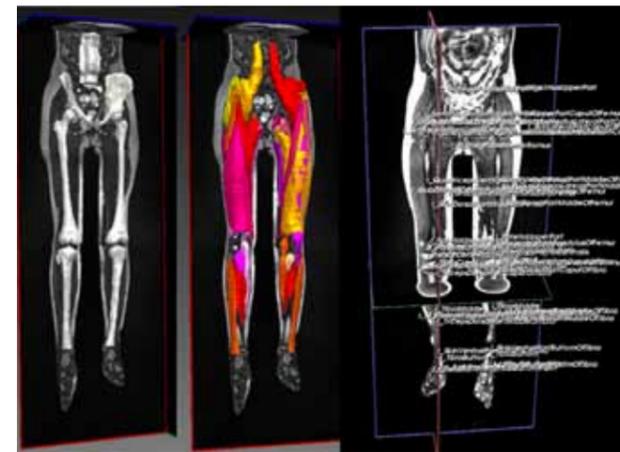
of treatment for each patient using as much as possible the information available from medical imaging and gait analysis. To achieve the above mentioned final goal, as a first



Maria Jimenez Costa
PhD in Computer Science, Siemens.



And all partners from wp11 for the actual content

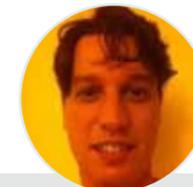


important step a software for automatic segmentation of limb structures from medical images has been developed. This software has been developed to work specifically on MRI images, which allow the extraction of the geometries of bones and muscles due to the good contrast shown among soft tissues, and are thus considered a gold-standard modality for the musculoskeletal geometry. The results are indeed encouraging: in fact, the quantitative evaluation results of the segmentation from MRI performed well in all MD-Paedigree datasets so far: the implemented method was successful at automatically extracting an exhaustive set of individual structures as well as important landmarks.

Clinical Assessment and Validation

A general outline of the general principles for assessing and validating models

In MD-Paedigree the early testing and validation of our model's robustness and adaptability is essential to assure the best outcomes and usability in a clinical environment. Thanks to an initial analysis, carried out also by conducting interviews with stakeholders, we identified the most pressing needs of the clinical users of MD-Paedigree. As the requirements analysis is an ongoing process, their outcomes merge into a parallel clinical validation process which has been designed to thoroughly improve the derived models through a testing pipeline composed

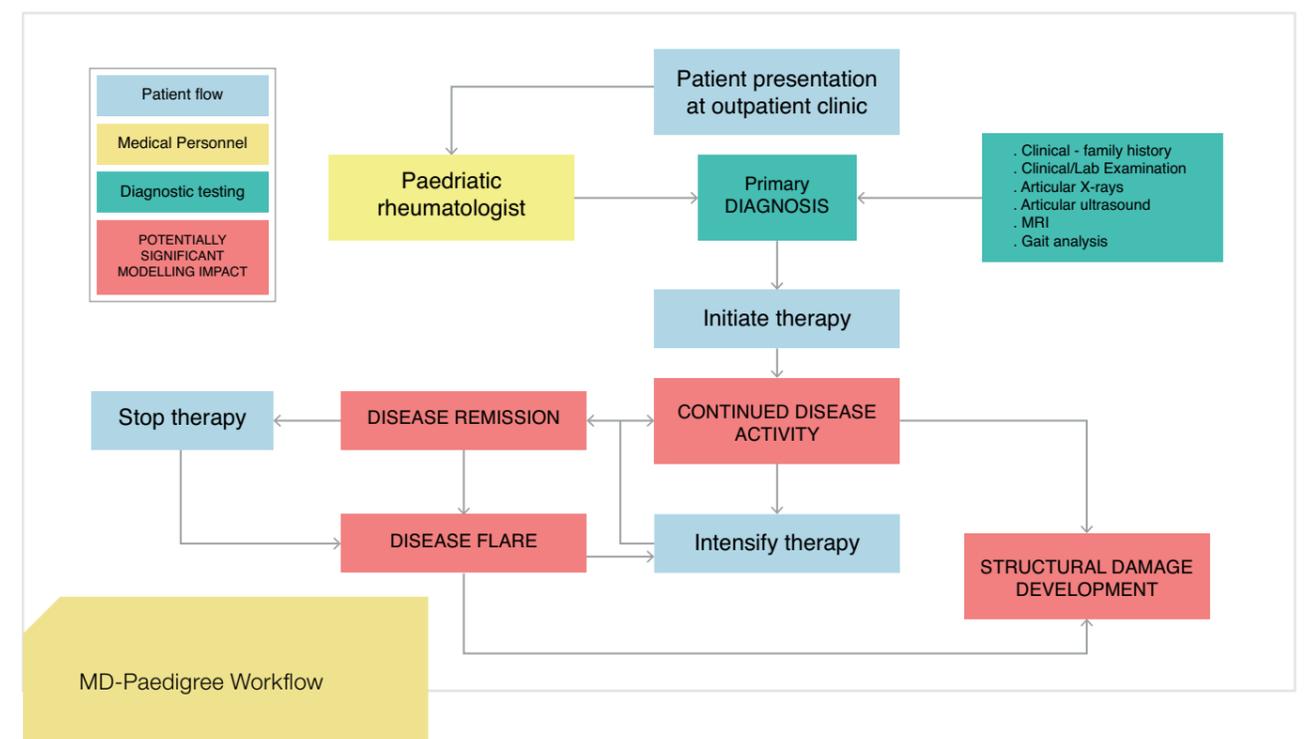


Marcello Chinali
Pediatric Cardiologist, Ospedale Pediatrico Bambino Gesù



And all partners from WP2 for the actual content

by different stages: initial testing and debugging, internal validation, a statistical approach for validation and an external validation. Finally the models undergo a usability evaluation through the Infostructure. The validation process is expected to lead to improved clinical workflows and a proposal for "innovative clinical workflows based on outcome analysis of all patient cases", which will represent the core of the project in terms of clinical outcomes and actual innovation in the everyday clinical practice.



INFOSTRUCTURE

DCV Curation Tools

Within MD-Paedigree, data curation/validation is a crucial aspect to ensure that the data submitted into the repository is relevant, syntactically well-formed, semantically interoperable and properly linked into the system.



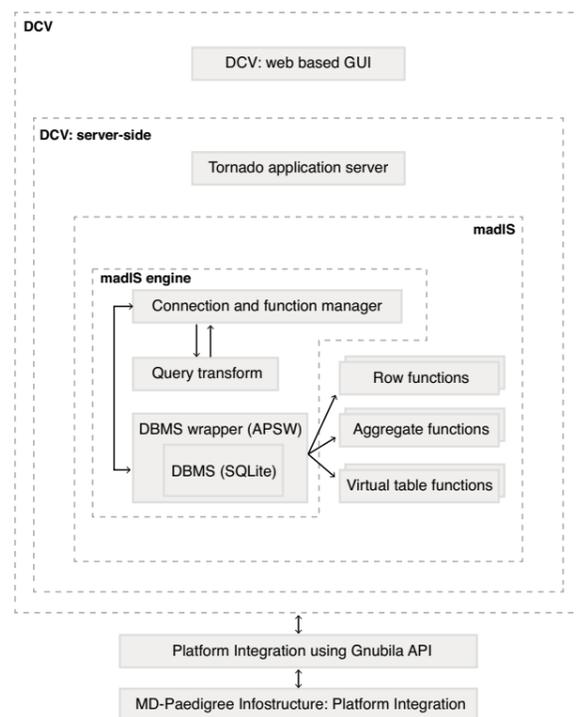
Anna Gogolou
Graduate Student Researcher at "Athena" Research and Innovation Center.



And all partners from WP15 for the actual content

The Data Curation and Validation (DCV) tool developed by ATHENA is a web application offering an advanced (semi)-automatic data cleaning process able to handle the heterogeneous MD-Paedigree data. This tool was based on a former tool developed by UoA during the European FP6 Health-e-Child project. In MD-Paedigree, DCV is enhanced with data cleaning mechanisms facilitating the detection of numeric outliers, missing values as well as alphanumeric typographical errors. DCV also offers a user-friendly interface for defining and running data cleaning rules over a relation such as functional dependencies (Figure 1), conditional functional dependencies and denial constraints. An additional extremely powerful functionality of DCV is the computation of new derived columns either through discretisation criteria or by computing and executing arithmetic operations (e.g. for computing medical scores). Complicated computations for millions of rows of data are executed in minimal time with the extremely powerful madIS engine¹. Furthermore, DCV provides visualisation of data through

¹ <https://code.google.com/p/madis/>. Retrieved: 17.02.2015

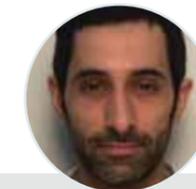


interactive barcharts and piecharts which help users to identify the distinct values of a column's data, as well as scatterplots and linecharts which give a graphical representation of correlations between two attributes. Last but not least, DCV keeps a history of all actions that affect the values of data. The user can undo/redo history or save workflows and re-run them in other projects or with other data.

Graphical User Interface

A new prototype for the case- and ontology-based retrieval service

A graphical user interface has been developed by HES-SO for the **Case-based retrieval service** to develop services to allow for searching the infostructure for a large variety of information needs. The search modalities will include free text data – virtually in any language - and linked data to ontological resources developed by and maintained in MD-Paedigree. A prototype of a generic **Ontology-Based Data Access (ODBA) Service** was developed by the ATHENA, that will provide a flexible querying front-end for the MD-Paedigree platform, addressing Ontology-based Query Formulations that will give enable users to formulate queries using familiar vocabularies and conceptualisations. Our goal is to develop a flexible module that will support query formulation by different types of users (ranging from clinicians and researchers to IT experts and computer scientists), as well as to provide a querying interface to other MD-Paedigree subsystems like KDD tools and the Sim-e-Child/PCDR repository.

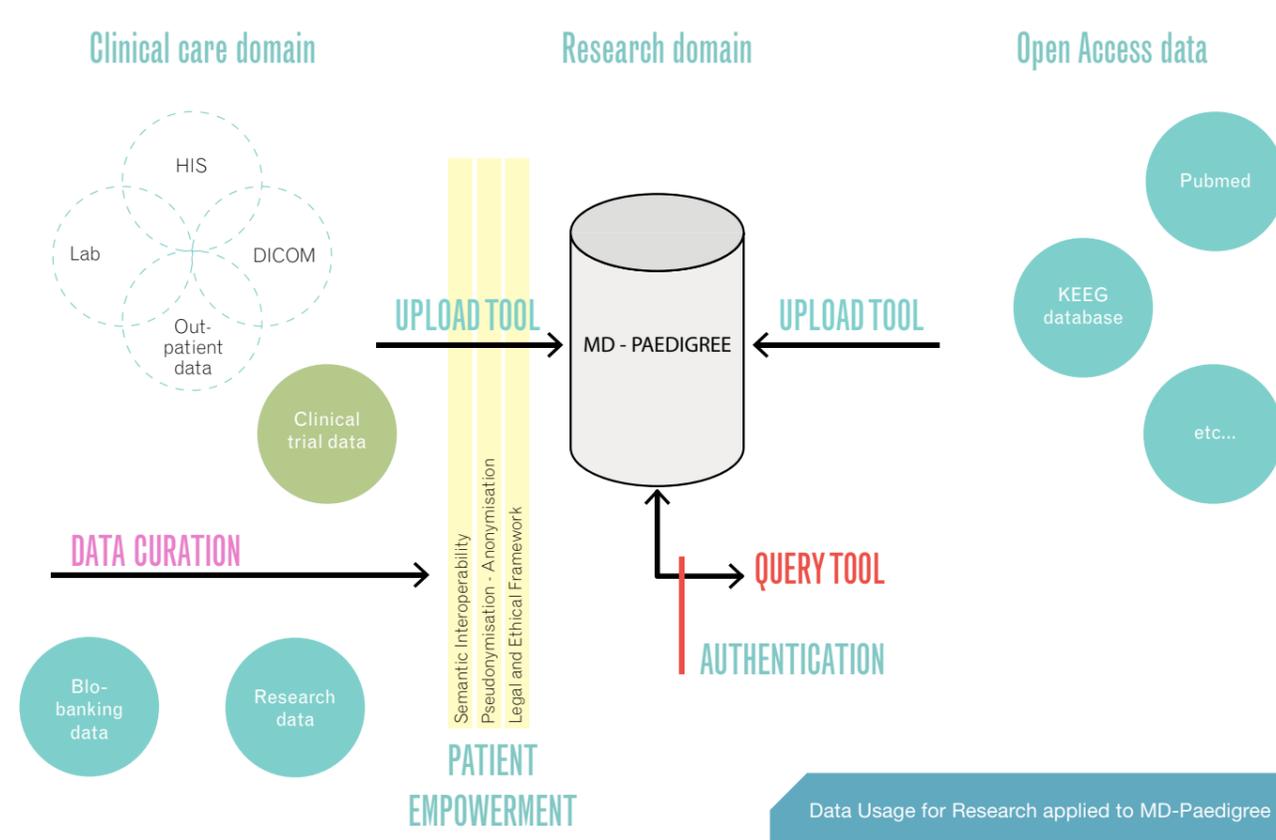


Patrick Ruch
Professor at the University of Applied Sciences Geneva (HES-SO)



And all partners from WP15 for the actual content

Number	Age	Name	Workpage summary	Score
15	11 years	Fuorescenza (2011212) Fluorescenza (2011212) Valore percentuale (2011212)	Scorre la serie "Fluorescenza globale e segmentata". Titolo: Ricerca: contenuto. (..)	5.0
16	11 years	Stabilità (2011212) Assessorio (2011212) Classe (2011212)	Scorre l'insieme della serie "Stabilità analitica". Titolo: Ricerca: contenuto globale. (..)	5.0
17	11 years	Valore medio (2011212) Insufficienza placentare (2011212) Valore medio (2011212)	Scorre l'insieme "Valore medio del feto". Titolo: Ricerca: contenuto globale. (..)	5.0
18	11 years	Stabilità (2011212) Valore medio (2011212) Valore medio (2011212)	Scorre l'insieme "Stabilità". Titolo: Ricerca: contenuto globale. (..)	5.0
19	11 years	Stabilità (2011212) Insufficienza placentare (2011212) Pressione sanguigna (2011212)	Scorre l'insieme "Stabilità (2011212) Insufficienza placentare (2011212) Pressione sanguigna (2011212)". Titolo: Ricerca: contenuto globale. (..)	5.0
20	11 years	Pressione sanguigna (2011212) Temperatura periferica (2011212) Azione (2011212)	Pressione sanguigna di circa 117mm. Titolo: Ricerca: contenuto globale. (..)	5.0
21	11 years	Insufficienza placentare (2011212) Emorragia (2011212)	Pressione sanguigna con FC circa 120/min. Titolo: Ricerca: contenuto globale. (..)	5.0



MD-Paedigree Cloud Integration

MD-Paedigree has a relatively complex architecture composed of different layers. The Cloud is one of them. Cloud computing is a way to provide and to use a large number of computers connected through a real-time communication network. In science, cloud computing is a synonym for distributed computing over a network. This means the ability to run a program or application on many connected computers at the same time. In common us-

age, the term "the cloud" is essentially a metaphor for the Internet. Marketers have further popularized the phrase "in the cloud" to refer to software, platforms, and infrastructure that are sold "as a service", i.e. remotely through the Internet. Typically, the seller has actual energy-consuming servers which host products and services from a remote location, so end-users don't have to; they can simply log on to the network without installing anything. The major models of cloud

computing service are known as Software as a Service (SaaS), Platform as a Service (PaaS), and Infrastructure as a Service (IaaS).

FedEHR: Patient centric data

A highly secure patient-centric and vendor-neutral EHR (Electronic Health Records) repository.

In accordance with the latest data modelling concepts in the literature, FedEHR proposes a storage model that is fully centred on the patient. All the data that is stored in the system is organised around a data structure representing a patient model. The current description of FedEHR architecture provides an evolutionary structure of data starting from the patient. Currently the data structure is oriented around medical concepts of medical events and clinical variable.

These abstract models can be refined and specialised using metadata definitions created from physicians' descriptions of diseases and exams. Leveraging on the cloud, FedEHR provides a distributed database for heterogeneous medical information integration from different geographical locations. It gives a unique and integrated view of data and offers a variety of tools to navigate and analyze data. FedEHR is composed of 3 modules : Cloud, Big data, Analytics.

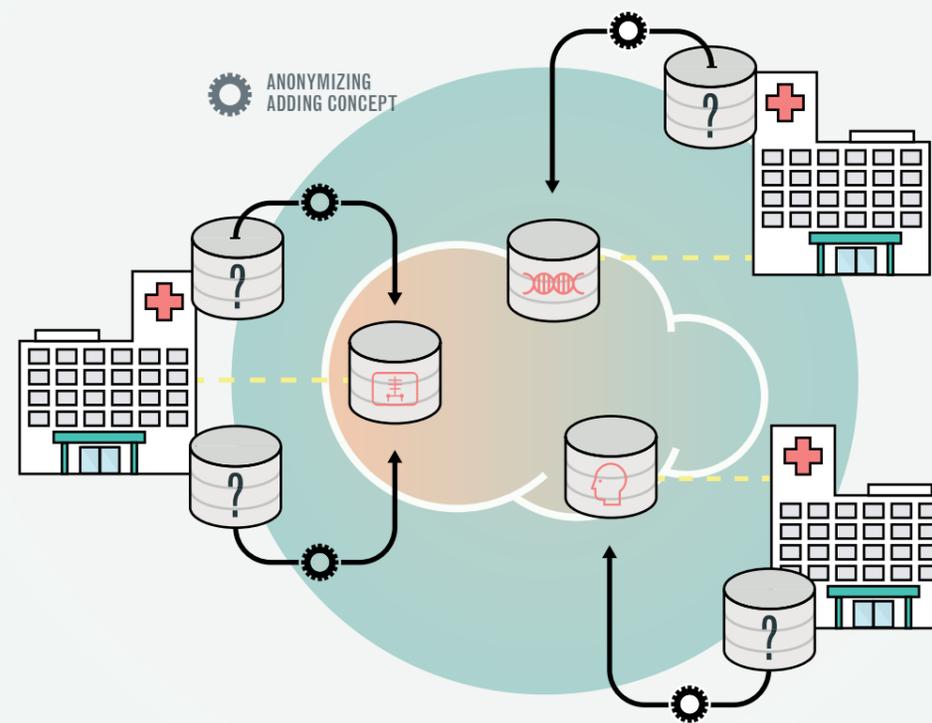
Big Data Federation Service

To design, instantiate and manage patient-centric vendor-neutral distributed big data silos.



MD-PAEDIGREE: ALFA-PROTOTYPE

THE CONSORTIUM IS CURRENTLY DELIVERING THE FIRST VERSION OF THE MD- PAEDIGREE INFOSTRUCTURE PLATFORM TO BE TESTED



The Big Data Federation Service allows to setup silos of medical sensitive data in the private cloud network and to federate them into a single database. Aggregated data can then be queried, filtered, processed securely and irrespectively of its geographical location and complexity. At the very heart of

FedEHR, Big Data makes it possible for healthcare professionals to access massive amounts of heterogeneous medical data, to analyse trends, patterns, simulate and test treatments, or even advice on similar cases and associated outcomes found in the network of connected electronic health records silos.

eCRF

An application for Electronic Clinical report forms

According to the need and in order to simplify the process of importation of new data, MD-Paedigree's Gnubila partner has decided to develop and provide the project a tool called eCRF (electronic Clinical report form). This application consists in a configurable survey exposed through a web interface hosted by a server installed in each data acquiring centre. This tool has been conceived and developed with the assistance of UCL partner following a semi agile process whilst the customer has been consulted at each step of definition.

DPS generic Importer MD-Paedigree's Sheffield university and gnubila partners have developed a generic importer based on The Data Publication Suite (DPS) connection abilities.

A pivot exporting XML format that can

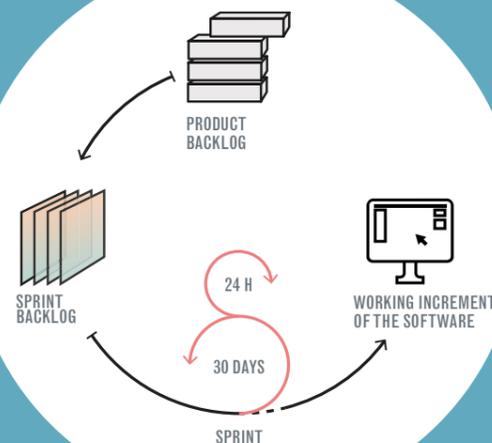
manage both data structure, semantic annotations and data values has been defined by MD-Paedigree's infostructure team. Depending of the needs, anonymisation can be processed by the DPS transport, done by the java complementary importer or using a hybrid plugin called by the DPS. This generic connector allows to reuse the DPS software developed for VPH-Share for connection to hospital routine system. The DPS graphical interface is used to model data structure as a tree and some annotation are added to indicate FedEHR repository which element of FedEHR repository of the XML corresponds to a patient and which one correspond to a medical event. Once defined the connector is configured to run automatically periodically to enrich the repository.

FedEHR Cloud services

FedEHR Cloud establishes cross-enterprise security and common virtualized environments for computing resources management. Such innovative exoskeleton information systems allow healthcare professionals to rapidly, securely and anonymously share medical information across the healthcare enterprise, while setting a robust ground for demanding applications to develop limitlessly.

Scrum Agile process

Agile development recognizes that testing is not a separate phase, but an integral part of software development



The e-infrastructure applications supporting the clinical models released by the Infostructure follow a Scrum agile process, with a view on user validation and interfaces quality improvement. Within this process user representatives are consulted on the products features, improvements and bug fixes to be dealt with. Scrum is an iterative and incremental agile software development framework for managing product develop-

ment. It defines "a flexible, holistic product development strategy where a development team works as a unit to reach a common goal", challenges assumptions to product development, and enables teams to self-organize by encouraging co-location or close online collaboration of all team members, as well as frequent face-to-face communication among all team members and disciplines in the

project. This way, the foundational Infostructure provides a solid technical base onto which new clinical models and tools can be developed and tested. Under an agile approach, requirements, programming, and testing are often done concurrently. Testing and coding are thus done incrementally and iteratively, building up each feature until it provides enough value to release to production.



MD-PAEDIGREE & VPH-SHARE: Sharing Tools, Data and Models for the Virtual Physiological Human

A Active negotiations are under way with VPH-Share to determine the most fruitful areas of co-operation. The current candidates are: DPS (Data Publication Suite) deployment, metadata integration, external data discovery/provision and exploitation of VPH-Share tools and/or infrastructure in operation of MD-Paedigree workflows. Attention will focus on those that are judged by MD-Paedigree to add most value to the project. VPH-Share brings together 20 International partners from academia, industry and health-care to build the collaborative computing environment in which Virtual Physiological Human practitioners will work together, to develop new medical simulation software. Central for this environment is the sharing of information - tools, models and data - between researchers and clinicians, helping them to work efficiently towards building a complete model of the human body, so allowing its investigation as a single complex system. Funded by the European Commission, and led by the University of Sheffield, VPH-Share is a four year project that is designed to facilitate the rapid construction of personalised biomedical models and simulations to assist diagnosis and treat-



Hannah Whitelam
VPH-Share Communications
Officer

ment. To ensure its usability it is building on the work of four flagship projects, @neurist, euHeart, VPHOP and Virolab, which have each shown the validity of personalised modelling for medical applications. VPH-Share is constructing a versatile framework in which these and future workflows may quickly be operated and adapted - from the first stages of clinical investigation to the running of virtual treatment simulations - in order to speed development and build libraries of research data. By compiling existing resources in one secure site, and making it easy for new materials to be added, VPH-Share is providing the essential tools, services and computational infrastructure to meet the needs of the whole Virtual Physiological Human community. MD-Paedigree includes the development and operation of scientific workflows similar in concept to those in VPH-Share's flagship workflows. One of MD-Paedigree's scientific workflows will operate in a hypermodelling framework that will be jointly developed by Sheffield and SCS, building upon the framework developed in VPHOP. This framework also underpins a major (£6M) UK-funded application in orthopaedics.

VPH Workshop On Clinical Data Management and Sustainability

The VPH Workshop on Clinical Data Management, organised by the VPH Institute and sponsored by MD-Paedigree, P-medicine and VPH-Share, successfully took place in Amsterdam on March 17-18th. The two and a half-days were dedicated to some of the most pressing topics for all partners involved: regulatory issues and legal framework concerning data management, from both legal and clinical perspectives, and long-term sustainability and future exploitation of the projects. Presentations were held by Samuel Iheanyi Nwankwo (Clinical data management: legal perspective), Norbert Graf (Data management and resue: clinical perspective), Edwin Morley-Fletcher (Privacy issues and legal framework in paediatrics data: the case of MDPaedigree and MD-Paedigree Sustainability Reasons and opportunities for an MD-Paedigree Spinoff), Haridimos Kondylakis (Tools and repositories for data storage or distributed data access) and Keith McKormack (ICT Projects Sustainability). The great interest shown for the topics discussed is significantly leading to another initiative, shared by all participants: the proposal for a White Paper, which shall be developed in the next months.



In collaboration with:



Healthy Data?

how to protect personal data whilst embracing the benefits of mass information?

There are great expectations as well as concerns regarding how Big Data applications may be leading to the 'algorithmic regulation' of an ever-wider range of phenomena. This goes in parallel with an exponential increase in the amount of data being collected, stored and processed, driven not only by the explosion in web-based transactions and social media, but also by the spread of new sensors 'smartifying' whatever we touch and do. By its very nature as an 'evidence-based domain', and even more so because of the potential of mobile devices, healthcare is a particularly data-intensive sector. It has been deemed to be the first area where knowledge will relatively soon be likely to reach a 'singularity threshold', becoming 'frictionless' and capable to smoothly flow from research to practice, from 'bench to bedside'.

Even if such futuristic expectations may still have a long way to go, Big Data healthcare certainly represents a major concern in the data regulation debate and consistently underpins a significant part of the revolution in health maintenance and disease treatment that modern IT promises to deliver. Three political, academic and business discussions are currently at the core of the EU debate in this area: the need to ensure that citizens' data are adequately protected; the need for Open Access to data for research purposes; and the need for Europe to develop a vibrant Big Data industry capable of investing a growing amount of resources into breakthrough innovations in health, leading to truly personalised medicine. These issues run largely parallel with the loss of trust in data privacy promises, the Open Access debate and the continuous growth of health data still awaiting transformation into biomedical knowledge by adequate data crunching and data analytics applications. Protecting privacy In reality, only a small percentage of clinical data is routinely being used for biomedical research, and there is still an uneasy trade-off between individual privacy concerns in the healthcare setting and the potential for learning things that can greatly benefit patients. It is important to strike the ap-

propriate balance between allowing information to be extensively used whilst pinpointing inappropriate usage.

There is, for instance, an interesting issue at stake with regard to the so-called 'differential privacy' approach, by which sensitive information about individuals is to be protected, not only through anonymisation, but also through an algorithm and an interface that serves as trusted curator. The algorithm has the effect of introducing random noise into individual's data within the dataset, without the need of removing specific data fields. In practice, when a researcher wants to analyse the dataset, he needs first to submit a query to the curator, who will then inject some randomisation into the answers, this way protecting the privacy of the individuals in the dataset whilst producing accurate answers to the research queries.

The value of a dataset is the sum of its value in each analytical context, and it is the research results, services and products generated from data that will provide the value in the Big Data ecosystem.

Whatever the preferred de-identifying approach, the issue of the rights of patients to their data or 'the data subject's legitimate interests', has unsurprisingly become a major concern to regulatory policy, with the aim of letting patients participate in some way in the advantages derivable from their data. One basic principle, from which extensive debate has stemmed, is the 'right to be forgotten', i.e. when a data subject no longer wants its data to be processed and when there are no legiti-



Prof. Edwin Morley-Fletcher
Project Manager,
President of Lynkeus SRL

IN THE AGE OF BIG DATA HEALTHCARE, EDWIN MORLEY-FLETCHER CONSIDERS HOW TO PROTECT PERSONAL DATA WHILST EMBRACING THE BENEFITS OF MASS INFORMATION

mate grounds for retaining it, the data must be deleted. The right of data subjects to be forgotten implies, de facto, some sort of ownership of data relating to them and therefore the right to eventually donate or sell that data, even though-with regard to data – we obviously lack a clear definition of what belongs to whom.

Another basic principle is 'informed consent': consent should be given explicitly by any appropriate method, enabling a freely given informed indication of the data subject's wishes; it can in any moment be withdrawn and data completely deleted.

Owning your data

An interesting suggestion for circumventing some of these hurdles has come from the 2013 World Innovation Summit for Health (WISH) report.

The suggestion is that patients should form coalitions aimed at having their data handled by common trustee organisations. Such 'data management co-operatives' would safely store and manage all health data (medical, m-health, genome etc.) in individual accounts, and the citizens adhering to these co-operatives would not only have access to them from anywhere anytime, but they would also be able to share subsets of their data, or all of them, with doctors, friends or biomedical and pharmaceutical research. Being explicitly the owners of their data, their informed decision to share their own data for research would not be subjected to the same data protection regulations as when third parties request access to personal health data, and they could reap some of the economic value of aggregated personal health data. Another approach that hopes to inspire regulation is what

some have termed 'enhanced privacy' or 'enhanced consent'. It is based on spreading awareness of the personal and social significance of anonymised individual patient and personal data for preventive and predictive purposes in healthcare, and for promoting 'data donation' mechanisms. This approach might particularly suit the need of granting consent for yet unknown research purposes, or it might define restrictions under which the consent becomes void. This could be coupled with the concept of 'personal data portability': an individual should be able to export or delete his or her data from the system at the end of a relationship with a particular service provider or researcher.

This 'data donation' approach, referred to in the workshop on the challenges of Big Data in the health sector organised by the Universidad Politécnica of Madrid in February, has been recently endorsed by the European oncology community. In a position paper, the community suggests that regulation should "avoid the notion of a 'specific' consent, which would result in researchers needing to obtain continuous patient re-consent every time new research is carried out". Patients should have the right to 'donate' their data and tissues to health research, as well as to retain access to the tissue and data donated, hence ensuring their ability to obtain relevant information related to his/her condition; they should also have the right to deny their consent and withdraw it at any time. At the same time, the process should be a 'one-time' consent, which means that "patients will be informed that their data/tissues will be used for future research, and they will be informed about the conditions under which their data and tissues will be stored, making the protection safeguards a part of their consent". The same posi-



tion paper also highlights that in the fields of public health and epidemiological research, based on population disease registers, “a derogation from the obligation of any form of consent is essential”.

This comes as a matter of satisfaction for those who, in a networking session on Big Data and data analytics’ impact on healthcare held as part of the ICT 2013 conference in Vilnius, had invoked Alexis de Tocqueville’s remark that inheritance laws “ought to be placed at the head of all political institutions, for... they exercise an incredible influence”. It was also suggested that ‘data inheritance’ mechanisms might be automatically applied after a certain period has elapsed from the data subject’s time of death, unless they have explicitly opted-out prior to death. This suggestion had come with the specification that a different treatment should, however, be considered for the parts of such data whose public availability could have detrimental consequences for the relatives of the deceased, e.g. genetic information.

Maintaining principles Significantly, the latest General Data Protection Regulation (GDPR) draft states that the principles of data protection should apply to any information concerning an identified or identifiable natural person, including the case of pseudonymised data, which could be attributed to a natural person by the use of additional information, but posits also that these principles should not apply to deceased persons. Once these regulatory hurdles have been overcome, it will be time to cope with the perspective ‘data glut’ issue. With the ever-increasing volumes of data being produced outstripping, and arguably being driven by, the computing power available to analyse them (quantum computing aside), there will be the need to find ways of reducing the dimensionality of a dataset and its complexity through feature selection methods. Manageable research spaces, with goal-oriented search techniques (such as model-driven analysis and feedback system control), need to be defined by mapping a dataset with many feature dimensions to one with significantly fewer, on the basis of existing medical knowledge or of statistical techniques.

As healthcare costs globally grow ever larger,
it may not be a question of how we implement Big Data
in healthcare, but how quickly

The long debate on the two diverging approaches, one bottom-up, based on statistical models, and the other top-down, driven by mechanistic models, should now lead to an increased awareness that both need to be jointly applied. Patterns discovered through knowledge discovery and data mining can enrich an already existing prior knowledge, and the latest statistical simulation models can incorporate a priori logic (e.g. formulating constraints, imposing dependencies etc.). There is the need to use analytics both on huge amounts of scarcely complex or unstructured data, as well as on smaller amounts of highly complex or semantically annotated data. Big Data correlations can help delimiting boundaries, even when one would say that “you can’t do it from the bottom-up, because you don’t know what to look for”. Similarity search, leading to patient stratification, and modelling techniques, leading to patient-specific prediction and simulation, can be strongly enhanced by Big Data validation.

Data does not possess inherent value in the absence of a means to make sense of it. The value of a dataset is the sum of its value in each analytical context, and it is the research results, services and products generated from data that will provide the value in the Big Data ecosystem. For health data, this value will mean better, quicker and cheaper diagnosis and treatment, as the application of Big Data to healthcare offers a way to accelerate research, improve treatment and reduce the burden on society overall. As healthcare costs globally grow ever larger, it may not be a question of how we implement Big Data in healthcare, but how quickly.

This article was originally published for HORIZON 2020 Projects Portal, Issue 4 horizon2020projects.com

Md-Paedigree vs. Watson

Comparative outline and complementarities

MD-Paedigree and IBM Watson are two highly different approaches towards clinical decision support systems, from either side of the Atlantic, first of all in their scale, but also in their initial goals, even though Watson is for sure getting closer with its more recent expected developments. Of course, theoretically, the two systems could integrate to provide innovative and advanced medical solutions. The following table roughly compares the two systems, **MD-Paedigree** and **Watson**:

PROJECT:	 MD-PAEDIGREE	VS	IBM WATSON 
Name means	Model-Driven Paediatric Repository		Named after the founder of IBM, Thomas J Watson (and implicitly, after the fictional Dr. Watson, Sherlock Holmes’ companion, who is often told: “elementary, Watson!”)
Developed by	EC funded projects		IBM
Originally developed for	Paediatric Cardiology		Jeopardy!
Home	EU		USA
Routine Use	Capturing routine data at Ospedale Pediatrico Bambin Gesù in Rome, and soon Great Ormond Street Hospital London and Deutsches Herx Zentrum Berlin		Memorial Sloan Kettering Cancer Center in New York, University of Texas MD Anderson Cancer Center, the Cleveland Clinic, the Mayo Clinic and the New York Genome Center
No. Of Clinical Centers	7		5
Underlying concepts	Statistical and mechanistic models used for patient-specific simulation and similarity search		Natural language capabilities, hypothesis generation, and evidence-based learning used for cognitive computing
Underlying Platforms	Cloud based access to Model-Driven Paediatric Repository		IBM Watson Health Cloud, Bluemix, Explorys
Underlying Technology	Big Data Analytics, Open-Source Cloud-based platform, APIs		Big Data Analytics, Open-Source Cloud-based platform, APIs
User Interface	Browser-based search interface		Natural language interface
Diversity of Data Sources	Flexible data inputs text/image		Largely Text/Language based
Precision/ Confidence	Anticipated to be accurate since it will be based on validated models and curated data		IBM states: “Watson does not make mistakes”
Focus	Primarily Paediatric Diseases (Cardiomyopathies, Cardiovascular Risk in Obesity, Juvenile Idiopathic Arthritis, Neuromuscular- Neurological Diseases, Genomics and Metagenomics), Similarity Search. Initially EU based with possible cross Atlantic reach		(Open) Currently developing fields: Life Sciences, Oncology, Genomics, Clinical Trial Match.
Builds On Existing Health based Projects	Health-e-Child, Sim-e-Child, Cardioproof		Healthkit, ResearchKit
Personalized Diagnosis	YES		Not Currently
Partner Base	Research, Commercial, EU		Industry (Apple, Johnson & Johnson and Medtronic), Several Hospitals, Social Programs, Education
Imaging Analysis Features	YES		<i>Medical Sieve</i> (under development)
Support Base	Support through partners		Direct commercial support (support contracts)
Ready Off-the-shelf with models and simulations	YES		NO
Specialisation for paediatrics	YES		NO

Obituary: Alexey Tsybal

Our highly esteemed colleague from Siemens, Oleksiy (Alexey) Tsybal, Head of WP9 within MD-Paedigree, suddenly passed away, just a few days after his 39th birthday, while at his home, in Erlangen. He leaves his wife and two small children, to whom go our deepest condolences, as well as to some of his friends and more direct colleagues at Siemens, like Martin Huber, Michael Suehling, and Dorin Comaniciu.

Alexey was a Ukrainian citizen who had been working in Erlangen for many years. Some of us got to know him at the beginning of the Health-e-Child project in 2006, and we all always appreciated his great generosity, open-mindedness and reliability in finding solutions and cooperating in our project's joint efforts, as well as his intellectual sharpness and remarkable scientific rigour. A PhD research scientist, Alexey has contributed a large number of remarkable reviewed publications in the areas of machine learning, case-based reasoning, and applications of AI techniques to biomedical domains. He also served as Associate Editor for IEEE Transactions on Information Technology in Biomedicine.

The CaseReasoner development, the outstanding clinical case retrieval and similarity search-based decision support system which was initially tested in Health-e-Child and Sim-e-Child and then further enhanced and integrated, as a web-based prototype, into MD-Paedigree's Infostructure, was very much his work. His sudden loss will have a profound effect on our project's progress in many areas: the interactive visualisation of personalised models, the integration of the non-imaging data into the system, the patient support of various clustering techniques, including graph-based clustering and data-driven clustering, the support of advanced discriminative distance learning solutions to increase the classification performance of the CaseReasoner, its application to the heterogeneous childhood obesity data, including in particular the personalized multi-physics cardiac models and, far from least, his leadership of WP9.

Of course, however large a hole he leaves in MD-Paedigree, it is nothing compared to the loss for his family and friends and it is with them our thoughts lie at this time.

Latest Publications

Edwin Morley-Fletcher, "Healthy Data?", H2020 Projects Portal, Issue 4 - <http://www.horizon2020publications.com/H4/files/assets/common/downloads/Pan%20European%20Networks%20-%20Government.pdf>

Edwin Morley-Fletcher "Innovation and Big Data", CERN 60th Anniversary Book, From Physics to Daily Life: Applications in Biology, Medicine, and Healthcare, First Edition. Edited by Beatrice Bressan. 2014 Wiley.

Oscar Alfonso, Jimenez del Toro* and Henning Müller*, "Multi Atlas-Based Segmentation With Data Driven Refinement" University of Applied Sciences Western Switzerland (HES-SO), Switzerland Department of Radiology, University and University Hospitals of Geneva (HUG), Switzerland.

Dimitropoulos H., Gogolou A., Kilapi H., Metaxas O., Stamatogiannakis L., Zacharia E., Ioannidis Y., "Bottom-Up Towards Supporting Personalized Medicine in the Cloud",

Drechsler K. et al., "Liver Segmentation in Contrast Enhanced MR Datasets using a Probabilistic Active Shape and Appearance Model" (submitted to IEEE CBMS 2014 for publication).

Itu L., "A method for modeling surrounding tissue support and its global effects on arterial hemodynamics (Awarded with the second place at BHI'14)

Jimenez del Toro O., Müller H., "Multi Atlas-Based Segmentation with an Intensity Feature Refinement" – (Awarded with the first place at IEEE BHI'14).

Manset D., *Health Surveillance. How Knowledge Transfer Changed Biology, Medicine and Health Care*, in CERN 60th Anniversary Book on "How Knowledge Transfer Changed Biology, Medicine and Health Care", WILEY, 2014. In Press. <http://eu.wiley.com/WileyCDA/WileyTitle/productCd-3527332618,subjectCd-PHC0.html>

Manset D., "Vers Un Big Data Européen, LeMonde.fr, http://lesclesdedemain.lemonde.fr/sante/vers-un-big-data-europeende-la-sante_a-11-3426.html

Neumann D. et al., "Image-to-Model Framework for Patient-Specific Cardiac Electromechanics", IEEE Int. Symposium on Biomedical Imaging, ISBI 2014.

Ruch P., "MD-Paedigree: A Big Data and Decision Support Tool for Mining Europe's First Social Medical Network in Paediatrics", http://issuu.com/sucreproject/docs/sucre-issue-3-healthcare_32e400ca213e4a

Klaus Drechsler, Stefan Wesarg et al., "Liver Segmentation in Contrast Enhanced MR Datasets Using a Probabilistic Active Shape and Appearance Model." Proceedings of IEEE CBMS, 2014.

K. McLeod, M. Sermesant, P. Beerbaum, X. Pennec, "Spatio-Temporal Tensor Decomposition of a Polyaffine Motion Model for a Better Analysis of Pathological Left Ventricular Dynamics", Medical Imaging, IEEE Transactions.

UPCOMING EVENTS

A list of some events to which MD-Paedigree partners are willing to attend: for more updates and confirmed attendances please visit our website: <http://www.md-paedigree.eu>

EVENT	WHEN	WHERE
Insigneo Showcase	8 th May 2015	University of Sheffield, UK
World of Health IT (WoHIT)/ ehealth Week	11 th -13 th May, 2015	Riga, Latvia
Health 2.0 Europe 2015	18 th - 20 th May, 2015	Barcelona, Spain
AEPC 2015: Association of European Paediatric and Congenital Cardiology	20 th -23 rd May, 2015	Prague, Czech Republic
MIE 2015: Medical Informatics Europe	27 th -29 th May, 2015	Madrid, Spain
EACD 2015: European Academy of Childhood Disability	27 th -30 th May, 2015	Copenhagen, Denmark
ISMRM 2015: International Society for Magnetic Resonance in Medicine	30 th May- 5 th June, 2015	Toronto, Ontario, Canada
FEMS 2015: 6 th Congress of European Microbiologists	7 th -11 th June, 2015	Maastricht, The Netherlands
e-health Summit	18-19 June, 2015	Vienna, Austria
FIMH 2015: 8 th International Conference on Functional Imaging and Modeling of the Heart	25 th -27 th June, 2015	Maastricht, The Netherlands
ECAI 2015: International Conference 7 th Edition	25 th -27 th June, 2015	Bucharest, Romania
IEEE Big Data Congress 2015	27 th June – 2 nd July, 2015	New York (USA)

NEWSLETTER INFO

ICIMTH 2015: International Conference on Informatics, Management and Technology in Healthcare	9 th -12 th July, 2015	Athens, Greece
MEDINFO 2015: eHealth-enabled Health	19 th to 23 rd August, 2015	Saõ Paulo, Brazil
Personalised Medicine 2015: 3 rd International Conference on Predictive, Preventive and Personalized Medicine & Molecular Diagnostics	1 st -3 rd September, 2015	Valencia, Spain
ESMAC 2015: European Society of Movement Analysis for Adults and Children	07 th -12 th September, 2015	Heidelberg, Germany
EG VCBM: Visual Computing for Biology and Medicine	14 th -15 th September, 2015	University of Chester, UK
IIHC 2015: 4 th Innovations and Investments in Healthcare Meeting	17 th -20 th September, 2015	Munich, Germany
PICS ~ AICS 2015: Pediatric And Adult Interventional Cardiac Symposium	18 th -21 st September, 2015	Aria, Las Vegas (USA)
EHFG 2015: 18 th European Health Forum Gastein	30 th September - 2 nd October, 2015	Gastein, Austria
MICCAI 2015: 18 th Medical Image Computing and Computer Assisted Intervention	5 th -9 th October, 2015	Munich, Germany
ICT 2015 Innovate, Connect, Transform	20 th -22 nd October, 2015	Lisbon, Portugal
EDF2015: European Data Forum	6 th -17 th November, 2015	Luxembourg

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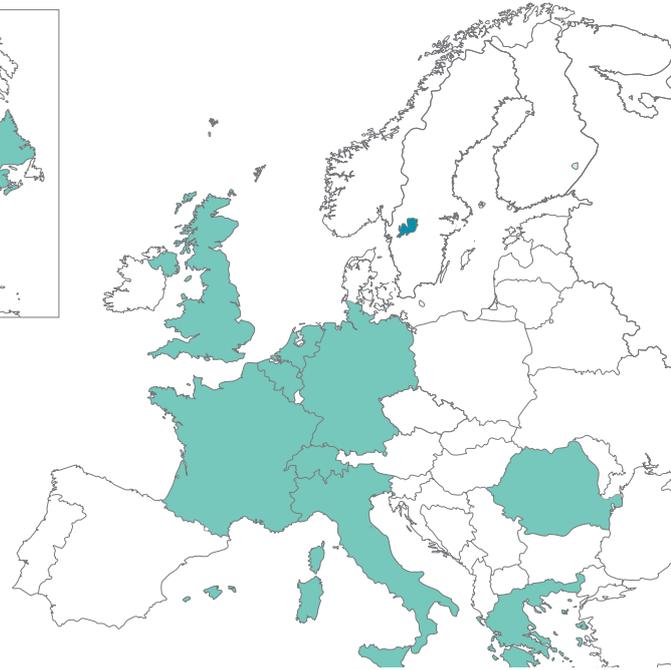
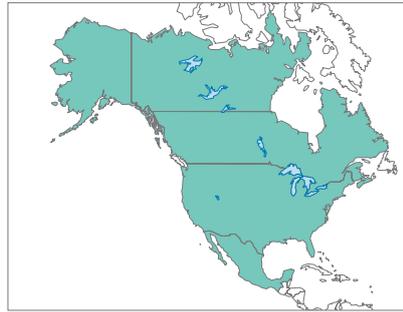
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MD-PAEDIGREE PARTNERS

MD-Paedigree is an international collaboration between 22 partners across Europe from industry, academia and healthcare.



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