DIGITAL PATIENT | ROADMAP

DISCIPULUS

Roadmap for the Digital Patient

DISCIPULUS

European Commission

SEVENTH FRAMEWORK PROGRAMME

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About the report

This report was prepared by the DISCIPULUS project, a Coordination and Support Action funded by the European Union, 7th R&D Framework Programme (FP7). DISCIPULUS developed an R&D roadmap for the development of the "Digital Patient". Its vision is to identify key steps towards realising the Digital Patient, which is a new paradigm in personalised medicine, across the whole healthcare system by focusing on the needs of clinical practitioners and healthcare professionals, biomedical and clinical researchers. This vision will be achieved through comprehensive solutions that involve advanced modelling and simulation tools, data acquisition and data management and advanced user interfaces. All this will enable the clinical and industrial translation of the Digital Patient.

Partners in the DISCIPULUS project were: University College London, United Kingdom; empirica Communication and Technology Research, Germany; The University of Sheffield, United Kingdom; Istituto Ortopedico Rizzoli, Italy and Universitat Pompeu Fabra, Spain.

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For further information please visit the DISCIPULUS website: www.digital-patient.net or contact the DISCIPULUS coordinator, Dr. Vanessa Díaz (v.diaz@ucl.ac.uk).

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About this report

The *Digital Patient Roadmap* presents a vision and a trajectory for the way in which advances in physiological modelling could greatly enhance the quality and accuracy of healthcare and lifestyle interventions, thereby improving the health of patients and the effectiveness of clinicians and clinical teams.

This Roadmap was developed by the DISCIPULUS Project, which was funded by the European Commission under the Seventh Framework Programme (FP7/2007-2013) in order to define a concrete strategy for the realisation and wide scale adoption of results emerging from the Virtual Physiological Human (VPH) Initiative. This initiative unites researchers from across the globe who are developing predictive models and simulations for different aspects of human physiology and pathology through advanced mathematical modelling. VPH models draw on multiple diagnostic modalities such as medical imaging, echo, ultrasound, electrophysiology and body sensors in order to provide simulations of the likely progress of a disease state and the predicted impact of various intervention options, in order to assist the clinician with optimising a drug treatment, an operation or other procedure.

This Roadmap proposes how the adoption of these advanced VPH models can be scaled up across healthcare and translated into real clinical practice. It also explores how simulations and predictive physiological models might be presented to patients, to guide them in self-management and in the prevention of disease through healthier lifestyles. The future vision is of multiple collaborating VPH models that interoperate with other information about a patient such as that obtained from electronic health records, sensors and bio-markers, in order to present clinicians, multi-disciplinary teams and patients with a whole system understanding of the patient's health status, both now and predicted for the future. This multi-system perspective is termed here the Digital Patient. It might be visualised, for example, as a Patient Avatar, although a wide range of alternative visualisations will be needed.

This Roadmap presents the Digital Patient vision from the perspective of the contributions from VPH modelling. It examines the VPH scaling up challenge from several scientific, technological and clinical perspectives, each of which forms a chapter in this report.

The report offers a novel maturity model for the adoption and scaling up of the Digital Patient. It also includes several example clinical scenarios: clinical situations told as stories from the point of view of the patient and of the clinician, as care might be provided now and in the distant future using the Digital Patient. These stories were developed by multi-disciplinary teams, including clinicians, industry and academia, to serve as illustrations and inspiration for brainstorming and Roadmap development during two large scale consultation meetings held in Barcelona in 2011 and 2012, subsequent interviews with thought leaders, and online discussions. The Roadmap therefore reflects the consensus opinion of over two hundred key stakeholders from across Europe, and the US, from many different perspectives and disciplines.

The Roadmap makes over 30 recommendations, grouped under the above challenge areas. These recommendations are summarised in the following section. It is essential that the opportunities from *in silico* medicine, as envisioned by the Digital Patient, are holistically advanced through the European Commission's Horizon 2020 programme. This report recommends that three classes of project are sponsored: those that focus on modelling methods and the further development of integrative models, those that focus on engineering the large-scale deployment of established modelling methods, and those that conduct clinical assessment studies *in silico* and through clinical trials, to determine the safety, efficacy, efficiency and benefits of these models.

On behalf of the DISCIPULUS Consortium

Dr. Vanessa Diaz

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Executive Summary

Digital Patient Research Roadmap: an Executive Report Rationale

The DISCIPULUS support action was funded by the European Commission as part of European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 288143. One of the primary goals of this support action was the production, through a consensus process among key stakeholders and experts, of a research roadmap for a new technological research objective called "Digital Patient". The full roadmap can be downloaded from the Discipulus web site.[1] During the final review meeting, it was noted that the roadmap does not include a short summary of the primary conclusions. This is the scope of this document, which should be considered by all means an addendum to the main roadmap.

Terminology and remit of the roadmap

The term Digital Patient is becoming quite popular. It has been recently used to indicate the technologies for digitally empowered collaborative environment that are being used to improve the patient engagement.[2] It is used to advertise a new health electronic record mash-up service.[3] It was used to indicate the totality of the Electronic health records of a patient, with regard to privacy, confidentiality and security.[4] It was also used to indicate those patients that communicate with their doctors using digital media, such as email.[5]

1 http://www.digital-patient.net/files/DP-Roadmap_FINAL_N.pdf
2 See "Engage! Transforming Healthcare Through Digital Patient Engagement" Edited by Jan Oldenburg, Dave Chase, Kate T. Christensen, MD, and Brad Tritle, CIPP, 2013 HIMSS Press.
3 http://thedigitalpatient.com/
4 http://www.apa.org/monitor/2013/05/slc-digital.aspx
5 http://www.ehi.co.uk/news/EHI/8584/doctors-must-respond-to-digital-patient

In the call that funded Discipulus the European Commission defined the Digital Patient as "a digital representation of the integration of the different patients-specific models for better prediction and treatment of diseases in order to provide patients with an affordable, personalised and predictive care". This definition is restricted to the context of patient-specific modelling, as developed in the Virtual Physiological Human initiative.

Initially the attention was primarily focused on the specialists working in hospital settings, but as the discussion developed it became evident that also the general practitioners working in primary care could benefit from these types of technologies.

So in this document the term "Digital Patient" should be intended as a framework of methods and technologies that once established will enable the doctor to look at the patient as a single complex system. This framework should be *descriptive* (which includes all data available for the patient), *integrative* (which supports a decision-making where the patient is seen as a whole) and *predictive* (which assists the doctor in using all the available knowledge to know in advance the effect of all available treatment options).

The management of many human health issues can be greatly improved by the application of accurate predictive models. There have been great advances in modelling of physiological processes in recent years, as the various Virtual Physiological Human initiatives show. One major step in utilising these advances will be to incorporate these models in a systematic way into the clinical decision-making process. There is also a need to make the clinical and research data available, more effective through feedback for building better predictive models. The Digital Patient will allow patients and clinicians to become more pro-active in instituting lifestyle modifications and clinical surveillance for the prevention of diseases by providing tools for health

prediction and simulation. The Digital Patient initiative aims to individualise the clinical decision making process. It will promote discussion on how to migrate from population-based prediction towards truly personalised medicine, which will emphasise the acquisition, integration, processing and application of patient-specific information.

The 'Digital Patient' follows the blueprint set out by the Virtual Physiological Human in that it is build 'around' models of disease/organs/pathologies and its approach is better characterised by the term 'middle-out',[6] which is based on identifying a level that is relatively well understood in terms of data and processes to then, connect this to 'upper' and 'lower' levels of structural and functional integration.[7] This is the fundamental driver behind this Roadmap and the path we have followed. However, it is also within this framework that all the work in genomics, proteomics, transcriptomics, metabolomics, etc. fits in. The term 'personalised medicine' has been used to describe medicine based on 'omics' but there is a more encompassing view emerging: personalised medicine must address the challenge with a holistic view. The article 'Big Biology - the 'omes Puzzle'[8] points out at the necessity of a 'phenome' and even an 'integrome'; this clearly highlights the necessity to integrate information at the gene scale within a wider context. This is the approach that we advocate in the Digital Patient Roadmap and there is a section of the integration of genetic data into 'upper scale' models. This 'integrative aspect' is highlighted as the fundamental element of systems medicine,[9] where molecular data (especially genomic information) in integrated with anatomical, physiological, environmental, and lifestyle data in a predictive model approach in order to produce 'virtual patients'. This brief outline is by no means the whole picture and there is an initiative – INBIOMEDvision - that has been devoted to look at the challenges of the bioinformatics community in the context of personalised medicine.[10] All these approaches can and will indeed contribute to the Digital Patient; however, the specifics of these domains are extensively covered in other roadmaps and reports, whereas the focus on modelling and simulation of this roadmap is unique.

6 Brenner S., Noble D., Sejnowski T., Fields R.D., Laughlin S., Berridge M., Segel L., Prank K., Dolmetsch R.E. (2001). Understanding complex systems: top-down, bottom-up or middle-out?. In Novartis Foundation Symposium: Complexity in Biological Information Processing, Bock G., Goode J. (eds), Vol. 239, pp 150–159 Chichester: John Wiley

7 Kohl P. and Noble D. (2009). Systems biology and the virtual physiological human. Molecular Systems Biology 5:292.

8 Baker M. (2013). Big Biology - the 'omes Puzzle. Nature, News Feature, Vol. 494, issue 7438.

9 Regierer B., Zazzu V., Sudbrak R., Kühn A. and Lehrach, H. (2013). Future of Medicine: Models in Predictive Diagnostics and Personalized Medicine. Adv Biochem Eng Biotechnol (2013) 133: 15–33.

10 Hermosilla I., López-Campos G., Kouskoumvekaki I., Shublaq N., López Alonso V.: Prospective analysis on Biomedical Informatics enabling personalized medicine. INBIOMEDvision, January 2013, http://www.inbiomedvision.eu/PDF/Prospective.pdf

In this roadmap we also omit a number of parallel initiatives, some of which are gaining considerable momentum: thesis include precision medicine, systems medicine, stratified medicine,[11] P4 medicine,[12] etc. The Digital Patient vision represented here shares with all these other initiatives the desire for a more integrative approach to healthcare, where information technology is seen as the primary mean to deal with the complexity involved.

Another term that appears in this document is *Patient Avatar*. One could be tempted to say that the Patient Avatar *is* the Digital Patient. But the conclusions that this roadmap reports suggest that the Patient Avatar is a *representation* of the Digital Patient. Whether it is the most effective representation in all cases, remains to be seen.

General recommendations

The DISCIPULUS project produced a number of recommendations that are reported in detail in Chapter 8 of the roadmap. Three recommendations are general in nature and they are presented below:

- *Digital Patient as a Grand Challenge*: *in silico* medicine in general, and the development of the Digital Patient in particular, must be recognised as a Grand Challenge, where fundamental research in biomedical science, mathematical and computational methods, bioengineering, and computer science must coexist with more applied and translational research. This cut across the separation between fundamental, applied, and translational research.

- *We need evidences for efficacy*: Only a few VPH projects have been completed so far, and of these, only some were able to model a significant number of real patients, and demonstrate a concrete improvement in health outcome measures. Regarding the validation of simulation models and evidence on their efficacy in improving healthcare, we recommend that in Horizon 2020 three distinct types of projects should be funded:

    - those that focus on modelling methods and the further development of integrative models, including targeting their pre-clinical or retrospective validation;

    - those that focus on engineering the large scale deployment of established modelling methods (as well as diffusion of models and applications following their clinical validation and assessment, see next point) and

11 https://www.innovateuk.org/documents/1524978/1814018/Stratified+Medicine+Innovation+Platform/566496f6-576d-472f-8643-2828a3f03a09

12 http://p4mi.org/

- those that conduct clinical assessment studies (*in silico* and by way of clinical trials) to determine the safety, efficacy, efficiency and benefits of these models and resulting decision support tools for patients and the healthcare system as a whole.

It is strongly advised to not require projects to develop all of these aspects simultaneously – it would be detrimental because it would overburden them.

- *The clinician at the centre of the Digital Patient vision:* Early in the development of the vision, VPH technology was described as a fully automated process, typically embedded within imaging workstations, which would provide push button answers to the clinical users. In reality, this vision was rapidly challenged on two fronts. First, because of their inherent complexity, many VPH models require support from an experienced technician. Technical input is necessary, not only to preprocess the data, but also to provide essential quality assurance checks. Second, for many projects, VPH solutions were designed from the outset to return to the clinical user an all-inclusive answer intended to be immediately used to make a clinical decision. It took time to realise that clinical experts are trained to aggregate heterogeneous information, exploring it to extract patterns even when information is very noisy or incomplete; these are tasks that computers will always find very difficult to complete. Convergence can be achieved on these two fronts by (1) accepting that VPH technologies are complex, requiring a new generation of hospital technicians specifically trained to use them and (2) by developing the Digital Patient in such a way that the technicians can prepare the data and models to the point of an exploratory analysis where the clinical expert can integrate the simulation results into his/her clinical reasoning and extract the maximum advantage from them. In other words, when approaching the stage of implementing VPH models into clinical workflows, we must put the clinical professional at the centre of the process.

Recommendations for specific scientific and technological challenges

Generation of data for model construction, validation and application

The generation, standardisation, validation, integration, and homologation of data have been identified by the wider VPH community to be of outmost importance for realising the Digital Patient vision. The following main application areas require targeted support:

1. Construction and validation of data-driven prediction models of clear biomedical relevance;
2. Application of data-driven prediction models within primary and secondary healthcare;
3. Construction and validation of causal and predictive models of clear biomedical relevance;
4. Application of causal models within primary and secondary healthcare;
5. Multidimensional phenotypic data analysis to uncover new important patterns that can serve as inspiration source for statistical and causal models.

Research and innovation should focus on:

- Exploration of suitable existing and possible new sources of information development of new acquisition methods, devices and technological tools, use of longitudinal data; both across the disease time course and the life span, including data on comorbidities, etc.
- Development and adoption of acquisition methods and technology to determine genotype and measure high level phenotypes: anatomical data obtained from next generation image modalities such as MRI, CT and US (ultrasound), new imaging and sensing technologies for acquisition of data in more physiological conditions such as standing, moving, exercising; new (wearable, multimodal) sensors and sensor data analysis to obtain functional data, also during daily life (point of life), lab-on-a-chip devices to obtain biomarker and gene-expression data, new phenomics technology
- Development and homologation of next generation acquisition methods (data independent from the acquisition system, the acquisition method, or the acquisition source)
- Exploitation and initiation of new developments in data formatting and data processing to enable enhanced data provision: advanced ICT solutions to preferably automatically collect and format the data and provide it to the Digital Patient for use and sharing. This includes de-noising and dimensionality reduction of the raw data and of the extracted feature space; data formatted in a predefined standardised and certified way (provided patient consent about the level usage is embedded) for research purposes.

Biomedical information management

Biomedical information management is a complex multifaceted problem including challenges such as the collection and sharing of data, the standardization of data collection

and the question of ontology, the dimensionality reduction, the question of security and privacy, computer and storage infrastructure needed to store enormous amounts of data retrievable rapidly, safely and from everywhere. These facets are interdependent and interact with each other, which renders biomedical information management extremely demanding. Despite many years of R&D projects and standardisation, EHR systems and diagnostic tools of different modalities often still use different information models and semantics to represent clinical data, making it challenging to scale up the corpus of data to support VPH model development and validation, and to ensure that deployed VPH models can safely reason on the holistic information about individual patients. Semantic interoperability remains a major challenge for healthcare and for research. We recommend to:

1. Develop patient-centred authorisation mechanisms that allow automatic requests for secondary use of clinical data after collection and anonymisation;

2. Develop methods to compute k-anonymity7 for anonymised secondary use databases of clinical data when combined with any other information available on the Internet;

3. Strengthen the efforts to develop dynamic semantic mediation strategies that allow clinical specialists to participate in multicentric data collection with clinical data available in their research warehouses, employing easy-to-use procedures to define the semantic mapping between the local warehouse structure and the collection ontology;

4. Develop automatic extraction of quantified phenotypical disease traits, and use these as similarity metrics to retrieve cases comparable to the one at hand from within the warehouse;

5. Develop new innovative storage and computing services that enable data intensive analysis of biomedical big data preserved economically over long term.

Mathematical modelling for the Digital Patient

The Digital Patient relies on the power of predictive modelling to be able to progress into a "medical avatar" as its final realisation. In fact, it can be argued that modelling is at the core and the most fundamental element of the Digital Patient as it is able to seize observations, data and explanations to formulate them and/or capture them in a mathematical and numerical form, in order to achieve the goal of explanatory/predictive medicine. It is the extraordinary and compelling power of multiscale predictive models that will help achieving the goals of the Digital Patient. Within this context, the areas that have been identified as priorities in modelling are:

1. Support the creation of online repositories to house and share disease-specific and patient-specific data and models to enhance collaboration within the VPH community, providing ubiquitous access (in compliance with data protection, privacy and confidentiality rules);

2. Prioritise the development of relatively simple models that address specific topics in patient studies, for the expansion of diagnostic methods and therapies in the clinic;

3. Develop hybrid methods and strategies to automatically and seamlessly combine phenomenological and mechanistic models, exploiting the use of VPH ontologies and annotated online repositories containing well documented and validated models;

4. Develop surrogate modelling methods that make possible to replace computational demanding sub-models, typically large PDE models (partial differential equation models), with estimators developed on pre-computed solutions, to provide a fast estimate of the model outputs and an upper boundary of the estimation error;

5. Develop integrative modelling frameworks that support the abduction cycle that applies inductive reasoning to observations to generate hypotheses on mechanistic relationships, verify these against reference observations, and where predictions are in good agreement with observations, incorporate this new mechanistic understanding into the inductive reasoning, so facilitating new discoveries;

6. Personalise not only anatomical data but also the physiological/pathological processes taking place (multiscale) by linking model parameters to easily obtainable patient data, leading to an individual patient model rather than a statistical patient model

7. Develop fast numerical restart methods that make it possible to employ user exploration of the information space to re-run the model with different inputs at very low computational cost when compared to the first run;

8. Develop a theoretical framework for the analysis of scale separation, and general homogenisation and distribution strategies to define space-time relations across scales;

9. Develop strategies to formalise and generalise the testing and validation of mathematical models, providing accurate and automatic estimations on the impact that incomplete data has in the personalised models.

Clinical user interface

Currently working prototypes are available and allow the 3D exploration of large amounts of information on human anatomy, physiology and pathology, referred to an average subject (generic) in fixed time point (static). Future research should prioritise:

1. Support for effective management of individualised data;

2. The extension of existing tools to support time-varying, dynamic data, and support multiscale interactive visualization for data defined at different time scales (data defined across different spatial scales);

3. The development of efficient methodologies for the rapid generation of image-based functionalised anatomical models for safety assessment and treatment planning;

4. Extensions to support novel human computer interaction and interactive visualization that allow the usage of large-scale data from heterogeneous sources for knowledge discovery;

5. Extensions to support effective information retrieval;

6. Extensions to support seamless interfacing with the existing healthcare systems under the criteria of clinical adaptability;

7. Extensions to support sound evaluations of digital patient technologies.

Translation and adoption

The area of translation requires the development or the adaptation of formal processes for verification, sensitivity analysis, validation (including clinical trials), risk-benefit, and cost-benefit analyses, and, ultimately, leading to product certification. Reference to the pharmaceutical and medical device industries provides guidance on suitable methodological approaches but further developments will be required.

1. Input is required from regulators to define the full translational path from verification to certification for different types of Digital Patient solutions. This will, by necessity, be a two way process as regulatory experts will need to be familiarised with the VPH concepts and the DP landscape;

2. Health Technology Assessment methodologies must be adapted and adopted to compare VPH solutions with current standard of care;

3. It is unlikely that current conceptual prototypes, developed as proofs of concept, can be effective for direct clinical translation. It will be necessary to re-engineer current prototypes for each specific clinical task, reengineering the user interface to specific prevention, diagnosis, prognosis, treatment planning, and monitoring purposes;

4. Sets of metrics are required including both objective indicators, and subjective indicators that capture the user experience; user cohorts must be stratified to represent realistic and relevant clinical scenarios (e.g. trainees, senior users with low IT exposure, etc.). Clusters of descriptors for patient analyses will have to be revised based upon novel hypotheses generated through VPH/DP technologies;

5. Health economic and business models must be developed to identify and validate the business case of implementing a specific clinical application for each group of relevant stakeholders, placing the DP within the hospital, clinic or surgery context, as well as for the health system as a whole;

6. There will be a significant demand for education and training. Training programmes will be required to provide technicians with a strong underpinning knowledge base. In early and mid-term stages of translation, training in principles of the respective VPH model/DP solution will be needed for clinical end users.

Digital Patient recommendations for Horizon 2020

The upcoming European Union Horizon 2020 Framework Programme for Research and Innovation foresees as one of its core objectives to further the health and wellbeing of European citizens. In line with this, the Digital Patient Initiative inquires into novel applications combining the power of advanced, computer-supported modelling and simulation of human organs and diseases with the innovation thrust of clinical professionals to progress rapidly towards a more individualised, predictive and preventive medicine, particularly in light of the increasing number of multi-morbid and elderly patients. Great benefits in terms of quality of life and quality of care for patients, better selection of treatment options, and more efficient healthcare provision will be forthcoming. On the basis of the recommendations included in this roadmap and the maturity levels identified, the following objectives for H2020 can be formulated:

Interactive health analytics (Maturity Level #1): Allow for novel tools to facilitate individualised knowledge fusion.

1. In support of integrative biomedical information management, foster the development of solutions based on open source components for the replication of heterogeneous clinical databases (containing, e.g., still and moving images, bio-signals, lab exams, clinical reports, clinical genomics, etc.) and of patient and other health (system) data collected outside the hospital (point of care, GPs, home, telemedicine) into a research repository, with automatic anonymisation and, fully in line with European Data Protection regulations, exposure outside the hospital for secondary use in clinical research. Proposed solutions should make possible the federation of multiple repositories, including semantic mediation, into regional or national resources for clinical and health system research.

2. To improve usability and usage, initiate the further improvement of user interfaces that provide explorative capabilities over large and heterogeneous collections of clinical databases. Invest in the combination of scientific information and data visualisation techniques to create interactive environments tailored for specific families of diseases, which allow the search for similar cases, the comparison of multiple cases across heterogeneous information, and the interactive exploration of high-dimensional datasets such as those produced by VPH simulations.

3. To allow for big health data analytics, it is necessary to develop advanced algorithms and methods for the automatic or semi-automatic efficient analysis of large collections of heterogeneous and long-preserved clinical data. This requires advanced storage systems that can execute restricted computation modules (storlets) in the storage close to the data. Priority should be given to approaches that combine heterogeneous information sources.

Individualised wellbeing and healthcare management (Maturity Level #2): Provide for improved clinical applications fully supporting individualised care.

1. Applications for individualised healthcare require modelling solutions to support clinical decision processes (from prevention to diagnosis, prognosis, treatment, rehabilitation, and monitoring) integrating and exploring subject-specific information across scales (from the molecule to the organism). VPH research allows constructing and validating such prediction models and integrating them into highly useable clinical decision support tools. These are at the core of personalised medicine as proposed by the Digital Patient. To support these modelling-based applications, solutions should include technologies to automate data extraction relevant to the health challenge at hand. Also, these solutions must provide for effective exploratory clinical interfaces in order to ease the clinical decision-making process.

2. Efficacy and effectiveness studies of individualised care tools and workflows are needed to speed up clinical acceptance and diffusion of such applications. Clinical studies and trials on prospective or retrospective cohorts aimed to investigate the differences in efficacy, effectiveness and efficiency of individualised care approaches based on VPH technologies developed in previous projects should be supported. Priority should be given to approaches that use VPH-style simulation to integrate information across scales. This research should also explore the development and accuracy of mathematically efficient models replacing computational demanding sub-models with estimators developed on pre-computed solutions and error estimators.

3. Research should be aimed particularly at those individualised computer simulation models/applications that have the prospect of improving treatment and thereby reducing the burden of the most important diseases in Europe based on the 2010 Global Burden of Disease study.[13] In term of Disability-Adjusted Life Years (DALY), these are cardiovascular and respiratory diseases (ischemic heart disease, stroke, COPD, vascular dementia, other cardio-circulatory), musculo-skeletal diseases (lower back pain, neck pain, falls, other musculoskeletal), cancer (lung, colorectal, breast), neurological (Alzheimer) and metabolic (diabetes) diseases, and on those diseases that have a considerable burden in term of quality life years lost due to disability (YLD), such as obesity, depression, chronic kidney and urinary disease, all forms of arthritis, etc. Such individualised computer simulations should deal with uncertainty and should work on strategies to formalise and generalise testing and validation of these models, providing estimations on the impact that incomplete data has in the personalised model. Furthermore, an extension and integration of such models towards dealing with multi-morbidity is urgently required, because such patients are by far the most costly ones when compared to those suffering from only one or two diseases.

Patient Avatar (Maturity Level #3): Develop novel, advanced modes of visualisation of medical conditions and implementation of Digital Patient solutions for both clinicians and patients.

1. Integrative interactive visualisation in healthcare is a most promising new area of application facilitated by technical progress in hardware and software. Development of model-based prototypes that provide testable

13 http://www.healthmetricsandevaluation.org/gbd/visualizations/gbd-heatmap

proof of concept for clinical use using realistic and relevant clinical scenarios should be supported. These prototypes should include interactive user interfaces specifically designed for the clinical exploration of large, heterogeneous, high-density collection of information. These should also develop tools that allow for an easy to understand visualisation of uncertainty in the Digital Patient output. Studies should include experiments to quantify the effectiveness of the proposed interfaces and tools, over cohorts of expert and in-training medical professionals as well as patients.

2. Development of methods for real-time interactive simulation is urgently needed. These are computational methods that allow generating computer predictions of VPH-style hypermodels as part of an interactive session, involving, e.g., different specialists, a clinician and a patient, etc. These may include pre-computing strategies, surrogate modelling approaches, or brute force hardware/solver optimisation for drastic speed-ups.

3. To allow for a better assessment of alternative exploration strategies and decision support when investing in Digital Patient applications, policy makers, health system managers as well as clinicians need better data on the impact of the new technology and the respective "business" case. This requires the development of novel health technology assessment methodologies, cost-benefit approaches and exploration planning tools adapted for Digital Patient solutions.

4. The rapid diffusion of Digital Patient solutions will demand their clinical assessment and economic evaluation against the current standard of care in realistic scenarios and routine application contexts.

Ex-post: notes from the review process

Once completed the research roadmap was reviewed by some experts appointed by the European Commission, and then extensively discussed during the review meeting. As a result of this interaction some additional recommendations emerged:

- The Digital Patient approach emphasises the complementarity between technology and user expertise, but this works also within teamwork. Multidisciplinary teams, such as those being established for cancer, would be supported by a Digital Patient approach, not only by providing each team member with information he/she could not find alone, but also by easing interdisciplinary communication.

- The separation between Digital Patient and Personal Health Forecasting should not be enforced. The Digital Patient can reach out to the patient, when it supports self-management, for example in chronic diseases, but also in more general context of prevention and wellness.

- In the design of clinical trials to assess Digital Patient technologies, where the randomised clinical trial design is not possible, consider existing frameworks for the development of complex interventions, such as that proposed by the UK Medical Research Council .

- The initial restriction to secondary care was too narrow: the GPs can provide some of the most compelling scenarios for the Digital Patient vision.

- Psychosocial dimension missing: subjective feeling of the patient is important and needs to be considered. Again, the GP is in the best position to know and use that information. The way people feel is important.

- Special emphasis was placed by the reviewers on the potential role of genomics in the prediction of therapeutic outcomes as well as the understanding and planning of primary prevention.

- The political, legal, administrative and also scientific difficulties that could and will be met if the Digital Patient and/or the Patient Avatar should be introduced into realistic local, regional, and national healthcare structures have been underlined. These will need to be addressed by the H2020 research framework.

- The roadmap must be disseminated to representatives of national health ministries, and of health insurances, and engage them in the debate.

Contents

1. Introduction

1.1 Motivation

The DISCIPULUS Co-ordination and Support Action funded by the European Commission, FP7 ICT for Health Programme (October 2011-June 2013) has been tasked with providing the Roadmap for the concrete realisation of the Digital Patient; a key development emerging from the Virtual Physiological Human (VPH) initiative. The VPH vision, defined as "*a framework of methods and technologies that, once established, will make it possible to investigate the human body as a whole*" is fundamentally a multidisciplinary development. When deployed, it will have a profound impact on healthcare and wellbeing and will present a radical departure from the way medicine is practiced in millions of hospitals across the world. It calls for a total transformation in the way healthcare currently works and is delivered to patients. Underpinning this transformation is substantial technological innovation with a requirement for deeper trans-disciplinary research, improved IT infrastructure, better communication, large volumes of high quality data and superior tools to those we have now. It also requires a healthy measure of political support; initial developments are likely to be costly but, once the initial deployment costs have been met, overall cost savings are expected to be significant.[1,2]

The Digital Patient builds on this vision with a particularly strong translational focus and is the "clinical penetration challenge" for the VPH Community. The consultation processes that have taken place in the course of DISCIPULUS have had strong clinical involvement; by bringing the clinician to the centre of the technological developments necessary for the Digital Patient to become a reality, we have gained a better understanding of the barriers to clinical uptake in general and the developments that are needed in order to overcome these. We believe the Digital Patient will be a significant improvement in the quality of life for the EU population. The vector of this improvement will be individualised computational models of patients. Perhaps for many, the words "medical avatar" would provide a closer representation of what is envisaged in the future by the Digital Patient.

The Digital Patient Roadmap is an Science & Technology Roadmap: experts from Europe and beyond have come together, discussed and exchanged ideas of what is needed in the different areas presented in this document in order to take the Digital Patient to the next level. It is clear that, whilst there are many achievements to celebrate, the current evolutionary approach to VPH technological development, embedded within individual VPH applications, cannot produce this next level. Instead, what emerged from this roadmapping exercise is that there is a need to step back and consider the broader ongoing technological needs that relate to the Digital Patient. This requires the clinician to be placed at the centre of development and a repositioning of the original ambition of a decision support system that could produce results at the push of a button. In order to do this we must work with our clinical counterparts in order to organically develop systems and services that address disease, health and wellbeing from a holistic, *in silico* perspective, producing *tools that work for them*.

The major deliverable of the DISCIPULUS Project is the Digital Patient Roadmap – the document before you. After 21 months of intense work, the community of experts who participated in the consensus process has proposed a number of Grand Challenges. These are presented in detail in subsequent chapters. A set of developments that will assist the long-term development of the

1 Rainer Thiel, Marco Viceconti, Karl Stroetmann. Assessing Biocomputational Modelling in Transforming Clinical Guidelines for Osteoporosis Management. User Centred Networked Health Care A. Moen et al. (Eds.) IOS Press, 2011. doi:10.3233/978-1-60750-806-9-432

2 VPH-Share, deliverable 7.4, February 2013 (available in BiomedTown)

Digital Patient from the conceptual ideal to the clinical reality have been identified within key areas (each identified as an individual chapter) and are presented together with the potential obstacles/bottlenecks that could constrain their adoption.

In order to place these recommendations in context, this introductory section includes a horizon scan of VPH research, a description of the process underpinning the building of the Roadmap as well as the building of the Digital Patient momentum and repositioning of goals within the community. These are described below.

1.2 RTD background for the Digital Patient: a horizon scan

Rationale

Since its inception in 2005 the Virtual Physiological Human (VPH) initiative has produced considerable momentum, most of which will be relevant background for the Digital Patient (DP). This brief horizon scan, whilst not exhaustive, will give a sense of the foundation on which the DP can be built. This topic is approached from the perspective of both a research project survey, and from a literature review.

There are a number of other RTD domains that are likely to be relevant to the DP: two important research communities in this context are those for Biomedical Informatics and for Personal Health Systems. More detail on these two very vital communities and their achievements can be found in the comprehensive outputs of two sister support actions to DISCIPULUS: Inbiomedvision[3] and PHS Foresight[4].

Here we shall focus our attention on developments where simulation plays a central role.

VPH in the literature

A search on PubMed using the terms "physiome" or "virtual physiological human" reveals that between 1996, when the term 'Physiome' first emerged, until today (May 2013), 156 papers have been indexed that include these terms. The complete bibliography is available in Annex 1.

Of course, not all papers using a 'VPH-approach' acknowledge it in the key words. This is particularly true in the first first years of the initiative when the term was not so widely adopted.

Among the most visible results we would like to mention the work of Peter Kohl, Blanca Rodriguez and Denis Noble with the PreDICT project; which provides one of the first examples of *in silico* clinical trials for cardiac drugs[5]; the work of Paul Morris, Julian Gunn, Pat Lawford and Rod Hose on the possibility of replacing the costly and invasive Fractional Reserve Flow test with a patient-specific simulation based on routine angiograms[6]; the work of Frederike Schulte, Davide Ruffoni and Ralph Müller that conclusively demonstrates the mechanoregulation of bone remodelling using VPH models of mice[7] and finally, the work of Tom Polasek *et al* that shows how *in vitro-in vivo* extrapolation coupled with physiological-based pharmacokinetic modelling and simulation can be reliably used to estimate metabolic drug clearance[8].

Other papers include a patient-specific computational model, capable of predicting postoperative flow for arteriovenous fistula (AVF)[9] , the development of smart sensors and virtual physiology human approach as a basis of personalised therapies in diabetes mellitus[10] or even a multiscience decision support system for HIV.[11]

For more translational aspects we recommend the excellent literature review by Winslow *et al.*[12] A list of VPH papers is presented in Annex 1.

Computer-based human modelling: an international affair

Computer-based Human Modelling is being used extensive-

3 http://www.inbiomedvision.eu/
4 http://www.phsforesight.eu/

5 Mirams GR, Davies MR, Cui Y, Kohl P, Noble D. Application of cardiac electrophysiology simulations to pro-arrhythmic safety testing. Br J Pharmacol. 2012 Nov;167(5):932-45. doi: 10.1111/j.1476-5381.2012.02020.x.
6 Morris PD, Ryan D, Morton AC, Lycett R, Lawford PV, Hose DR, Gunn JP. Virtual fractional flow reserve from coronary angiography: modeling the significance of coronary lesions: results from the VIRTU-1 (VIRTUal Fractional Flow Reserve From Coronary Angiography) study. JACC Cardiovasc Interv. 2013 Feb;6(2):149-57. doi: 10.1016/j.jcin.2012.08.024.
7 Schulte FA, Ruffoni D, Lambers FM, Christen D, Webster DJ, Kuhn G, Müller R. Local mechanical stimuli regulate bone formation and resorption in mice at the tissue level.PLoS One. 2013 Apr 24;8(4):e62172. doi: 10.1371/journal.pone.0062172. Print 2013.
8 Polasek TM, Patel F, Jensen BP, Sorich MJ, Wiese MD, Doogue MP.Predicted metabolic drug clearance with increasing adult age. Br J Clin Pharmacol. 2013 Apr;75(4):1019-28. doi: 10.1111/j.1365-2125.2012.04446.x.
9 Aron S AS Bode, Wouter W Huberts, E Marielle H EM Bosboom, Wilco W Kroon, Wim P M WP van der Linden, R Nils RN Planken, Frans N FN van de Vosse, and Jan H M JH Tordoir. Patient-specific computational modeling of upper extremity arteriovenous fistula creation: its feasibility to support clinical decision-making. PLoS One 7(4):e34491 (2012) PMID 22496816 PMCID PMC3319586
10 Carlos M Fernández Peruchena and Manuel Prado-Velasco. Smart Sensors and Virtual Physiology Human Approach as a Basis of Personalized Therapies in Diabetes Mellitus. Open Biomed Eng J. 2010; 4: 236–249.
11 Sloot, P., *et al.* (2008). "Multi-science decision support for HIV drug resistance treatment." Studies in health technology and informatics 138: 188-198
12 Winslow RL, Trayanova N, Geman D, Miller MI.Computational medicine: translating models to clinical care. Sci Transl Med. 2012 Oct 31;4(158):158rv11. doi: 10.1126/scitranslmed.3003528.

ly across the world for a number of applications, starting from the "generic person simulation" which is used in ergonomics[13] for example, and is an established educational tool in medical schools or teaching hospitals (as is a generic patient version) for the teaching of anatomy and physiology.

The Digital Patient is much more than this.

Patient-Specific Simulations are increasingly regarded as valuable tools in a number of aspects of medical practice including surgical planning[14] and medical intervention[15]. The idea is that real data (usually in the form of an image) is obtained for the patient; this image can be of the whole anatomy of the patient (through 3D scanning or motion capture, for example) or part of the patient (for example, the heart, trachea, skeleton, and so on) using medical imaging technology. The data is then fed into an appropriate computer simulation program, where real-time simulations can be performed based on the image. Operations and procedures can be simulated and 'practised' before the real procedure is carried out. From these simulations, predictions can be made about future events for the individual based on the original image. Such predictions are rooted in classical physics and typically are made possible through the use of established mathematical (or mechanical) models.

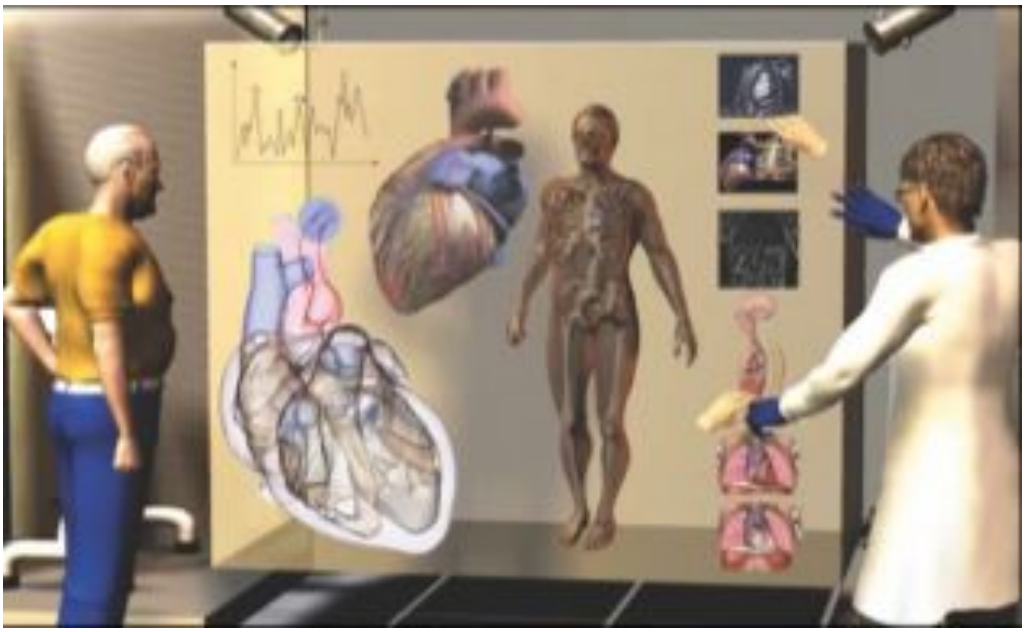
Until the 19th century, the use of mathematically based predictions was primarily confined to the study of inanimate objects, but in the 19th and 20th centuries, there was increasing interest in exploring their use in modelling human physiology. We have come a long way. Nowadays, evidence suggests that, whilst these predictions can be very accurate for certain physiological processes[16,17,18], such as cardiac function, blood flow, urine output, there is a need for greater refinement of predictive models for many other physiological functions, as well as (more rigorous) trials for existing models. Examples of this type of modelling can be found in the scientific literature from outside Europe, with key developments in the United States[19,20], Korea[21], Japan[22], China[23], Australia[24] and New Zealand[25] to cite just a few. The Digital Patient will incorporate this technology.

The 'Multiscale Person (or Patient)-Specific Simulation' is the highest level of patient-specific modelling and operates across multiple length- and time-scales, typically from: molecular, cellular, tissue, organ, through to the level of the system as a whole. A multiscale integrative approach will also be a core feature of the Digital Patient.

Within Europe, this type of technology underpins the VPH Initiative; multiscale mathematical models are essential components for building a virtual physiological human. Thus understanding the current state of research in terms of multiscale model development is fundamentally important to the roadmap. Outside Europe, multiscale modelling is an active area of research. Apart from the heart and vasculature (where examples were provided above), multiscale modelling is a key methodology which has been applied to the skeleton[26] and skeletal muscle[27], the gastrointestinal tract and its smooth muscle[28], the liver[29], the pancreas and insulin secretion[30], the lungs and respiratory system[31,32], the brain[33,34,35] and spinal cord[36], skin[37,38], hair[39], gene expression[40], the immune system[41,42], the kidney[43], and pathways in metabolism and internal transport[44]. Momentum is building, but as will be explained in this Roadmap, there is still much to be done. In particular, many of the models still require further development. To this end, it is important that we exploit all available expertise and the multiscale mathematical models that could be used in developing the first VPH prototype would be expected to come from groups within and outside Europe.

As previously mentioned, there are many examples of coun-

13 Chaffin et al. Digital Human Modelling for Vehicle and Workplace Design (SAE) 2001.
14 Ballester et al. in MICCAI 2009 (Eds: Yang et al.). 2009 (Springer-Verlag):275-82.
15 Deligianni et al. Computer Aided Surgery. 2004;9:215-26.
16 Guyton et al. Annu. Rev. Physiol. 1972;34:13-44.
17 Delingette et al. IEEE. T. Bio-Med. Eng. 2012;59:20-4.
18 Sermesant et al. Medical Image Analysis. 2012;16:201-15.
19 Chao Med. Eng. Phys. 2003;25:201-12.
20 Bartocci et al. CMSB '11 (Ed: Fages). 2011 (ACM):103-12.
21 Kim in Digital Human Modelling HCII 2007 (Ed: Duffy). 2007 (Springer-Verlag):136-143.
22 Deguchi et al. Sys. Comput. Jpn. 2006;37:93-104.
23 Qi IEEE/ICME International Conferences on Complex Medical Engineering (IEEE) 2007.
24 Chu et al. Concurrency Computat.: Pract. Exper. 2008;20:1095-111.
25 Hunter et al. Annu. Rev. Biomed. Eng. 2003;5:147-77.
26 Peterson et al. Bone. 2010;46:49-63.
27 Makssoud et al. Biol. Cybern. 2011;105:121-138 (Erratum: 2011;105:181).
28 Du et al. Crit. Rev Biomed Eng. 2010;38:1-30.
29 Mescam et al. IEEE. T. Med. Imaging. 2010;29:699-707.
30 Pedersen et al. IEEE. T. Bio-Med. Eng. 2011;58:3020-3.
31 Freed et al. Viscoelastic Model for Lung Parenchyma for Multi-Scale Modeling of Respiratory System Phase II: Dodecahedral Micro-Model (Pacific Northwest) 2012.
32 Grandment. Multiscale Modeling of the Respiratory System (Projet (French) REO).
33 Jirsa et al. Archives Italiennes de Biologie. 2010;148:189-205.
34 Bhalla. Neural Networks. 2011;24:949-49.
35 Mattioni M. Multiscale Modelling in Neuroscience: Integration of Computer Simulations of
Biochemical and Electrical Signalling in the Medium Spiny Neuron of the Striatum (PhD Thesis, University of Cambridge) 2012.
36 Niu et al. In Advances in Neural Information Processing Systems 25 (Eds: Bartlett et al) 2012 (NIPS).
37 Goodyer et al. Mathematical Modelling of Chemical Diffusion through Skin (Presentation, University of Leeds).
38 Mottin et al. PLOS One. 2010;5:e14350.
39 Akkermans et al. Phil. Trans. R. Soc. A. 2004;362:1783-93.
40 Bokes et al. J. Math. Biol. 2012;65:493-520.
41 Krischner et al. Immunol. Rev. 2007;216:93-118.
42 Hosseini et al. PLOS Computational Biology. 2012;8:e1002371.
43 Chu et al. Concurrency Computat.: Pract. Exper. 2008;20:1095-111.
44 D'Angelo. Multiscale Modelling of Metabolism and Transport Phenomena in Living Tissues. (Thesis for Docteur des Sciences, École Polytechnique Fédérale de Lausanne) 2007.



Patient and clinician © VPH Insitute

tries outside Europe that are producing models or engaged in multiscale modelling research for the human body (or that is applicable to the human body). Whilst an extensive survey of international research is outside the scope of this Roadmap it is important to appreciate the significant impact that has been made from the international scientific community. For this reason we have brought in literature evidencing VPH research from all over the world. In addition, the degree of international investment in this area highlights a wider belief in the utility of these models and their potential role in the development of Medicine in the 21st century.

> “I see the DP in the clinic as an opportunity to bring together all the information on a particular patient.”
>
> Consulting Surgeon

European projects survey

FP7 VPH Projects

Annex 3 lists all VPH projects funded in FP7, except those in call 10 that, at the time of writing, are still under negotiation. A brief description is included together with a link to each of their web pages. This data was collected by the VPH Institute.

If the Exemplar Projects, funded within the VPH NoE, are counted as independent projects, to date, 66 projects have been funded by the EC under the banner of the VPH. Of these 36% address the core development of the VPH, defining; research roadmaps and networks (5), the IT infrastructures (4) and specific information technology research (16).

Sixteen projects address the needs of the VPH in terms of fundamental information technology, and a further four target infrastructures. The remaining projects focus on one or more diseases, with the lion’s share of these relating to cardiovascular disease (13), oncology (7), musculoskeletal disorders (4), neurology (4), or infection & immunity (4).

Of the 66 projects funded, 22 are still underway, and a further 19 finished within the last 12 months, or are still running under short extensions; thus, 48% of the VPH projects can be considered complete. For this reason, the scientific impact of these research initiatives is not fully visible in the scientific literature and, in terms of translation, more publications are likely to emerge over the next few years.

Other large European VPH/Physiome projects

A systematic survey of the member states funding is beyond the scope of this document. However the impact of a couple of large and strategic projects, funded by national agencies should be mentioned:

The Virtual Liver Network[45] is a 50M€, five year project funded by the German Federal Ministry of Education and Research that aims to develop “a dynamic model that represents, rather than fully replicates, human liver physiology morphology and function, integrating quantitative data from all levels of organisation”.

The £6.7m 5-year EPSRC Frontier grant “Individualised multiscale simulation of the musculoskeletal system” awarded to the University of Sheffield Insigneo Institute is probably the largest single-institution grant on VPH research. Due to start in July 2013, it will focus on the core engineering chal-

45 http://www.virtual-liver.de/

lenges related to multiscale modelling, using musculoskeletal biomechanics as an exemplary problem.

The Digital Patient (VPH) community

The VPH community is still quite young. It was formed around the activities associated with the FP6 Coordination Action *STEP: A Strategy for the EuroPhysiome (FP6-ICT-027642)*, which concluded in March 2007, with the first EC-funded projects formally linked to VPH initiated in the summer of 2008. Because of the nature of the research, these projects involve mathematicians, biomedical researchers, bioengineers, computer scientists and clinicians. The clinical component of this story is particularly important to DISCIPULUS and the Digital Patient; the S&T challenges must be addressed with the clinical expert (the end user) at the core of the proceedings. This is not a simple task and DISCIPULUS has had to not only identify future technological directions, but has also had to change perceptions within the VPH community in terms of repositioning our original ambitions by redirecting developments towards more clinically-friendly (and compliant) systems.

1.3 Defining the Digital Patient vision and drafting the roadmap

We define the Digital Patient as a technological framework that, once fully developed, will make it possible to create a computer representation of the health status of each citizen that is descriptive and interpretive, integrative and predictive.

Descriptive - it provides unified access to all information about the patient's health determinants, including those related to life-style, such as physical activity; and interpretive - it helps to gain new understanding.

Integrative - it automatically combines all the available information so as to provide better decision-support based on a large volume of information.

Predictive - the integrated information is used to inform individualised simulations able to predict how specific aspects of subject's health will develop over time, as a function of different interventions.

Digital Patient technologies provide individualised (person-specific) future projections, systemic predictions based on mechanistic understanding of the disease process in an integrative and holistic view.

It is envisaged that all medical professionals (nurses, GPs, hospital specialists, etc.) will be able to access Digital Patient technologies for prevention, diagnosis, prognosis, treatment planning, monitoring, and rehabilitation purposes.

The Digital Patient provides clinicians (and patients) with highly visual and integrated views of relevant health and wellness information of the patient. These integrated views are combined with predictive models and simulations to provide projections of future possible health status, the course of illness and the outcomes of healthcare interventions. The Digital Patient technological framework includes VPH models, decision support tools and patient data records, and once fully developed and deployed, it will make it possible to create descriptive, integrative, exploratory, *in silico* representation of the present health status for each citizen as well as a predictive representation of potential future states, based on causal simulation models.

The complex territory of biomedical and technological research can be charted in four different dimensions:

1. Technological challenges: the Digital Patient is a multidisciplinary, multi-technological initiative, but each technological aspect must be discussed within a specialised context so as to ensure excellence;

2. Maturity levels: the Digital Patient is a long-term vision, but we should be able to target short-, medium-, and long-term goals, so as to ensure a progressive impact;

3. Exemplary clinical challenges: We need concrete clinical problems around which the technological discussion can evolve, so as to ensure proper clinical rooting and engagement of clinical and industrial stakeholders;

4. Use cases: General categories of use in the clinical practice present different perspectives that need to be addressed separately.

Technological challenges

In order to define the technological challenges, the overall concept of the Digital Patient was decomposed into its component parts: from the initial inputs in terms of data and information to the ultimate goal: translation and adoption. The main areas of technological challenges are illustrated in the figure overleaf.

This process yielded the different chapters of this Roadmap, each highlighting the range of different technological challenges in these areas.

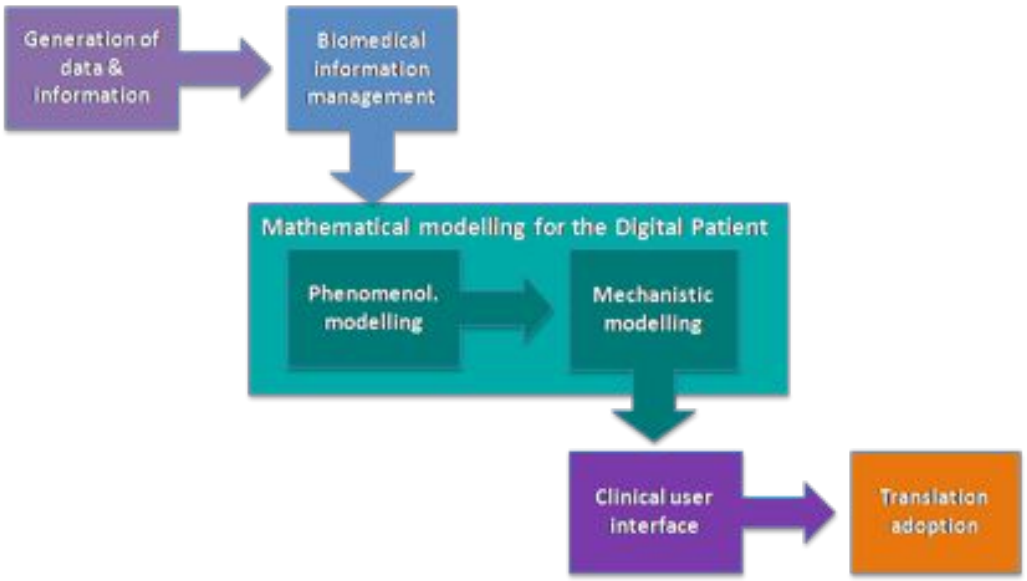
The different chapters are (in order): generation of data, biomedical information management, mathematical modelling, clinical user interface and, last but by no means least, translation and adoption. Exemplary clinical scenarios and respective technological challenges are provided in a sepa-

rate chapter.

The limits of each area are inevitably fuzzy. The detailed charting of this research territory is the primary scope of this roadmap.

Maturity levels

Three maturity levels (and potentially a fourth) were identified for Digital Patient technologies as illustrated in the figure on page 15. Maturity levels indicate a measure of 'what is achievable now' and 'what will be achievable in the future', or, more simply, the different 'ages' of the Digital Patient.



Technological challenges: Main areas

Interactive health analytics consider the development of exploratory interfaces that enable a more holistic exploration of the data currently available at multiple points of care for each patient; here the goal is improved fusion of all existing knowledge about each patient – individualised knowledge fusion.

Individualised health management implies that the available clinical data are not only explored, but truly integrated into simulation-based decision support systems that guide fully-individualised treatment decisions; the goal is individualised care.

The patient avatar involves a more global integration of data collected at the point of care and at the 'point of life', as well as a broader range of simulations of pathophysiological processes, not necessarily related to the specific disease in question. The result is truly integrative medicine, capable of coping with patients with poly-disease and complex cases more effectively; the goal is the full realisation of the Digital Patient vision.

Once the Digital Patient technologies are fully deployed, every hospital in Europe will generate a volume of integrated clinical data about real individuals on a daily basis. This "one million Digital Patients" database could subsequently be used for what-if simulations to inform public health decisions; the goal here is ePublic health (potentially the 4th level), where policy decisions can be made on the basis of reliable computer simulations of the different scenarios.[46]

A Digital Patient is a technological platform which enables interactive health analytics (ICT support to the exploration and the understanding of the patient health status from a large amount of digital data), individualised health management (individualisation of prevention, diagnosis and treatment), personal health forecasting (citizen-centric health management, where the ICT provides to each of us predictions on how our daily choices will impact our health and well being status).

Use cases

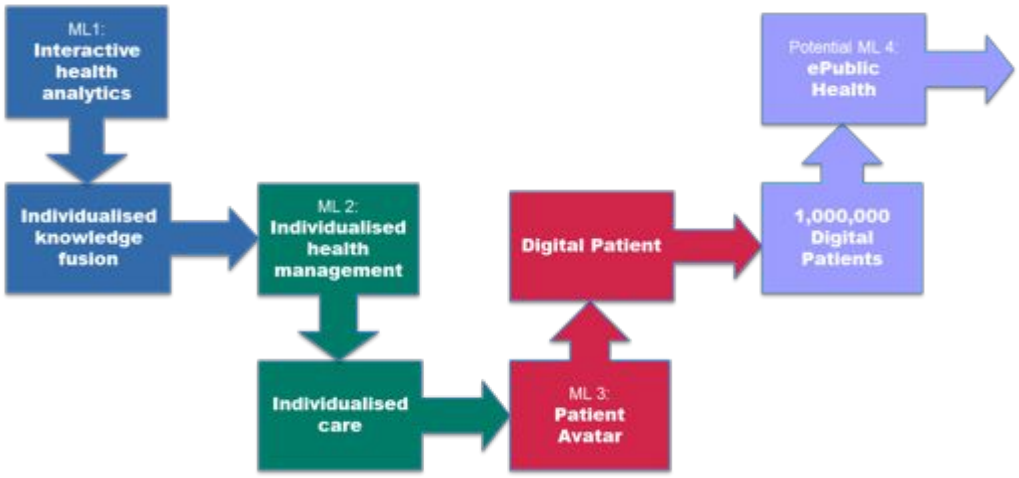
Throughout the development of the Roadmap we worked intensively with the notion of 'use cases' or clearly "what is it for?". After consultation with clinical experts, their views were that they could use the Digital Patient for:

1. Decision: To provide decision support systems based on the Digital Patient technologies, with particular reference to prevention/procrastination, diagnosis, prognosis, treatment selection and monitoring, and disease management

2. Explanation and presentation: To support the communication between clinical scientists and frontrunners, and the medical specialist (understanding- and information-based medicine), her/his peers (consultation, teamwork), care providers, and the patient (patient-doctor communication)

3. Execution: To provide computer aided medicine systems that support the clinical specialist in the prevention/procrastination, planning, execution, and assessment of the treatment

46 Maturity level 4: ePublic Health has been considered a very long term challenge and thus not discussed here in detail. It should be considered in future support actions / research roadmaps.



Digital Patient Maturity Levels

4. Translation: To facilitate the integration of new insights and knowledge into clinical practice, facilitated by the digitisation of medicine.

Whilst the Digital Patient technologies involved in each of these use cases would, in the main, be the same, each provides a different set of metrics by which the efficacy of each use case can be evaluated.

Community building and writing the Roadmap: a consensus process

The Digital Patient Roadmap has several facets:

- stimulation: to awaken, within the VPH community, a common view about the long-term technological needs of the Digital Patient, to motivate members to embrace the technological challenges involved, and to develop an appreciation of how a successful outcome could be achieved
- insight: to identify the specific expertise, most likely in mathematics, computer science, etc., that is necessary to bring the plans into fruition and, most importantly, bring clinical experts to the core of the discussions
- outreach: to attract people with essential expertise to VPH and motivate them to become involved in the Digital Patient Roadmap as a source of problems requiring fundamental research and as an arena within which fundamental research outcomes can be applied and tested. The first step in developing a consensus process was to seek to establish a core set of issues from which to start the discussion and to identify a small, but active, set of participants who would help to establish firm foundations from which the discussion could be driven forward and expanded into a broader participation with a wider range of topics.

The process

Direct participation and consultation: Two consultation meetings (the first one in March 2012 and the second in November) set the scene for the community building exercise and the start of the consultation and consensus process. By design, the first meeting was relatively small (circa 60 people in total) and by invitation only. Here, the primary focus was the clinical experts and their needs. The second event was an open meeting with more than 150 experts from all over Europe, and beyond, participating in discussions centred on a number of exemplar clinical scenarios and the technological challenges required in order to achieve the clinicians' vision of the Digital Patient. In order to be as inclusive as possible, the DISCIPULUS project provided bursaries for those attending: everybody was invited. At the 2nd consultation meeting (November 2012), an individual session was devoted to each topic. An animator provided a grounding in the form of a brief summary and then orchestrated a debate to elicit aspects of the problem that would prove fruitful for future investigation. The session also provided an opportunity to create a small editorial team who would assist the animator in producing an extended article on the topic. These articles (also called chapters) form the various sections in the remainder of this document.

Examples & framing the discussion

Exemplary clinical challenges were used to frame the discussion. In a preliminary phase the community of experts was polled, asking them to indicate specific clinical conditions that would fit the following description:

- Have a significant socioeconomic impact;
- Have associated a champion who is a clinical opinion leader;
- Cover enough diversity to be assumed a representative sample.

We received input in the following clinical sectors:

1. Neurology
2. Orthopaedics

3. Cardiovascular diseases
4. Metabolic diseases
5. Respiratory diseases
6. Oncology
7. Internal medicine
8. Immunity and infectious diseases
9. Geriatrics and paediatrics

The first six of these were specifically targeted during the second DISCIPULUS meeting, and many examples in this roadmap are drawn from those clinical domains. It should be stressed that the scope of this roadmap is to define the technological research in general, thus the specific diseases here mentioned are only used as examples.

Creating the Roadmap

During and after the meeting a number of key leaders emerged from the community who were willing to assist in the production of the scientific content of the Roadmap. More than 200 scientists have endorsed this Roadmap by direct participation in the debates and/or the writing of the individual chapters. This is evidenced in the List of Contributors (Annex II). As each chapter was completed, they were added to the draft roadmap and posted on Dropbox and on Biomed Town to enable interested parties to make further contributions if they so wished.

In addition, a discussion forum was created on the DISCIPULUS pages on Biomed Town and its presence was made public by widespread dissemination. Participation in the debates was open to all. The topics were introduced for discussion a few at a time to retain focus according to a pre-announced schedule covering the period December 2012 to May 2013. Some of the original experts encouraged colleagues and contacts with relevant expertise in key areas to join the discussions, which proved very fruitful.

Roadmap structure

Chapters 2-6 are the final versions of the articles produced on the various topics that emerged from the DISCIPULUS discussions followed by exemplary clinical scenarios.

In the conclusions, we summarise the recommendations about how advanced technology might influence the future of the Digital Patient in Horizon 2020.

Since this is a technological research roadmap, it was natural to adopt the technological challenges dimension as its primary structure. In the following, the reader will find one chapter for each of the technological challenges identified above. Within each chapter, aspects related to different maturity levels will be discussed. The exemplar clinical challenges, and their relative use cases are used to provide tangible examples of the challenges at hand, and to illustrate the way in which a specific technological development could help to solve them.

2. Generation of data for model construction, validation and application

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2.1 Introduction

The realisation of the Digital Patient vision is heavily dependent on the availability of massive amounts of data for a range of purposes. These purposes can be ascribed to three categories: (i) for *building models* (i.e. gathering and structuring information to identify interactions and translating them into numerics, see Chapter 4); (ii) for *validating models* (i.e. comparing the models against some "ground truth" to try and falsify/corroborate them, see Chapter 4); (iii) for *populating models* with patient-specific information (i.e. deploying and validated models in a clinical context, see Chapter 6).

In many cases of VPH research the stumbling block is not the modelling method but the lack of information with sufficient quality, extension and resolution to inform the model properly with quantitative data. On the other hand, the theoretical structure underlying both the creation and application of the Digital Patient provides arguably one of the strongest settings for generating maximal information out of biomedical data, irrespective of whether these data are sampled for specific R&D purposes or for primary and secondary healthcare purposes.

Additionally, the theoretical structure underlying VPH is one of the most potent tools we have for identifying which new types of data, and thus which new measurement technologies, are needed for making progress in a whole range of biomedical fields. In other words, to realise the Digital Patient vision we need to keep considerable focus on facilitating the generation, standardisation, certification and integration of data targeting the following main application areas: Construction and validation of data-driven prediction models; Application of data-driven prediction models within primary and secondary healthcare; Construction and validation of causal and predictive models; Application of causal models within primary and secondary healthcare; and Multidimensional phenotypic data analysis to uncover new important patterns that can serve as inspiration source for statistical and causal models.

Consequently, one needs to support the development of methodology and technology for generation and integration of genomic and high-dimensional longitudinal phenotypic data spanning the whole phenotypic hierarchy. The sources of data and, down the line, information for VPH models are varied, however. This diversity was evident in the description of this chapter, where a plethora of data and information was discussed at length during meetings, online and off-line discussions.

As a result, the first section following this introduction (2.2) defines the challenges related to genetic data and phenomics. The next section (2.3) describes sources of data and sensing (and the challenges associated with collecting the data and turning it into useful information) in order to firmly root the DP in the clinic. Next, challenges in data acquisition methods (section 2.4) and homologation (section 2.5) are indicated. In section (2.6) the importance of data certification is emphasised, this is followed by a section (2.7) where data provision including (pre-)processing and formatting are highlighted. Finally, a list of recommendations is given in section (2.8).

> "The biggest [hurdle] is to obtain relevant data and standardised common understanding of what the data represents."
>
> General Practitioner

2.2 Genetic data and phenomics

2.2.1 Models that link genotype to phenotype

Some concepts reported in this chapter were already exposed, in reduced form, in Gjuvsland et al. 2013.[1] These concepts are the basis of this section of the Roadmap in the context of the Digital Patient.

The future main core of the mathematical structure linking genotype to phenotype will plausibly be system dynamics. Only in this way is it possible to make a causally cohesive link between genetic and phenotypic variation. The simple reason for this is that use of data-driven models alone is not sufficient to describe, and analyse, how emergent dynamic phenomena (i.e. phenotypes) are generated by the interactions of lower-level systemic entities. Thus we cannot use data-driven models to link genotype to phenotype based on mechanism, in a systematic and comprehensive way, but such models are most needed to explain, discover and describe cellular, organismal and population patterns. A theoretical structure making use of both modelling modalities will enable the integration of genetics, genomics, bioinformatics and multiscale models with physiology in a population context, forming a meeting point for many of the themes in this Roadmap.

The analysis of -omics data routinely produces vast networks of associations, e.g. between genetic variability, pro-

1 Gjuvsland, A.B., Vik, J.O., Beard, D.A., Hunter, P.J. & Omholt, S.O.: Bridging the genotype–phenotype gap: what does it take? J Physiol. 2013 April 15; 591(8): 2055–206.

tein expression, and disease-related phenotypes.[2] Analyses of network structure have yielded many valuable biological insights. Cause and effect can to some extent be identified by Bayesian network analysis, though this framework struggles to incorporate time and feedback, the main characteristics of dynamical systems.[3] Several other modelling frameworks have been applied to infer features of the underlying *dynamic processes*[4], e.g. Boolean networks and simple Petri nets. However, utilizing -omics data in models of physiological mechanisms, such as differential equations or continuum mechanics, poses fundamental challenges in parameter identifiability as well as computation.[5,6,7] Current physiological models are often much more complex than existing phenomics data can support. Being able to iterate between different levels of model complexity, recognizing pattern and focusing in on mechanism, will be essential in making use of the best data we are likely to get.[8]

Phenotype space is a vast place, and the development of phenomics will always demand prioritizing what to measure.[9] This prioritization will benefit tremendously from being guided by computational models of how phenotypes are created and maintained in causal terms and not by simple conceptual models. At the same time, for this modelling work to really become transformative, it is mission critical that it becomes nourished and confronted by massive amounts of data that only a mature phenomics technology can provide.

Full understanding of how genetic variation causes phenotypic variation of a complex trait requires a mathematical representation that extends from cells to tissues, organs and the whole-organism level. Such representations will have to encompass a hierarchy of descriptions at different length- and time-scales spanning 9 and 15 orders of magnitude, respectively.[10] There is in principle no limit to the complexity of biological models that can be used to link genetic variation to high-level phenotypes. A much improved phenomics, spanning the whole phenotypic hierarchy, may quantitatively and qualitatively enrich the intimate relationship that exists between experimental measurement and multiscale model construction and validation. This will give us an extensive understanding of how different types of genetic variation propagate and are manifested within different environmental and physiological settings and genetic backgrounds. Next three paragraphs illustrate these issues.

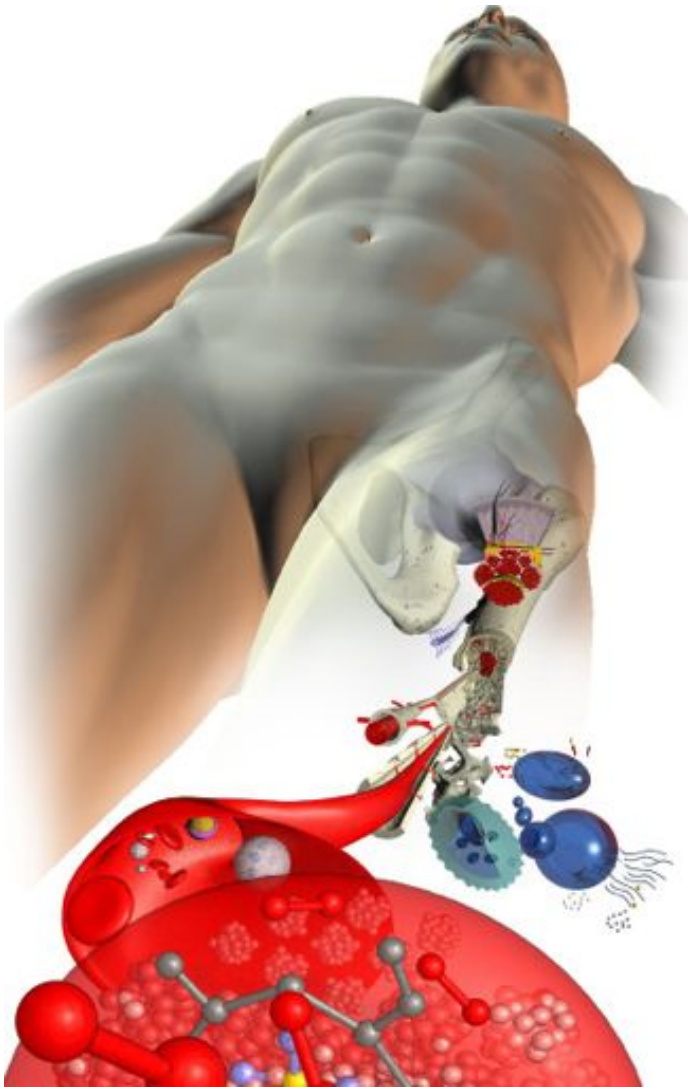
2.2.2 Models of the effects of ageing

It is an embarrassing fact that age is still the best predictor for many complex diseases. A major reason for this is that biological ageing (senescence) leads to frailty, a syndrome of decreased reserve and resistance to stressors resulting in vulnerability to adverse outcomes.[11] This implies that we sorely need to understand frailty in quantitative terms if we are really going to get a grip on the etiology and treatment of complex diseases. That is, we need to make the physiology of the ageing individual a mathematical object. The data requirements for this endeavour may be much more complex than for understanding the physiology of the young, because ageing is a stochastic process and manifests itself in many different ways and anatomical locations.[12] New phenomics technology will be essential for the construction of multiscale physiological models of the effects of ageing. Engineers can take much of the credit for the very fast improvements in genome sequencing technology we are now witnessing. Considering the diversity of technologies required, the development of a mature phenomics technology will need to involve far wider sectors of the engineering community than we have seen up to now for genomics.

2.2.3 Models linking proteins to cells and tissues

As outlined in two recent papers,[13,14] the idea of a 'functional tissue unit' (FTU) centred on a capillary is an attractive way of dealing with the need to link the spatial organisation of cells and extra-cellular matrix in a tissue with vascular transport. This idea leads to several issues that are relevant for this chapter. One is the need to develop metrics that capture the spatial organisation of the FTU for all tissues in the body and to undestand how these metrics change with disease (e.g. obesity and diabetes). Another data requirement is the need to obtain quantitative measures of the spatial distribution of cell receptors (for example) for physiologi-

2 Joyce AR & Palsson BØ (2006). The model organism as a system: integrating "omics" data sets. Nat Rev Mol Cell Biol 7, 198–210.
3 Sieberts SK & Schadt EE (2007). Moving toward a system genetics view of disease. Mamm Genome 18, 389–401.
4 Machado D et al. (2011). Modeling formalisms in Systems Biology. AMB Expr 1, 1–14.
5 Tarantola A (2004). Inverse Problem Theory and Methods for Model Parameter Estimation. SIAM: Society for Industrial and Applied Mathematics, Philadelphia, PA, USA.
6 Tarantola A (2006). Popper, Bayes and the inverse problem. Nat Phys 2, 492–494
7 Aster RC, Borchers B & Thurber CH (2012). Parameter Estimation and Inverse Problems, Sec-ond Edition, 2nd edn. Academic Press, New York.
8 Tenazinha N & Vinga S (2011). A survey on methods for modeling and analyzing integrated biological networks. IEEE/ACM Trans Comput Biol Bioinform 8, 943–958.
9 Houle D, Govindaraju DR, Omholt S. (2010). Phenomics: the next challenge. Nat Rev Genet. 2010 Dec;11(12):855-66. doi: 10.1038/nrg2897.
10 Hunter, P. J. & Borg, T. K. Integration from proteins to organs: the Physiome Project. Nature Rev. Mol. Cell Biol. 4, 237–243 (2003).
11 Fried LP et al. (2001). Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56, M146–M157.
12 Wilkinson, D. J. Stochastic modelling for quantitative description of heterogeneous biological systems. Nature Rev. Genet. 10, 122–133 (2009).
13 Bernard de Bono and Peter Hunter, Biotechnol. J. 2012, 7, 958–972
14 http://nkokash.com/documents/OBML12.pdf



VPHI Visuals

cally based pharmaco-kinetic (PBPK) modelling of drug profiles in tissue and drug occupancy of receptor sites. Here again we need also to understand how these distributions change with disease. All of this is possible with current technology. This provides an argument for new fast, quantitative imaging technologies for spatial distributions of cell types around capillaries and the membrane based proteins that then communicate between the tissue environment to the cell interior including their genotype information.

2.2.4 Imaging and sensing for model purposes

Using routine clinical imaging or sensing examinations is not sufficient. As mentioned above, imaging and sensing for modelling purposes are substantially different from those done for routine clinical use. The imaging or sensing technology moves from a generator of visual patterns that a trained clinician can interpret to measurement instrumentation that is used to quantify a number of physical properties. In order to be truly effective, the sequences and the protocols for the acquisition of data must be optimised for the modelling purpose.

At the same time, high level phenotypes must be measured next to the parameters mentioned above for which technologies for high-throughput patient specific phenotyping need to be further developed. Alternatively, if patient specific data are not available (e.g. because current methods are too invasive, too costly, or locally not available) it must be possible to rely on atlases built from generic data that can be derived from a Digital Patient database.

While data to fill a subject-specific model in a clinical context need to be acquired from a living subject, in some cases *in vitro* measurements can be a viable alternative to provide data to build and to validate models. In the latter case, highly invasive (and possibly more reliable) measurements are possible, including dissection, destructive mechanical testing, chemical analysis, high-dose imaging, etc.

In this context the following main chain of technological challenges is recognised:

1. Exploration of suitable existing and possible new sources of information
2. Development and adoption of acquisition methods and technology to determine genotype and measure high level phenotypes
3. Development and homologation of next generation acquisition methods
4. Exploitation and initiation of new developments in data certification
5. Exploitation and initiation of new developments in data formatting and data (pre-)processing to enable enhanced data provision

Consequently, key topics of the main technological challenges that can be defined in the technological research domain regarding the generation of information follow a chain. In this chain, important technological challenges relate not only to acquisition and storage technology of data but certainly also include next generation solutions for homologation and certification of data. Finally data provided to the Digital Patient system should be standardised, provided with uncertainty ranges, and certified for different uses. It is evident that, although the provided data is preferably source independent, the source must still be traceable and comply with privacy and security guidelines. The elements of this chain are described in the sections below.

2.3 Sources of data and sensing

Today we estimate parameters based on higher level phenotypic data. In order to construct reliable causal models new technology is needed for measuring low-dimensional phenotypes (ie parameters of the models). To enable this, high-throughput and high-dimensional phenotyping needs to be developed.

Furthermore, to be able to predict the ageing trajectory and thus propensity for disease, high-dimensional longitudinal data are needed. The simple concept developed by Eberhard Voit can be used at first to validate this.[15,16] However, this resonates heavily with the concept developed in the section 2.2 above, where it was stated that we need to make the physiology of the ageing individual a mathematical object.

The data that will provide the information used to represent the Digital Patient will indispensably originate from multiple sources, acquired by various acquisition methods, and represented in different formats.

We envisage activities to explore existing and new sources of medical data and the information that can be obtained from these sources.

Examples of medical data that can serve as input for the Digital Patient are multi-modal and include:

- anatomical and geometrical information, for example heart muscle and valves, coronary vasculature, musculoskeletal structure, morphology of organs;
- functional information such as blood pressure and blood flow rates, EEG and ECG;
- different metrics of tissue property such as bone tissue density, cartilage quality, vessel wall composition;
- information on relevant biomarkers from micro-biological, haematological laboratory tests and histological data;
- knowledge about a patient's genetic risk factors;
- information about treatments and, in particular, response to specific drugs;
- lifestyle information such as diet, smoking, exercise, socio-economic status.

All this can be used, first, to "fill" the Digital Patient with data so that this data is available as a reference in future diagnosis, treatment planning, or life-style management. Second, it can serve research purposes via the use of statistics (hence, becoming information). Third, it can help in building new models based on generic data. Finally, both, data and information can be used to provide patient-specific input for personalised models that predict disease development or outcome of intervention for each individual patient.

In addition to the multi-modality of data acquisition systems, the source of information can also be of different types. Currently, the majority of data is acquired as part of a diagnostic protocol in a primary- or secondary-care environment by the general practitioner or medical specialist respectively.

Sources of information – trends

Secondary care: Specialised diagnostic acquisition systems secondary care centres become more and more complex and provide even more complex data. Medical devices, instrumentation technology ICT will need to be advanced and optimised to make these data available for the Digital Patient.

Primary care: Translation from secondary care to primary care diagnostics is promoted in order to achieve early and cost-effective patient stratification. Consequently the technology involved must be made available for primary care. Ultrasound technology for 3D, time-resolved imaging, sensor based non-invasive electrophysiological measurements devices, and lab-on-a-chip technology for biochemical and biological tests (just to name a few examples) are promising technologies that need to be advanced to achieve this goal.

Home care: Lifestyle and behavioural information would be especially valuable for early detection and monitoring of diseases. There are a variety of sources including social networks and mobile applications as well as the more conventionally used questionnaires and clinical assessment scales. Engaging society in the active collection of research data through social networks (crowd sourcing) should be exploited. Research on how to validate the quality and reliability of such data, and how to identify and correct for potential biases will be necessary.

Mobile: It is envisioned that, in the future, an increasing proportion of data for the Digital Patient will be captured automatically, through a variety of near patient devices and mobile applications. Wearable, or even transcutaneous and implantable, sensors measuring primary function will be used to monitor life-style, or disease and cure. These new sources of information need to be advanced in order to make them available and affordable on a large scale.

15 Albert Sorribas; Jaume March; Eberhard O Voit. Estimating age-related trends in cross-sectional studies using S-distributions. Statistics in medicine 2000;19(5):697-713.

16 A systems-theoretical framework for health and disease: Inflammation and preconditioning from an abstract modeling point of view. doi:10.1016/j.mbs.2008.09.005

With respect to the source of information, several important trends can be observed. These trends are depicted below and show that sources of information cover the complete area between point of care and point of life. The Digital Patient will need to make use of this full range by supporting research that advances both the medical devices that gather information as well as the IC systems required to transfer the data in a validated, certified and safe way to the Digital Patient resources.

New developments in acquisition methods – brief outlook

Secondary care: The most sophisticated data acquisition systems for morphological as well as functional information will be available and will need to be exploited optimally. In addition to on-going efforts to improve these systems in order to increase sensitivity and specificity, attention should be paid to IT-based systems that advance effective usage and data transfer. Software that integrates image analysis and physiological modelling needs to be developed and validated for use in model-based diagnosis and selection of intervention. ICT systems that carry this software should be developed for the basic, as well as the most sophisticated, imaging modalities that will be used in the hospitals and care systems of the future. New lab-on-a-chip based techniques including automated optical- or sensor-based data acquisition systems have to be developed to perform well- defined and standardised clinical tests.

Primary care: Due to advances in technology, automation of data acquisition, and miniaturisation of devices the primary care system will take over part of the diagnosis currently performed in the hospitals. For example, handheld ultrasound devices will enable imaging of anatomy and morphology and provide a means of patient stratification especially in the cardiovascular and oncology domains. Also, new near-patient sensor technology will allow the general practitioner to perform basic functional measurements such as ECG and EEG and to acquire data as input for the Digital Patient. To make this shift valuable for the Digital Patient, dedicated research and development activities as well as validation studies are needed.

Home care: Part of the shift of data acquisition will be extended to the home-care environment. High fidelity measurement and monitoring systems to measure patient behaviour and well-being in the home situation connected to personal as well as shared database systems, will provide a wealth of information available for the Digital Patient. Data from regular checkups or from continuous monitoring of e.g. the cardiovascular system, pulmonary function, the skeletomuscular system, and the renal system can be performed in a home environment under the condition that this is guided and validated by high-end technological systems taking care of automated data acquisition and transfer managed by secondary or primary care providers.

Mobile: Finally, new developments in portable and wearable sensors will enable the monitoring of physiological function at activity level as well as the collection of life-style data. Sensors based on flexible and stretchable chips form a promising technology in this field. Special attention needs to be paid to measurement inaccuracies due to motion artefacts either by developing sensors that are not sensitive to un-targeted motion influences or by data analysis systems that can identify and eliminate motion artefacts from the raw or processed data. Wireless connection with servers at home, or at sites of primary- and secondary-care providers, as well as local storage systems that can be read-out at these sites can be used to permanently store information for later use.

2.4 Acquisition methods

For each of the sources of information, different acquisition methods are either available, or need to be developed. We foresee on-going activities in the deployment of new technologies to optimise and extend acquisition methods. As previously mentioned, there will also be a shift to primary or even home-care acquisition systems. A compact outlook to new developments and the role for the Digital Patient is given following the trend stratification provided in the previous section.

2.5 Acquisition homologation

Similar information can be obtained from different systems or sites, different acquisition modalities and even different acquisition sources. A major challenge will be to come to a strategy and technology for homologation, i.e. a system that makes the value of specific information independent from the acquisition system, the acquisition method, or the acquisition source. To this end we need advanced calibration technologies.

If the information acquired for and provided to the Digital Patient is intended to be used not only for routine clinical use (in which clinicians interpret results from standard qualitative medical imaging sequences and functional measurements) but also for modeling purposes (in which the data is also used to quantify physical properties that serve as quantitative patient specific model input), then additional requirements regarding the accuracy and uncertainty of

the data are essential. To this end the methods used for the acquisition of information must be such that information is given as a standardised set of data and preferably provided with uncertainty ranges.

With homologation of acquisition we aim to introduce a methodology in which data acquisition methods and procedures are optimised for their use as well as made valuable, independent from the source and acquisition system. This does not necessarily mean that all acquisition systems and procedures need to be standardised. After all this would imply an unrealistic homogeneity of acquisition systems across different health care providers. What should be standardised are the protocols that define the conditions in which the data are acquired and the ways the data are represented. To enable modelers to use the data in a proper and justified way, acquisition systems should be calibrated and benchmarked against a Gold Standard. In addition the data that is acquired should be presented in a strictly defined format (see Data formatting section) and should contain information about uncertainty (see Data certification section). These uncertainty ranges then can be used by the models (but also by physicians when the data are used for diagnosis) to derive uncertainty of their predictions. On the other hand an optimum must be found in order not to interfere too much in daily clinical practice and to keep the imaging and measurement procedures safe and friendly for the patient.

2.6 Data certification

One of the main pitfalls of the Digital Patient framework is that it will be built on information that is unreliable or too unspecific due to various sources of uncertainty. This can be caused by several aspects such as poor definition of the contents of the data, too low precision and accuracy, fragmentation due to missing data. Technology and protocols need to be developed that guarantee well-calibrated acquisition systems, uncertainty analysis, and certification of information. Validation and certification of data will have to take into account requirements of the system in which the data is used.

Uncertainty of data mainly originates from incompleteness, imperfection, imprecision and ambiguity. For example, electronic health records (EHRs) may include missing field values, or parts of medical images may be occluded by foreign objects present during an examination. Imperfection is usually associated with different kinds of noise artefacts, and imprecision, with inherent limitations of the equipment used for data generation or acquisition. The diversity of medical devices, the parameter variations used in the data acquisition process, as well as the differences between the examined subjects, are also a common source of imprecision, since calibration errors can be introduced. Ambiguity usually appears with annotated data, as different kinds of terminologies or opinions from different experts may be partially overlapping or even contradictory. Considering the specific characteristics of different patients, uncertainty can also be introduced in the translation of population-level findings to individual patients. Therefore, uncertainty-aware technology and protocols need to be developed that guarantee well-calibrated, robust data acquisition systems, and certification of information. Both the validation and certification of data will have to take into account the target system requirements.

The prevalence of sparse or even missing data in EHRs is high, and it can seriously affect data analysis and lead to models of inadequate quality. Discarding cases with missing data can significantly limit the datasets and introduce bias, whereas most of the existing missing data imputation techniques can lead to model approximations that are valid under specific assumptions. In order to minimise the probability of missing information, systems that intelligently detect and restore missing information have to be developed. In this process, machine learning techniques should contribute to the development of models that learn from data and user responses so as to accurately predict missing or probably incorrect values (outliers); whereas user feedback can be promoted by time-efficient intelligent user interfaces.

Intelligent approaches to uncertainty handling should be supported by a sound mathematical framework enabling more intuitive, however formal, approximations of reality that inherently address information incompleteness. Such formal uncertainty-aware approximations should enable knowledge representation and reasoning that is tolerant of imprecision and imperfection. The generality of the mathematical framework should ensure applicability to any relevant modality and data type.

Multi-scale data is essential to the digital patient concept. Having such data, multi-scale data analysis and mining can be applied to extract knowledge about relations of data within and between different scales. This definitely resonates with the concepts developed in section 2.2 but it goes beyond this. The extracted knowledge should enable reasoning across scales to infer missing, or to validate existing, information. Since different scales are usually characterised by different levels of uncertainty, data validation can be based on the relations extracted from scales of lower uncertainty to infer information about scales of higher uncertainty, and thus progressively extend the analysis across all scales for which data are available. Such a data mining-based approach is also applicable for validation of data acquired from multiple modalities, since the information inferred from one modality can be used for the verification of a hypothesis made about another modality. Ultimately, this can lead to a self-validation process for automatic data quality enhancement.

Explicit knowledge from domain experts is necessary for the development of robust models from data, and extraction of implicit knowledge of high confidence with data mining techniques. However, due to time and cost limitations, annotated, ground truth, data are usually very limited. In order to increase the volume of such data, efficient, low-cost data annotation methods, such as semi-automatic and crowd sourcing approaches should be developed. Data annotation should be based on semantics, unambiguously representing domain knowledge, on robust opinion aggregation/decision fusion methods that will enable uncertainty reduction by considering the annotations of multiple experts, and on validation mechanisms for automatic assessment of the annotation quality. Methods to support semi-automatic annotation include accurate (unstructured) data segmentation, active learning, and ontology learning techniques.

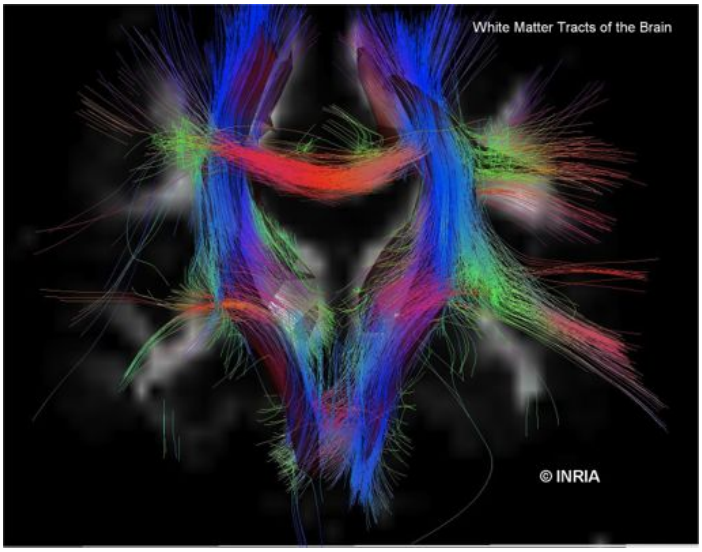
Content-based retrieval of multimodal data can contribute both in the data annotation and validation process by enabling comparisons between relevant data. In this context, efficient, less parametric alignment/registration techniques for automatic detection of spatiotemporal correspondences between data, similarity metrics that consider the multiple modalities and scales for effective retrieval, and indexing techniques for efficient high-dimensional data searches have to be developed.

Aspects to be considered in data provision systems:

- Quality of the data
- Legitimacy of data processing
- Ethical and anti-discriminatory measures
- Right of access
- Right to object to the processing data
- Confidentiality
- Security of processing
- Procedures for the notification of processing to supervisory authorities
- Other legal aspects.

2.7 Data provision

Data needs to be provided to several subsystems of the Digital Patient framework. Information management systems, modelling systems, direct user interface systems, and translational research activities will require different ways of data provision. Through a close collaboration between these different domains, transparent and secure ways of data transfer must be defined and developed. A brief list of relevant aspects to be considered in the development of data provision systems is shown below.



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Data protection and privacy issues will be formally treated under the legal environment of each country where the research is taking place. For example in EU countries, the application of Directives as 95/46/EC (Data Protection Directive) will guarantee a uniform approach towards these issues. One of the purposes of these European Directives is to ensure a common standard for data processing across Europe so that the transfer of personal data can take place between European countries in an environment protective of fundamental rights and freedoms, in particular privacy.

Depending on the legal environment, additional information will be provided to the appropriate authority with a detailed description of the proposed data collection (and their usage) and the methodology that will be employed for collecting, using and storing of personal data.

2.7.1 Data (pre-)processing

Biomedical data processing is a crucial aspect for accomplishment of the objectives proposed in the Digital Patient framework. The main purpose of data processing methods is to extract quantitative and objective information from all the available and relevant sources of biomedical data, so as to improve our knowledge on the system under study and provide valuable diagnostic and therapeutic markers. The information obtained from these analyses is also of primary

importance for the creation and validation of patient-specific models and, thus, for the Digital Patient framework.

The field of biomedical data processing has significantly evolved during the last decades and a wide variety of methods have been proposed in the literature. However, the appropriate processing and analysis of biomedical data remains a difficult task and a number of specific research challenges remain to be overcome.

As stated above, biomedical data acquisition is often performed asynchronously, in noisy and non-stationary conditions. Different pre-processing methods, including filtering, artifact removal, and registration of data from different sources have been proposed to improve the signal-to-noise ratio, and constitute a fundamental basis for further analysis. Biomedical data are currently collected from a variety of heterogeneous observation modalities (signals, images, textual data...), carrying information at different spatial and/or temporal scales. Data fusion and data association methods have been shown to be useful for the combined processing of these heterogeneous modalities, but most current developments are still problem-specific. Moreover, although some multi-resolution processing methods, such as wavelet transforms, filter banks, pyramid methods, etc. have been proposed and applied to the biomedical field, there is still a lack of methodological tools to process data obtained at different observation scales in an integrative manner.

Another major problem is related to the fact that data acquired from living systems represent an indirect measurement of the phenomena of interest and carry a mixture of activities from different, intertwined processes (sources) and regulatory mechanisms. Specific source separation methods have been recently proposed for biomedical data, and this field is in active development. However, discriminating the useful from the useless sources in these cases is still an open problem, particularly when the number of sources exceeds the number of observations, and in the presence of the significant intra- and inter-patient variability, which is a characteristic of biomedical data. Future development of these processing methods may have a major impact on improving the observability of living systems and, thus, the identifiability of biological or physiological models.

A common limitation of most current biomedical data processing methods is that they are based on unrealistic, generic underlying models and on strong hypotheses about the statistical properties of the data that are difficult to meet in real applications. Only a minority of the approaches is based on the integration of explicit biological or physiological *a priori* knowledge. All the above-mentioned challenges underline the profound interaction that has yet to be developed between the biomedical data processing and modeling communities. On the one hand, biomedical data processing is mandatory for the creation and validation of multi-scale models, as well as for parameter identification and model personalization. On the other hand, these models represent one of the most appropriate ways to integrate more realistic

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a priori knowledge into the data processing methods. The development of these interactions is essential to conduct the concepts of the Digital Patient to the clinical field.

Finally, a number of generic challenges that have been mentioned elsewhere in this document have a direct impact on biomedical data processing. For instance, the need for advanced computer and storage infrastructures, and for collaborative research tools. The Digital Patient would be the ideal framework for the development and application of these interdisciplinary challenges.

2.7.2 Data formatting

We recognise that the data that constitute the basis of the information to be generated can be of different forms and will require different ways of formatting as to enable easy assessment as well as possibilities to search and visualise specific entities.

Different types of data can be distinguished and appropriate formats need to be defined in order to capture these data including (if applicable) their uncertainty and annotation. The format on which information is captured before it is provided to the Digital Patient must be such that is unambiguously comprises all information that is gathered on the one hand and allows for data validation (see section on Data certification) on the other hand. A brief description is provided below.

Types of data of importance:

- Narrative, textual data e.g. from anamnesis and textual recordings of physical examinations and functional tests
- Numerical data/ parameters stored in predefined data-

base formats e.g. sequences of blood pressure recordings combined measurements of different type
- Results of laboratory tests, vital signs, recorded signals
- Images from different modalities stored e.g. in DICOM format. These can be photographs, videos, drawings, 4D (3D space + time) etc.

The format used to temporarily store the data before they are provided as input for the Digital Patient can be different from the format used in the Digital Patient. However, a one-to-one two-way exchange without data loss should be the aim.

Concluding recommendations

The generation, standardisation, validation, integration and homologation of data have been identified by the wider VPH community to be of utmost importance for realising the Digital Patient vision. The following main application areas require targeted support:

- Construction and validation of data-driven prediction models of clear biomedical relevance
- Application of data-driven prediction models within primary and secondary healthcare
- Construction and validation of causal and predictive models of clear biomedical relevance
- Application of causal models within primary and secondary healthcare
- Multidimensional phenotypic data analysis to uncover new important patterns that can serve as inspiration source for statistical and causal models

Research and innovation should focus on:

1. Exploration of suitable existing and possible new sources of information (see section 2.3)

- The Digital Patient will have to adapt to current trends, where data acquisition will move from the secondary care (hospitals) to the primary care (general practitioner) and home situation. New acquisition methods include internet communities, for example. As a consequence acquisition devices and technological tools must be prepared for this
- The Digital Patient will have to make use of longitudinal data (multi scale in time); both across the disease time-course and the life-span
- The Digital Patient will have to collect and extract knowledge from clinical data of different types, and deal with multiscale issues of biological complexity: molecules to cell, to tissues and organs including organisation, information, communication (signalling)
- Data and information on comorbidities, family disease history and lifestyle (living conditions, nutritions, habits, etc.) will have to be collected, analysed, datasets reduced, etc to be used in predictive models
- Where the technology is not mature for clinical deployment, the Digital Patient will complement the patient-specific data with estimates of the missing information from atlases, etc.

2. Development and adoption of acquisition methods and technology to determine genotype and measure high level phenotypes (see section 2.4)

- The anatomical data will be obtained from next generation image modalities such as MRI, CT and US (ultrasound).
- New imaging and sensing emerging from technologies will be needed where the acquisition is conducted in more physiological conditions (standing, moving, exercising, etc.)
- New (wearable, multimodal) sensors and sensor data analysis will be used to obtain functional data, including acquisition during daily life (point of life).
- New technology such as lab-on-a-chip devices will be used to obtain biomarker and gene-expression data.

3. Development and homologation of next generation acquisition methods (see section 2.5)

- Data should be independent of the acquisition system, the acquisition method and the acquisition source

4. Exploitation and initiation of new developments in data verification (see section 2.6)

- Data should be quantitative, validated, and include information about quality and uncertainty in order to predict uncertainty of the model predictions and medical decisions that are based on these data

5. Exploitation and initiation of new developments in data formatting, data processing to enable enhanced data provision (see section 2.7)

- Advanced dedicated ICT solutions are needed preferably to automatically collect and format the data and to provide it to the Digital Patient. Patient consent on the level of usage of the data must be included. This includes de-noising and dimensionality reduction of the raw data and of the extracted feature space.
- Systems that integrate all kinds of multimodal information and visualise it in a clever way should be developed to provide real time feedback on quality and validity of data.
- Data must be formatted in a predefined standardised and certified way in order to make it available for the Digital Patient for later sharing (provided patient consent about the level usage is embedded) for research purposes.

3. Biomedical information management

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3.1 Overall introduction

Biomedical information[1], i.e. data, is crucial to biomedical research, science in general and also increasingly in the medical practice, as it forms the basis for good scientific decisions, wise management and use of resources, informed decision-making, and ultimately high-quality and cost-effective health care practice (from prevention to treatment and follow-up). Whereas the mere acquisition of biomedical data has become relatively trivial and affordable, the management of these data remains a daunting challenge, despite decades of research. The likely reason for the lack of breakthrough is that biomedical information management is a complex multifaceted problem, whose resolution ultimately requires:

1. the integration of novel individual solutions into a framework that is robust and safe yet still flexible enough to accommodate evolving needs,

2. the adoption of novel tools by the scientific community and the entire community of end users, and

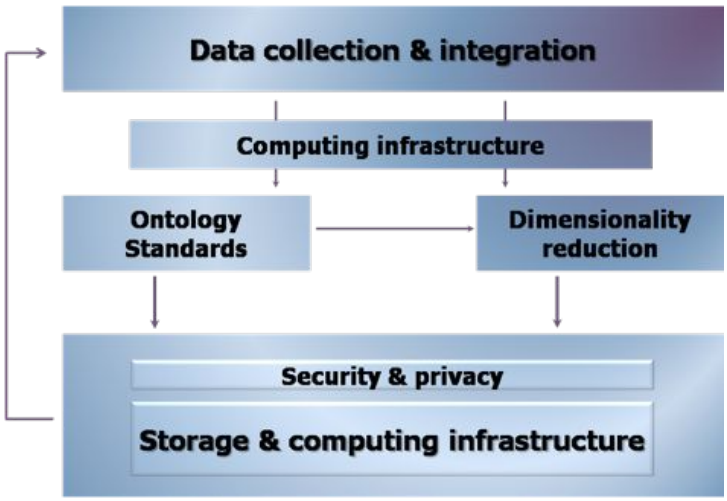
3. a paradigm shift within the scientific and the broader community such that data are gradually considered as a public good.

The most challenging facets of biomedical information management are:

- The collection[2] and the sharing of data: tools and incentives are required to facilitate and encourage individual groups, teams or consortia to share their data with the rest of the scientific and medical community
- The standardization of data collection and the question of ontology: tools and frameworks have to be established and developed to align existing ontologies and incentives have to be identified to cultivate a concept of unified ontology
- Dimensionality reduction: methodologies have to be improved to deal efficiently with the heterogeneity and the complex structure of available data, and with differences in origin, quality and ontologies
- The question of security and privacy: frameworks are required to insure data protection, safety, cautious usage and exchange, anonymity during exchange, retrieval, usage, and in storage
- The question of computer and storage infrastructure: infrastructure is needed to store enormous amounts of data that simultaneously need to remain retrievable rapidly and from everywhere

> “We have to find ways to better inform patients about the DP – this will increase their motivation to take part in trials for DP technology validation”
>
> Norbert Graf , Professor, Department of Paediatric Oncology and Haematology, University of Saarland

These facets (see Figure below) are interdependent (e.g., dimensionality reduction requires high-end computer infrastructure) and interact to render biomedical information management extremely exigent. Identifying these interactions and dependencies is a challenge *per se*, but is important as all fields are directly or indirectly contingent on each other. The necessity for powerful computing infrastructures is omnipresent



Flowchart of Biomedical Information Management: The necessity for powerful computing infrastructures is omnipresent

The following sections focus on challenges in biomedical information management.

3.2 Data collection and sharing

3.2.1 Data collection: a common need

In recent decades the amount of data acquired, analyzed, and stored has increased enormously due to successful developments in data generation methods, computational simulation and modeling techniques, and communication technologies.[3]

1 The notion of biomedical information encompasses both the “raw” data and the information that can be extracted and/or reconstructed from this data (cf. chapter 2) using various data-processing modalities. This chapter focuses primarily on the “raw” data, thereby leaving out certain challenges associated with the management of information stricto sensu (e.g., intellectual property) and including some aspects that do not readily or fully translate to the management of information.

2 Here and throughout this chapter, the “collection” means transfer, deposition, and integration as opposed to generation or acquisition, which is the focus of Chapter 2

3 M Baker, “Quantitative data: learning to share”, Nature Methods, 2012, 9, 39–41.

As science becomes increasingly data intensive and collaborative, data collection and sharing become increasingly important for the rapid translation of research results into knowledge, protocols, products, and services to improve human health. The sharing and reuse of primary research datasets has the potential to increase research efficiency and quality: data can be re-used to explore related or new hypotheses, particularly when combined with other available datasets, leading to new knowledge discovery. Data sharing is becoming even more crucial in the Virtual Physiological Human (VPH)[4] community where the integrative research approach requires the fusion of knowledge coming from different tissues and organs at different scales (see Chapter 2).

Every hospital and research laboratory in the world has a wealth of biomedical data safely locked up, which, if shared with other experts, could dramatically improve basic and applied research as well as clinical practice, and considerably accelerate the development of biomedical technologies. However, data sharing includes not only the deposition and preservation of data (c.f., 3.3) but also the provisioning of suitable access for their use and re-use, and consensus tools for their processing.

For many years, the data-repository problem has been mainly governed by the genomics data-sharing needs, but it is now beginning to receive attention across all medical and biomedical fields. This is demonstrated by the larger space and relevance that data sharing-related topics are gaining in the literature (e.g., the special issue of Nature[5] and Science[6,7]; the increasing number of papers with 'data sharing' as the keyword (resulting in more than 700 references on PubMed); and from the support for data sharing given by funding agencies such as the National Institute of Health[8] and by the most recent EC-funded VPH Calls for Proposals.

3.2.2 Data sharing: an open problem

While the need for data sharing in biomedical research and health care is undisputed, users are still reluctant to share data even if a number of software solutions have recently become available[9] world-wide. Based on the literature[10,11], the reasons for this hesitation to share even a limited quantity of data can be summarised as follows:

1. Fear of not being able to publish work derived from the data, associated with proper attribution of the work, and licensing issues;

2. Privacy and ethics concerns for data involving patients' information;

3. Uncertainty about whether the data are securely stored on a remote server or grid/cloud infrastructure;

4. Limited time, resources, and/or institutional authorization to set up and manage the IT resources needed to offer and preserve the data;

5. Uncertainty about the benefits of making the data available;

6. Limited time and resources to recover from the internal ICT services, manage, and properly describe and annotate the data to be shared;

7. Low user-friendliness of lack of access to the currently available data management systems.

Additionally, the proliferation of many different and unconnected software systems for data sharing is making the retrieval of already shared resources and the identification of the best location to store the data also very difficult for users who are potentially willing to share and re-use data.

3.2.3 Addressing the data sharing challenges

Once data have been generated or acquired according to appropriate standards and guidelines, which is a difficulty *per se* (cf. Chapter 2), the main challenges are to incentivise data owners to share their data and prompt them to use appropriate and standardised sharing tools that may vary depending on whether the data are required for modeling activities, direct user interface systems, or translational research activities for instance.

For the purpose of data sharing, data can be classified into four categories:

- Data generated by the patients themselves
- Data acquired in the clinic (formal care)
- Data generated by devices (e.g., medical imaging data)
- Research-based data (e.g., results of simulations).

Each of these data categories raises different issues and challenges in terms of data collection, ethical and privacy issues, and technical issues associated with data sharing.

4 http://en.wikipedia.org/wiki/Virtual_Physiological_Human
5 vol. 461, issue no. 7261, September 2009
6 http://www.sciencemag.org/site/special/data/, February 2011
7 http://sciencecareers.sciencemag.org/career_magazine/previous_issues/articles/2011_02_11/caredit.a1100014, February 2011
8 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html
9 N Pearce, AH Smith, "Data sharing: not as simple as it seems", Environmental Health 2011, 10:107.
10 http://www.plosone.org/article/info:doi/10.1371/journal.pone.0021101
11 http://www.plosone.org/article/info:doi/10.1371/journal.pone.0018657

Some urgent challenges to be tackled in the future are:

1. Understand the incentives/disincentives to data sharing for each four data categories, based on the definition and analysis of specific user cases and the application of a multidisciplinary approach;

2. Define policies and strategies to guide the data collection and sharing;

3. Develop case/pilot studies with the aim to verify the appropriateness of the proposed guidelines and policies in specific contexts (policies and strategies for data sharing need to accommodate the various target groups within the community of end-users);

4. Develop new software tools or integrate/refine existing ones to support the collection (i.e., deposition and storage) of the different data categories

3.3 Ontology and standards

In an ideal world, we merge different sources of standardised and validated information (cf. Chapter 2) and access well integrated and consolidated data, as if they constituted a unique semantically homogeneous database. Despite the considerable effort invested in the field already, the reality is different and besides well-established differences in data acquisition protocols, which call for the standardization of acquisition and representation methods (cf. Chapter 2), management systems are not interoperable either (whether technically or semantically). Three main reasons for this are: a) data structures used in local systems differ, b) semantics differ across databases, and c) no consensus has been reached about whether data should be stored centrally to facilitate a common access, or whether they should be left where they are generated and simply accessed in part of in their entirety when needed. The solution might be somewhere in between both extremes, but the question remains as to where exactly.

A current trend is to extract data from Electronic Health Record (EHR) systems, which is often done via explicit exports, and store them for specific uses in central databases such as the cancer or the diabetes register. Whereas such centralised databases provide some evident advantages, one disadvantage is that duplicated data are unnecessarily generated and are ultimately not scalable. On the other hand duplicates might serve to generate dedicated sets of pre-collected data, which in turn can make data mining and exploitation much simpler.

Identifying where to draw the line between centralization and decentralization requires more research, which needs to cover additional aspects, such as computing and storage infrastructure (c.f., section 3.4). Further factors that will influence the conclusions are performance, scalability, security (for *ad hoc* access), availability, redundancy, ownership, semantic consolidation, data size, persistence, and use cases (healthcare, research, policy making). These aspects become even more relevant once we look at data as coming from a multitude of various sources. If the solution is to be found somewhere in the middle between centralization and federation, a system must at least be able to work in a federated manner, because a central database (e.g. a cancer registry) can be seen as one among other federated data sources but the opposite is not true.

Whether federated or centralised or any mix of these, there is still the problem of semantic interoperability between data sets. Do we need one single standard, formalizing concepts and relations? At first glance this sounds appealing, but reality is different here also and the decades of research on this matter have not yet yielded any clear answer. The time may have come to radically change approaches, but it remains unclear whether the 'politics' behind standardization efforts can be overcome. It may be worthwhile to keep trying to establish the 'ultimate' ontology, as such an ontology could serve as a reference or consistency canvas. Yet such endeavour should not stop the development of *ad hoc* and useable ontologies.

An interesting parallelism can be drawn between the problem of data collection and that of standards: unique and central versus multiple and distributed. Research needs to be done on how we can align terminologies and ontologies. This may be more relevant than trying to build a unique standard, in particular because many standards (terminologies, taxonomies, ontologies) are designed with a specific use in mind and are optimised for what they are designed for, which causes generic standards to lack specificity. Urgent challenges to address include identifying what the right mix is between making 1) a unique all encompassing ontology 2) a set of common ontologies, and 3) very specific ad hoc ontologies and establish how they can be aligned. Automatic ontology mediation is a particularly demanding research topic that would push interoperability forward. Some of the ontologies can be designed by other communities (foaf, dc, etc.), which would increase the likelihood of interoperability with both communities and data sources outside the pure healthcare (social media, financial, authorities, etc.). An additional open question is that of the re-use of existing ontologies. Copying such ontologies in "yet another ontology" is most likely not the right answer. An alternative is dynamic linking to existent ontologies. But how to do this remains unclear. These problems look very similar to the duplication of data in the specific registries, mentioned above. Also the associated difficulties are similar: ownership, maintenance, scalability, etc.

The conclusion is that there is a need for research on the

paradigm of data collection and semantic harmonization itself: we need to find the ideal mix between unique and central approaches versus *ad hoc* and federated approaches, for both access to data and semantics.

3.4 Dimensionality reduction

Regardless of whether data comes from body sensors monitoring a patient in his daily life, from heterogeneous clinical applications and medical devices generating cumulative lifelong patient record or even from populations of patients for research purposes, we need to better face the questions of a) how to extract the very subset of information necessary for a particular application and ignore the rest, and b) how to reduce the dimensionality of big data to a set of information helping the end user, be it a clinician or a research fellow.

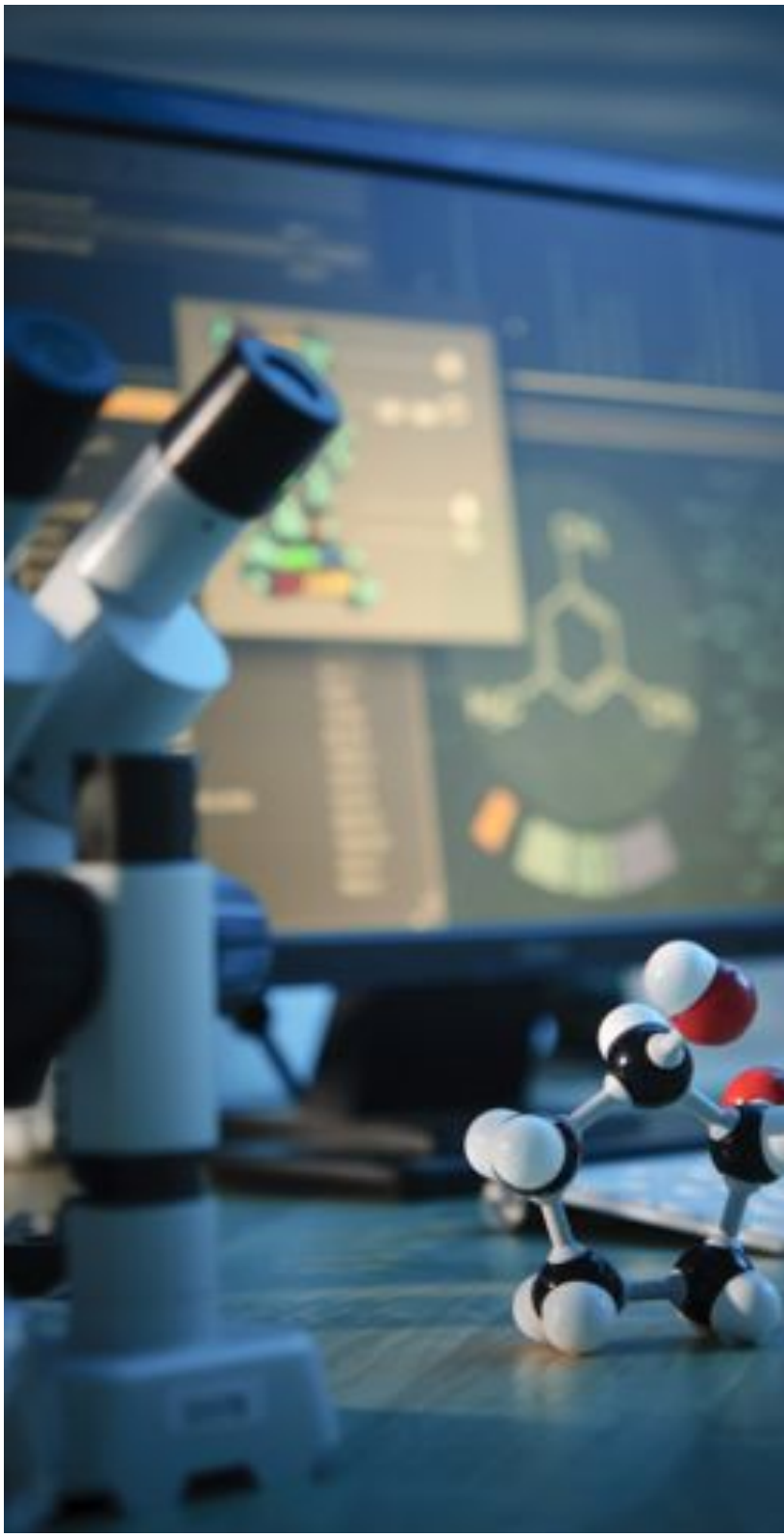
The answer lies in the application of various techniques of data mining and knowledge discovery. Data need to be analysed from many different points of view, they need to be categorised, and relationships between variables have to be found. Such approach enables the finding of similarities and rules derived from data clustering and associations, the detection of anomalies and data summarization or regression.

Whereas the tools available for data mining are already well-tailored to achieve efficient dimensionality reduction in other fields, they are insufficient in the biomedical field. This has at least two reasons. First, data are collected from various sources without originally being created for dimensionality reduction and various data types need to be merged. Human-entered data for instance needs to be combined with machine-generated data, free text with structured data. Second, quality and credibility of data sources vary. Thus, dimensionality reduction has to account for the origin of the data, the context of their creation, the level of persistence in their collection, and the particularities of their representation, which calls for very particular methods.

Results of data analysis serve as inputs for simulation models, decision support, prediction making, optimal care proposals, treatment evaluation, specific data visualization, and many more "knowledge-intensive" tasks.

The challenges to face in terms of dimensionality reduction include:

- Description of problem: How to set parameters describing the problem well enough that the expected result of an analysis can be obtained?
- Evaluation of data: How to filter data using the parameters?



- Cleaning of data: How to identify erroneous or faulty data and ignore them?
- Interpretation of data: How to understand data in order to analyse them and how to subsequently understand the analysis?
- Querying data: How to use *ad hoc* queries to filter data

according to a user's current needs?

- Privacy (anonymisation): How to use all necessary data without breaking accessibility rules?
- Relation to future use: Is it possible to create generic "reduced" sets for multiple usage or has analysis to be done specifically for each application?
- Secondary data usage: Is the data usable for research purposes?
- Short-time versus long-term goals: How do we move on from the mining of data that are already well defined and homogeneous to extensive analysis of huge hybrid data sets using generic methods.

Dimensionality reduction is an interdependent problem. The direct link to data collection and integration has already been mentioned. Dimensionality reduction needs to respect standards of data structure and content as well as common terminologies and ontologies to enable data interoperability. Different types of data pre-processing (including natural language processing) for analysis may be applied. Utilisation of different computing infrastructure (centralised or decentralised) is inevitable. And information security and privacy are always in question. As in other cases, progress in dimensionality reduction depends on that achieved on other key topics, including computer infrastructure.

The clinical challenges associated with osteoporosis illustrate the challenges described in this chapter and provide several tasks to apply the approach:

To model personalised fracture risk various information is necessary, including current bone parameters values and other indicators of a patient's condition (e.g., muscle volume, training, etc) and of his/her environment. This information should be extracted from a patient's clinical documentation (e.g. EHR), which may not necessarily have been collected in the context of the current incident or may have been provided by other clinical specialists, and from home monitoring systems, all of which provide intrinsically heterogeneous and numerous data. Besides being voluminous and having to be stored, shared by the person collecting them, and understood by clinicians across multiple disciplines, these data have to be accessible rapidly and reduced to the subset of data that is useful for personalised fracture modelling. This information might also need to be compared to information from other individuals, which brings up the necessity for safety and privacy rules.

Data intensive research in this area and the building of extensive prevention programs require quantitative, accurate, properly annotated, and properly collected data about populations.

3.5 Infrastructure security and privacy

IT infrastructures are evolving from closed systems to open systems connected to the Internet, connections between the physical and the cyber worlds bring about a Cyber-physical system of systems that is itself connected to the Internet, and new communication devices with better interoperability and new protocols are emerging daily. Whereas changes in the IT infrastructure landscape are happening at bewildering speed, a lot of research is still needed to ensure secure interoperability among IT systems, particularly the ones that manage sensitive data. The sharing of biomedical information and knowledge, its promotion, and our success in making eHealth systems more efficient and economical are contingent on our ability to improve the security of our systems' interoperability (including semantic interoperability), integration, and interconnectivity. This includes the adoption of well-established data protection directives (e.g., Directive 95.94 EC) concentrating on questions related to data quality, the legitimacy of data processing, ethical and anti-discriminatory measures, right of access, right to object the processing of data, confidentiality, security of processing, procedures for the notification of processing to supervisory authorities, and other legal aspects.

Besides the rapid evolution in the mere technicalities of IT infrastructure, the way we understand IT infrastructures and the businesses behind them are changing too. On the one hand, businesses are outsourcing their infrastructure and relying increasingly on virtualisation, which represents a lot of benefits in terms of costs savings, efficiency, and/or adaptation to the market. However, virtualised environments bring about new security- and privacy-associated challenges. On the other hand, the "everything-as-a-service" business model is gaining in popularity. In line with the trend towards customisation/personalisation, users ask for ways to combine services and tailor them to their individual needs. Services provided through the Internet are becoming increasingly diverse, the delivery of business software as a service (SaaS) is gaining in prevalence, and cheap cloud and composed services are driving the trend

towards massive centralisation and interdependence, without however offering any kind of guarantee. Moving from yesterday's static services to the Internet services available in the near future, the need will grow for good-reputation service composers and providers that transparently mix-and-match service components depending on the availability, quality, and price of the individual services, and on the reputation of the security attributes. Consequently, future applications will consist of multiple services coming from many different providers. This increases uncertainty as to whether a particular service or service supplier will really offer the end-user the security claimed. Consequently, creating safe and trusted services without sacrificing the desired and required functionality, usability, performance, security, and cost efficiency is a great challenge. This is particularly true in the present dynamic environment in which threats and attacks are a daily reality. In this context, establishing how to guarantee the secure composition and execution of services, how to identify and characterise reliable service providers, and how to determine whether any service that provides enough security and privacy also fulfils the requirement associated with a particular application is a priority. In the absence of a widely accepted notion of online trust, more research is also required in developing trust anchors for users and reliable indicators of trust for business and governments.

Finally, changes also happen in the way "consumers" use the Internet. Increasingly more personal information is being uploaded to the Internet with the aim of socialising, even though sharing some of this information in cyberspace can hurt one's career and personal life. Even though people's awareness of privacy issues has increased, the general trend is towards lower levels of concern. The significant changes in attitude observed among end-users raise interesting questions about the role of privacy-enhancing technologies and privacy-related research in the future. As individuals experiment with different personas or are forced to create separate profiles for different websites and providers of online services, the notion of personal data privacy on the Internet comes with a phenomenal proliferation of digital identities. From a privacy point of view, there are pros and cons for both multiple separate identities and a unique online identity. The challenge for the future is to develop identity management systems that give individuals plenty of control over access to private information, while remaining useful online. Addressing this challenge requires us to answer the questions of how identity management is to be achieved on the multitude of devices that people use on a day-to-day basis; how digital identities can be linked to individual people, if this is desired in the first place; or how trust can be established between service providers who have no prior business relationship and services users. These questions are fundamental to the challenge of developing suitable identity management for the future Internet.

3.6 Computing infrastructure and storage infrastructure

Digitalisation of clinical data is creating an unprecedented challenge in ICT, which is exacerbated by the heterogeneity and complexity of i) the actors (end-users, data providers, modellers, etc.), ii) the data quantity, quality, and origins, and iii) the methods to (pre)process, analyse, and model data. Hence, computing infrastructure plays a key role by enabling bridges between all actors of the value chain involved in bringing the digital patient model into the clinic. The aim of this section is to describe how this transition to the clinic could be achieved by identifying clear deliverables from the conception to the deployment and scale up of the solutions. It further highlights possible bridges to existing projects (both national and European) while acknowledging the fact that any developed solution should be an acceptable compromise between the needs and the cultural habits of a given community and the cost, the risk, and the innovation associated with it (centralised versus decentralised approaches, open-source, etc.).

3.6.1 Software for 'intelligent' computation distribution management

In many sectors (e.g. energy), rationally allocating resources according to the task to perform, the end-user needs, the capacity of the network, and the costs is critical. Resource allocation conditions the feasibility of complex task managements at controlled costs in a heterogeneous landscape (e.g., when different sources of energy are available or the capacity of production and peak demand vary). Allocation of energy resources should allow the maximization the system's utility to the user in terms of CPU time, network bandwidth, and energy while taking into account that the workload schedule is not known in advance but approximated by a probability distribution.

Data management and access to computational structures for the Digital Patient are quite comparable to existing services in the energy sector. Both deal with massive heterogeneous and complex data and rely on computational infrastructures for the delivery of a transparent, easy, and secure access to end-users. MDs, biologists, or patients do not want to know how this workflow management is performed, but they want to have real time access to pathology models, recommendation for treatment, and personal medical records without choosing how the calculation is distributed, how the data is accessed or where it is stored.

This active field of research is constrained by many bottlenecks, including the low level of interoperability addressed in 3.2 and the necessity to bridge technologies (e.g., EU projects like EDGI, DEISA, HPC Europa projects). Other constraints, such as the fact that digitalised medicine is a new

> New, innovative storage and computing services that enable data intensive analysis of biomedical big data are needed."
>
> Simona Cohen, IBM Research

growing field and that actors, needs (academics and industrials), and usages are heterogeneous, are more specific to the life science business models and the scientific communities requiring the data.

Achieving progress in computing and storage infrastructure research implies transversal approaches including both health and ICT specialists. These approaches should take into account the projects already running, interface them, and for instance propose to generate a show case consisting of a European solution to health applications using high throughput medical data for clinical models and clinical help.

3.6.2 Access to computational infrastructure ecosystems in Europe

Clouds, supercomputers centres, supercomputer-based grids, cluster-based grids, and desktops grids constitute the pillars of the e-science infrastructure. All these pillars have their own advantages that create high value for end-users according to their specific needs. Nevertheless it is difficult to federate, build, and finance the porting of complex research applications, like the ones related to various fast-growing fields in health research and biology. Thus, these pillars are often separated from each other and cannot be used simultaneously by the end-user.

To facilitate the emergence of new ICT beneficial to medicine, the use of different computing resources for different types of computations is mandatory. To successfully encourage such behaviour, key European players operating or involved in proving European solutions need to become associated and collaborate with supercomputing centres, the grid or the cloud, and with medical and modelling communities. Such initiative should undoubtedly be built on existing projects to avoid redundancy and optimise cost and efforts.

3.6.3 Storage for Big Data

The ever-growing efficiency of medical devices, body sensors, and genomic sequencing machines creates a deluge of diagnostic imaging data, medical records, genomic data, and scientific publications, all of which need to be preserved for many years. Sound use of this data holds the potential to change the landscape of healthcare and cure Europe at reduced cost. To enable such a breakthrough, advanced new computing infrastructure is needed where storage for big data with offloaded functions plays a key role, as data warehouses are where the data resides most of its lifetime. Such pioneering scalable storage should allow easy sharing and exchange of the data (while maintaining security and confidentiality requirements, c.f. 3.3), support computing close to the data, including powerful analytics, and preserve the data for decades. The ENSURE EU[12] project is carrying out initial research on such advanced storage services extending the OpenStack object storage[13], which is an open source resource.

3.6.4 Computational storage services

Computational storage services utilise the concept of bringing the computation close to the data rather than moving the data out of the storage to the computer. This can be done through "storlets", which are novel computational modules that are executed within the storage. For example, storlets for biomedical analytics can reveal new insights; storlets for biomedical data compression can make data storage volume requirements tractable; storlets can increase security as access control, de-identification, obfuscation, data reduction, and encryption processes can be done close to the data before it leaves the storage premises. This consolidated platform for objects and computational processes executed close to the data adds flexibility to the storage infrastructure and extends its capabilities over time. It upgrades generic storage systems to a richer system optimised for the healthcare and life sciences domain.

3.6.5 Preservation-aware storage services

Regulations and ROI incentives require maintaining the biomedical data over long periods of time. For example, the pharmaceutical industry needs electronic data storage for 50 to 100 years or longer, X-rays are often stored for periods of 20+ years, whereas EU directives suggest a lifetime electronic health record (EHR). Preserving digital objects is more difficult than preserving analogue data as there are unforeseeable changes that will take place in servers, operating systems, data management products, applications, and even users. As the data is increasingly becoming "born-

12 http://ensure-fp7.eu
13 http://openstack.org

digital" and paperless, there is a need for preservation-aware storage that is able to adapt to changes over time, enables interpretation, and uses the complex biomedical objects for the far future.

3.7 Summary recommendations

In summary, we recommend the following main actions:

1. Develop patient-centred authorisation mechanisms that allow automatic requests for secondary use of clinical data after collection and anonymisation

2. Develop methods to compute k-anonymity[14] for anonymised secondary use databases of clinical data when combined with any other information available on the Internet

3. Strengthen the efforts to develop dynamic semantic mediation strategies that allow clinical specialists to participate in multicentric data collection with clinical data available in their research warehouses, employing easy-to-use procedures to define the semantic mapping between the local warehouse structure and the collection ontology

4. Develop automatic extraction of quantified phenotypical disease traits, and use these as similarity metrics to retrieve cases comparable to the one at hand from within the warehouse

5. Develop new innovative storage and computing services that enable data intensive analysis of biomedical big data preserved economically over the long-term

14 http://dataprivacylab.org/dataprivacy/projects/kanonymity/


Computational Storage
Privacy

4. Mathematical modelling for the Digital Patient

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4.1 Overall introduction

Medicine has evolved rapidly in the last 25 years. Nowadays, it uses novel data gathering technologies to enable large-scale collection of observational data on complex biomedical systems, enabled by data-mining in order to exploit population studies, which are the basis of evidence-based medicine. It is worth mentioning that there are recent technological breakthroughs in diagnostic and interventional imaging as well as a new generation of therapeutic devices; the first facilitates the creation of image-based models to further personalise patient models, while the second opens the possibility of exploring in parallel multiple treatments and their expected effects.

However, a new paradigm shift is about to occur: personalised medicine promises to revolutionise the practice of medicine, transform the global healthcare industry, and ultimately lead to longer and healthier lives. The Digital Patient is part of this new paradigm, grounded on the principle that it is possible to produce predictive, patient-specific mathematical models for personalised healthcare.

In many ways, modelling is able to complement data-mining, and the power of combining such approaches lies within leveraging their strengths for transforming observational data into knowledge. Building a model is a useful (and thrilling) scientific activity because it aims to reproduce the main features of a real system with the minimum number of parameters. The objective is to gain a better understanding of how each of the different components contributes to the overall process. In this manner, modelling in medicine, fed by clinical research data, should aim to support clinical decision-making systems, and ultimately help the clinician to provide improved prevention and screening, diagnosis, prognosis, and/or a prediction of response to treatment.

The development of *robust* patient-specific models, as they become available, will significantly advance prevention and treatment of disease. Although models in healthcare can potentially have many uses, there is an increasing urgency to address the prevention of chronic diseases through lifestyle improvements as the best path to a healthier population. For example, chronic diseases are overwhelming western countries' healthcare systems. Between 70% and 80% of Europe's healthcare costs are spent on chronic care, amounting for some €700bn annually.[1] Chronic diseases account for over 86% of deaths in the EU.[2,3] However, much of this disease burden is preventable, or may be delayed or diminished, through a combination of primary prevention measures, screening, and early intervention. While primary prevention focuses on healthy living, secondary prevention (early screening and diagnosis) and tertiary prevention (early intervention to slow the progression of diseases already identified) also play important roles in reducing the burden of chronic disease.[4]

Ideally, we would have a full understanding of all biological processes in both health and disease, as well as of the relationships between structure and function at all scales, and this complete knowledge would be represented usefully in a collection of inter-compatible mathematical models at all relevant scales, validated against experimental and clinical data, customizable for individual patients, and accessible through a convenient and interactive user interface for use by health professionals and patients. With this resource, one would be able to simulate diseases and pathologies and to explore patient-specific therapeutic intervention strategies, including evolution over time and realistic evaluation of prognosis. This is, of course, the long-term vision of the Digital Patient.

In reality, our understanding at all scales is only partial, and available data is incomplete, as explained in other chapters of this document. Nonetheless,

1. current knowledge of anatomy and physiology is extensive on many levels and much of it has already been successfully represented in mathematical models, and

2. relevant data is abundant, despite being incomplete and despite the many issues of standardisation, accessibility, and interoperability.

Given this state of affairs, this chapter focuses on the challenges that must be met for the constitution of the constellation of mathematical models that will underpin the Digital Patient. Here, we address the goal of "generalisation and wide use deployment of the concept of integrative modelling."[5] At the outset, we point out that the "Digital Patient" will certainly not be a unified, monolithic, all-encompassing mathematical model of the human body from gene to organism. Rather, it will consist of many sorts of models that will be invoked as needed, depending on the nature of the question at hand, the types of data available, and the degree of understanding of the subject under scrutiny. It is important to say that in this chapter we describe the overall picture with only a limited focus on the details; however, in order to address this, we have included numerous useful references for parts we could only touch upon because of space constraints. Lastly, we acknowledge that some aspects are up for debate, since the field is a rapidly

1 http://digitalresearch.eiu.com/extending-healthy-life-years/report/section/executive-summary
2 Doyle, O.M., Tsaneva-Atansaova, K., Harte, J., Tiffin, P.A., Tino, P., Díaz-Zuccarini, V. "Bridging Paradigms: Hybrid Mechanistic-Discriminative Predictive Models". IEEE Transactions in Biomedical Engineering, 60(3).
3 Meth-Cohn, D. "Extending Healthy Life Years in Europe – an Alternative Approach". Journal of Holistic Healthcare, 2012.
4 http://www.epha.org/a/5131
5 Hunter et al. 2013, Interface Focus 3:20130004

evolving one, with a wide range of contributions from many different disciplines. We would like to emphasise that what has been traded off in detail has been gained in richness of diversity, in the spirit of what is needed for the development of a Digital Patient.

Although clear boundaries among types of models are hard to define (which will facilitate the development of what will later be defined as "hybrid" modelling methodologies), this chapter will roughly demarcate two major modelling categories that will systematically appear throughout. This categorisation is not absolute, but rather delineates the terms of reference that are used when distinguishing between different types of models that embrace a large variety of modelling techniques and fit different purposes in the context of the Digital Patient:

Phenomenological models are *related to the empirical observations of a phenomenon*, where a phenomenon is understood as an observable fact or event. When considering how to achieve the realisation of the Digital Patient, these models occupy a central position whenever a quick means is needed to represent pathologies quantitatively for both basic science and practical applications.

Mechanistic models, on the other hand, *aim at reaching a better understanding of the mechanisms that underlie the behaviour of the various endpoints of the biomedical process*. Mechanistic models often investigate the molecular and cellular basis of biomedical processes through their physico-chemical properties. They are able to consider events at different orders of magnitude for both spatial scales (from intracellular to cell, tissue, and organ) and time scales (from the 10^{-14} s of the molecular interactions to the hours, months and years of the biomedical processes).

The diversity among the available models is clear, but their "integration" does not imply that they will all necessarily be interlinked. Further along in this chapter, we address several different pathologies and present modelling strategies for each of them. The models range from probabilistic, data-driven ("phenomenological") models with no "mechanistic" underpinning, to multi-scale, multi-physics models based on state-of-the-art understanding of the underlying anatomy and physiological mechanisms. However, while recognising that different communities favour one or the other approach, it would not serve the present purpose to focus on the relative advantages or disadvantages of "phenomenological" versus "mechanistic" modelling, since most models combine elements of both, and the real challenge lies in providing appropriate tools for quantitative exploration of a variety of clinical challenges. We will invoke both approaches, as appropriate, addressing the following key challenges to be faced for achievement of the integrated Digital Patient on the following topics:

- Selection of mathematical modelling approach
- Model personalisation in the face of multiscale complexity
- Impact of data quality on model personalisation
- Coping with complexity
- Formalisation and generalisation of model testing and validation strategies
- Translation and clinical utilisation of models

4.2 Key challenges

4.2.1 Selection of mathematical modelling approach

To realise the Digital Patient, a first scientific challenge that needs to be addressed is the selection of the most adequate mathematical modelling approach. There is not a unique way of creating a model and many aspects determine this selection, such as model purpose and/or data availability. In a broad sense, the choice might be between phenomenological and mechanistic mathematical models, but a recurrent topic when modelling any disease is the strong link and dependency between these two modelling approaches. One example is the case of complex multi-omics structured data (embracing genotype information, metabolomics datasets, and subclinical and clinical phenotypes), which would use both data assimilation and novel mechanistic methodologies to elucidate pathological mechanisms.

Another particularly relevant example is faced when dealing with *the challenge of comorbidities*. Comorbidity is the term used to address diseases, often chronic ones, co-occur-

ring in the same individual; i.e. an illness may develop, but health conditions also depend on another simultaneously occurring pathological process elsewhere, like for example inflammation, diabetes, or respiratory problems. As a result of this complexity, it is likely that modellers will often find themselves in between the two types of modelling methodologies, since there is no clear practical separation between phenomenological and mechanistic methods.

Finally, efforts from the modelling community are needed to use existing VPH reference ontologies to annotate the resulting models and to make them available through VPH common model repositories. This formalisation will enable interoperability between models in general. Examples of initiatives pursuing this objective are the two EU-funded VPH projects VPH-Share[6] and p-medicine[7]. These two projects are collaborating together and seeking complementarities. VPH-Share is working to provide the essential services and computational infrastructure for the sharing of clinical and research data and tools, facilitating the construction and operation of new VPH workflows, and collaborations between the members of the VPH community. In this project, evaluating the effectiveness and fitness-for-purpose of the infostructure and developing a thorough exploitation strategy are key activities to create confidence and engage the communities. P-medicine intends to go from data sharing and integration via VPH models to personalised medicine. The emphasis is on formulating an open, modular framework of tools and services, so that p-medicine can be adopted gradually, including efficient secure sharing and handling of large personalised data sets, enabling demanding Virtual Physiological Human (VPH) multiscale simulations (e.g., *in silico* oncology), building standards-compliant tools and models for VPH research, drawing on the VPH Toolkit[8,9] and providing tools for large-scale, privacy-preserving data and literature mining, a key component of VPH research.

An important consideration valid for mechanistic and phenomenological models is that biomedical systems characterisation is more rationally and robustly addressed when driven by a comprehensive, rather than selective, use of all the available information, provided the varying degree of accuracy of the components of the evidence base is correctly recognised.

Among the wealth of methods available for phenomenological modelling, Bayesian techniques for multi-parameter evidence synthesis have demonstrated a rational and exhaustive use of the whole body of information available for decision models.[10] Recently, methodologies resulting in a combination of Bayesian inference for partially observed Markov process models and nonlinear dynamical systems approaches have also been developed.[11]

Other techniques encompass formal methods. It is worth noting that novel concepts and terminologies originally developed in the theoretical computer science domain (for example executable models, expressivity, abstraction, statistical model checking, stabilization, reachability analysis, formal verification), which are scarcely known by other modelling communities (for example engineers and physicists), are providing important insights and tools for modelling and analysing complex biological systems. The key concept here is the distinction between the mathematical model and the computational model. The two terms are tightly related, since the computational model is a mathematical model executed by a computer.

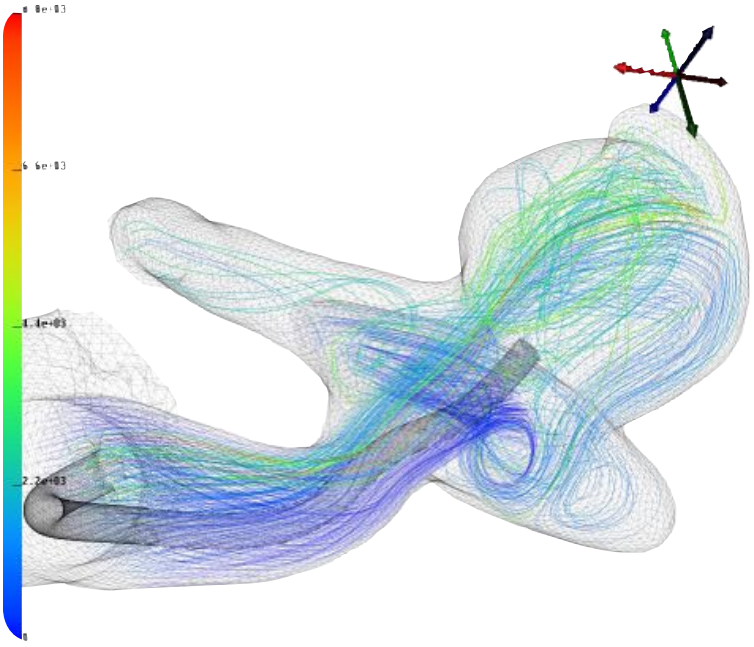
Other approaches (including process algebra, hybrid systems, Petri nets, state-charts) provide a battery of methodologies.[12] One example is the verification of a property representing a condition of illness or the effect of a drug; we could imagine that at the clinical level, computer-aided therapies and treatments will develop into intervention

6 http://www.vph-share.eu
7 http://www.p-medicine.eu
8 http://toolkit.vph-noe.eu
9 http://www.computationaloncology.org

10 see an example in Ades AE, Welton NJ, Caldwell D, Price M, Goubar A, Lu G. Multiparameter evidence synthesis in epidemiology and medical decision-making. J Health Serv Res Policy. 2008 Suppl 3:12-22
11 EDWARD L. IONIDES, ANINDYA BHADRA, YVES ATCHADÉ AND AARON KING Iterated Filtering, The Annals of Statistics 2011, Vol. 39, No. 3, 1776–1802
12 Fisher J, Henzinger TA (2007) Executable cell biology. Nat Biotechnol 25: 1239-1249; Bartocci E, Corradini F, Di Berardini M, Merelli E, Tesei L (2010) Shape calculus. a spatial mobile calculus for 3 d shapes. Scientific Annals of Computer Science 20: 2010; Heiner M, Gilbert D, Donaldson R (2008) Petri nets for systems and synthetic biology. In: SFM. Springer, number 5016 in Lecture Notes in Computer Science, pp. 215-264; Setty Y, Cohen IR, Dor Y, Harel D (2008) Four-dimensional realistic modeling of pancreatic organogenesis. Proc Natl Acad Sci USA 105: 20374-20379; Bartocci E, Cherry EM, Glimm J, Grosu R, Smolka SA, et al. (2011) Toward real-time simulation of cardiac dynamics. In: Proceedings of the 9th International Conference on Computational Methods in Systems Biology. New York, NY, USA: ACM, CMSB '11, pp. 103-112. doi: 10.1145/2037509.2037525. URL http://doi.acm.org/10.1145/2037509.2037525

strategies undertaken under acute disease conditions or due to external factors (like infections) to contrast cascade effects. In non-acute states, predictive inference will propose prevention plans for comorbidity management.

Additional methodologies are based on dynamical systems theory, particularly chaos and fractals.[13] In healthy tissue, a full repertoire of receptors and ion channels respond to mechanical micro-stress events and generate small highly variable noise in a variety of physiological signals such as heartbeat, blood pressure, gait, and nephrons[14] etc. In disease or aging conditions, we commonly observe a reduction of such variability and more smoothness. This difference in biological signals has been used to extract useful information about the state of the patients and to create diagnostic tests. The mathematical characteristics of these signals resemble those found in deterministic chaos, fractals, and self-organizing emergent properties of complex dissipative systems; in many cases, the physiological signals are studied by means of wavelets. Cardiovascular physiological signals provide a rich literature of fractal and/or chaotic



Source: Eurobioimaging

behaviour, particularly related to the His-Purkinje network of the heart[15] [16]. While the gait of healthy adults follows a scale-free law with long-range correlations extending over hundreds of strides, the fractal properties of gait are modified in Parkinson's disease. Notably, we observe a decrease in the gait correlation and changes in stride length and gait variability.[17,18,19] In the case of Alzheimer's disease, the analysis of the fractal dimension of the EEG is used to discriminate patients affected by the disease from control groups with an accuracy of 99.3%, sensitivity of 100%, and a specificity of 97.8%.[20]

4.2.2 *Model personalisation in the face of multiscale complexity*

The formulation of mathematical models for medicine represents a real challenge, not only because we do not fully understand all the pathophysiological mechanisms, but also because many illnesses are prolonged in duration and, in the case of chronic diseases (like for instance stroke, diabetes, arthritis, osteoporosis, atherosclerosis, etc.), are generally managed rather than cured. Including ageing as one of the elements in personalised models is an example in itself of such complexity, and we have devoted a box to that (see Box at the end of the chapter).

One possible strategy to model disease over time is to use hypothesis-based models that combine mechanistic and phenomenological elements corresponding to the degree of understanding of the different components. These models should be adjusted to represent specific time-points in the patient's evolution in order to calculate expected progression of clinical indicators based on probabilistic models that are, in turn, rooted in population data. This approach takes advantage of state-of-the-art knowledge of the (patho-)physiology while also exploiting the mass of data becoming available from clinical trials and epidemiology, on one hand, and GWAS and other molecular data, on the

13 Seely AJ, Macklem P. Fractal variability: an emergent property of complex dissipative systems. Chaos. 2012 Mar;22(1):013108. doi: 10.1063/1.3675622

14 Laugesen JL, Mosekilde E, Holstein-Rathlou NH. Synchronization of period-doubling oscillations in vascular coupled nephrons. Chaos. 2011 Sep;21(3):033128. doi: 10.1063/1.3641828.

15 Sharma V. Deterministic chaos and fractal complexity in the dynamics of cardiovascular behavior: perspectives on a new frontier. Open Cardiovasc Med J. 2009 Sep 10;3:110-23. doi: 10.2174/1874192400903010110

16 Schmitt DT, Ivanov PCh. Fractal scale-invariant and nonlinear properties of cardiac dynamics remain stable with advanced age: a new mechanistic picture of cardiac control in healthy elderly. Am J Physiol Regul Integr Comp Physiol. 2007 Nov;293(5):R1923-37. Epub 2007 Aug 1.

17 Hausdorff JM. Gait dynamics in Parkinson's disease: common and distinct behavior among stride length, gait variability, and fractal-like scaling Chaos. 2009 Jun;19(2):026113. doi: 10.1063/1.3147408

18 Hausdorff JM, Ashkenazy Y, Peng CK, Ivanov PC, Stanley HE, Goldberger AL. When human walking becomes random walking: fractal analysis and modeling of gait rhythm fluctuations. Physica A. 2001 Dec 15;302(1-4):138-47

19 Beuter A, Modolo J. Delayed and lasting effects of deep brain stimulation on locomotion in Parkinson's disease. Chaos. 2009 Jun;19(2):026114. doi: 10.1063/1.3127585

20 Ahmadlou M, Adeli H, Adeli A. Alzheimer Dis Assoc Disord. 2011 Jan-Mar;25(1):85-92. doi: 10.1097/WAD.0b013e3181ed1160. Fractality and a wavelet-chaos-methodology for EEG-based diagnosis of Alzheimer disease

other hand. In appropriate cases, and as pointed out in the VPH Vision document (Hunter *et al.* 2013), "the VPH initiative may be of substantial help by providing mechanistic model descriptions of the phenotypic effects originating from genomic network variation[21]. Such causally cohesive genotype–phenotype models are very advanced multiscale physiological models with an explicit link to molecular information and with the capacity to describe, for example, how genetic variation manifests in phenotypic variation at various systemic levels up to the tissue, organ and whole-organism level."

Consider also the amount of data routinely collected on the millions of patients treated in worldwide healthcare systems, not to mention the rapidly expanding knowledge of human genetics. We are now at a point where computing power and mathematical modelling are becoming able to make use of such vast amounts of information, despite the inevitable noise from 'random variation'. New perspectives may be required in which systems can learn from data, even generated at the individual level. One may even conjecture that it may be possible to develop individual disease models for each person.[22] For example, consider the case of identical twins with similar lifestyles; one develops a chronic disease 30 years before the other. Is it possible to create models that are capable of accommodating such apparent discrepancies? The answer is positive in principle, because models can input lifestyle information as well as physiological, metabolic, and genomic data. Nevertheless, this will require not only the coupling between models at different time and length scales, as well as the description of different physical phenomena, but also between different (phenomenological and mechanistic) modelling paradigms. Until recently, the complexities of many diseases have made them almost intractable for modellers, biologists, and clinicians. Current computational capacities should enable effective modelling of systems that are relevant for therapy. A more systematic, all-encompassing, intelligent and informed update of the models would provide a way forward in order to overcome fragmentation and to address lack of data.

It should be stressed that this is also a technological challenge. For example, multiple interacting processes are typically well described individually by different modelling approaches, like ordinary vs. partial differential equations (ODEs vs. PDEs). When such heterogeneous models are coupled naively, the resulting hypermodel[23] may become difficult or impossible to solve. It is thus necessary to develop better – and where possible generic – ways to deal with such coupling problems, so that they can be embedded in open access software libraries for common research use, even if individual researchers or teams lack a deep understanding of the underlying complex mathematical, numerical, and computational techniques involved.

Last but not least, it is key to highlight the role of boundary conditions for models. These boundary conditions will have to be personalisable, robust and efficient.

4.2.3 Impact of data quality on model personalisation

Biomedical data sources commonly include incomplete entries mainly because of the difficulties at the data collection stage (see chapters 1 and 2 for more details). On the one hand, this complicates the modelling process that needs to cope with this situation, while on the other hand it reduces the confidence of the conclusions derived from the models that have been built. Bayesian statistical inference provides a mathematically consistent framework for encoding uncertain information at the time of observation by obtaining a posterior measure over the space of "trajectories" of the biomedical process. For example, although missing data and the difficulty of dealing with lifestyle or self-reported questionnaire data will decrease the quality of the data, the statistical inference provides a powerful means to constrain probability measures over the causal spaces. Bayesian methods could also make use of the available information to predict missing values.[24] The impact of using these methods would need to be evaluated during model validation.

There will always be issues with the quality of data collected routinely in hospitals, especially if the aim is to use models in clinical practice, because data quality depends on many factors, including human skill. This issue could potentially be addressed by the development of new methods able to integrate the knowledge from experts and the data collected.

4.2.4 Coping with complexity

21 Shublaq, N., Sansom, C., Coveney, P.V. 2013 Patient- specific modelling in drug design, development and selection including its role in clinical decision- making. Chem. Biol. Drug Des. 81, 5–12. (doi:10. 1111/j.1747-0285.2012.01444.x)

22 Doyle, O.M., Tsaneva-Atansaova, K., Harte, J., Tiffin, P.A., Tino, P., Díaz-Zuccarini, V. "Bridging Paradigms: Hybrid Mechanistic-Discriminative Predictive Models". IEEE Transactions in Biomedical Engineering, 60(3).

23 Within this document we use the term 'hypermodel' to describe a concrete instance of an integrative model, built as the orchestration of multiple computer models that might run on different computers at different locations, using different simulation software stacks. Typically a hypermodel is a computational model that might operate on multiple spatial scales, perhaps from molecular through cellular to organ and patient level, and/or on multiple temporal scales, from acute response upwards, and/or might include descriptions of physical, chemical and biological processes.

24 Nguyen, V. A., Koukolikova-Nicola, Z., Bagnoli, F., & Lio , P. , 2009 Noise and non-linearities in high-throughput data. J STAT MECH THEORY doi:10.1088/1742-5468/2009/01/P01014

The complexity of most diseases and the different answers that various types of data would provide remind of the popular tale "The Blind Men and the Elephant" by John Godfrey Saxe (1816-1887). The author writes about a group of blind men who touch an elephant. Each person feels only one part, such as the side or the tusk; so when they describe to each other what they have found, they are in complete disagreement.

For many diseases the most important step is the identification of key model parameters, which can often be measured with only limited accuracy. This issue becomes more critical when multiscale models exhibit nonlinear behaviour, where small variations in certain input parameters could produce significant differences in the output predictions. Clearly some parameters cannot be directly measured on the patient of interest, so one has to use values derived from estimated population mean and variance or from animals. When identification of key parameters that could actually be determined or estimated is problematic, non-parametric models might also be effective.

It is becoming evident that in order to approach the complexity, model order-reduction techniques are sorely needed, while to overcome the sparsity and the variable relevancy and quality of the data it is often important to consider coupling mechanistic with phenomenological modelling.

For single-scale models, researchers have developed a number of methods to account for uncertainties and variability, most of which require Monte Carlo techniques. However, in the case of large multiscale models intended as the orchestration of multiple submodels, transformation of some or all of these submodels into stochastic models leads to heavy computational costs. For example, in the VPHOP project referenced below in the Exemplars section, a full cell-to-organism multiscale musculo-skeletal model in which only the daily physical activity and the related risk of falling were modelled as a stochastic process. The estimation of the risk of bone fracture over 10 years required over 65k core-hours of calculations for each patient. While the final VPHOP hypermodel runs 50 times faster, this was achieved by introducing considerable simplifications in some of the most complex processes.

The applied mathematics community has developed a number of methods – such as Markov-Chain Monte Carlo[25] and the method of Morris[26] – that address aspects of this problem. Nonetheless, we need to target these general model-

25 Persi Diaconis. The Markov chain Monte Carlo revolution. Bulletin of the American Mathematical Society. 46 (2009), 179-205. MSC (2000): Primary 60J20. Posted: November 20, 2008

26 Jeffrey S. Morris. "Statistical Methods for Proteomic Biomarker Discovery Based on Feature Extraction or Functional Modeling Approaches" Statistics and Its Interface 5.1 (2012): 117-136.

> "Models should be as simple as possible."
> General Practitioner

ling techniques to the specific problems, validate them extensively, and make them available to the VPH research community in ways that make their widespread adoption possible given their considerable complexity. We also need to strengthen the stochastic physics background of our students and post-docs as our research sector develops in this direction.

In the case of phenomenological models, an illustrative example is the study of links between morbidities and risk evaluation for a specific pathology. The phenomenological model aims at organising the wealth of observations within a formal structure. One aspect of this challenge is that the connection between data availability and the creation of the phenomenological model is often bridged by human experts, causing a major bottleneck in their ability to understand and engineer complex biomedical systems.

4.2.5 Formalisation and generalisation of model testing and validation strategies

In general, scientific progress towards creating and validating any model generally relies on asking the right questions, and this is far from a banal statement. Different modelling methodologies often answer slightly different questions and, as a consequence, different studies use methodologies that are difficult to cross-compare. Differences between an approximate and an exact model are usually remarkably less than the disparity between the exact model and the real biological process.[27] In such cases, the knowledge that an "expert system" could provide to understand a specific pathology and predict its course is often placed into question rather than believed and built upon.

One fundamental aspect of personalised models of any kind is that they should always be subjected to a sensitivity and robustness analysis, concepts that are intimately linked to the notion of "validation". The sensitivity analysis aims to identify the most influential model parameters, including dependencies among input parameters and between inputs and outputs. The robustness analysis aims to evaluate the probability that the model will not deviate much from a reference state in the face of perturbations. If a given biological process itself is robust to external perturbations, then analysis of successful models that represent that process will be valuable to further our understanding of the biological mechanisms underlying the real system's robustness. Moreover, models will only be adopted in the clinic

27 D. J. Wilkinson, Stochastic modeling for quantitative description of heterogeneous biological systems, Nat. Rev. Genet., 2009, 10, 122-133

once they have satisfied the sensitivity and robustness requirements that will make them useful in practice. Only by knowing their limitations and how well they are able to make credible predictions or diagnoses with small or large differences in the input data will clinicians feel confident enough to use them as a tool for personalised diagnosis and treatment, since this is directly linked to issues of patient safety. Here lies one of the main challenges of the Digital Patient: clinical acceptance of the patient models that will be developed in the future. This is further discussed in the sections below.

4.2.6 Translation and clinical utilisation of models

Even though mechanistic models are complex in nature, some have already entered the clinical arena in the form of software applications embedded in diagnostic or therapeutic devices. Examples of such models are pressure wave propagation models as implemented in the Nexfin monitor, by BMeye B.V. to evaluate central blood pressure and cardiac output from finger plethysmography. Another example of a device is the pacemaker with IAD (Medtronic and others), where a model-based decision algorithm controls the defibrillation action. At an early stage in the promotion of models for clinical use, the more or less generic models used in the applications above could be expanded and personalised to increase the use of validated models in the clinic.

In pharma, clinical pharmacology is an integral part of clinical trials and the approval of a new drug. Empirical (non-mechanistic), semi-mechanistic (e.g. pharmacokinetic/pharmacodynamic – PKPD models) and more mechanistic methods (e.g. physiologically based pharmacokinetics – PBPK models) have been part of quantitative pharmacology, or pharmacometrics. New mechanistic models in drug development are trying to include more information about the biology, pharmacology, disease, and physiology in order to describe and quantify the interactions between xenobiotics and patients, including beneficial effects and side effects that result from such interfaces.[28] A new emerging area called systems pharmacology is being developed as "an approach to translational medicine that combines computational and experimental methods to elucidate, validate, and apply new pharmacological concepts to the development and use of small molecule and [...][biological] drugs"[29] to determining mechanisms of action of new and existing drugs in preclinical and animal models, as well as in patients. Approaches related to pharmacometrics – in particular PKPD modelling – are increasingly being applied in the development of novel therapeutics. The impact of these investments is being supported by both pharmaceutical research organizations and regulatory agencies.[30]

> "Many of the models that will underpin the development are single systems e.g. heart, joints, renal function. But they are isolated. We need to see how organs react with each other. Not individual teams to cover fields they know but to encourage teams to work together."
>
> Clinical Scientist

Non-mechanistic methods such as non-compartmental analysis (NCA) require regulatory approval for new drug application (NDA). NCA provides a framework to use statistical moment analysis to estimate pharmacokinetic parameters dependent on total drug exposure. Some of the parameters obtained from NCA have a practical meaning and can be interpreted, such as the volume of distribution or clearance. However, the parameters provide little insight into physiology, nor how patients will behave towards a different set of conditions. NCA still plays an important role in bioequivalence studies and rapid analysis, but the utility and impact of pharmacokinetic data has increased massively since the arrival of the more mechanistic population approaches.

In the cancer field, models of the MAP kinase pathway around the EGF receptor can be used for the individualization of the treatment of some cancers[31], and models of the Warburg effect advise the dynamic dosing of new glycolytic inhibitors of tumorigenesis.[32,33] A final example is the differential network-based drug design models for parasitic diseases such as malaria and trypanosomiasis.[34]

These examples indicate that simple models that cover a relatively small part of a pathology or mechanical process are most likely to be adopted for clinical use soonest. As men-

28 JS Barrett, MJ Fossler, KD Cadieu, MR Gastonguay, "Pharmacometrics: A Multidisciplinary Field to Facilitate Critical Thinking in Drug Development and Translational Research Settings". The Journal of Clinical Pharmacology, 2013.
29 L Cucurull-Sanchez, KG Spink, SA Moschos, Relevance of systems pharmacology in drug discovery. Drug Discovery Today, July 2012.
30 Van der Graff, P., CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e8
31 K Oda, Y Matsuoka, A Funahashi & H Kitano, A comprehensive pathway map of epidermal growth factor receptor signaling, Molecular Systems Biology 1:2005.0010, 2005
32 H Pelicano, DS Martin,, R-H Xu and P Huang, Glycolysis inhibition for anticancer treatment, Oncogene (2006) 25, 4633-4646
33 D. A. Tennant, R. V. Durán and E. Gottlieb, Targeting metabolic transformation for cancer therapy, NATURe RevIeWS | Cancer, 10, 267-277, 2010
34 Tekwani BL: Current antiparasitic drug targets and a paradigm shift in discovery of new antiparasitic drugs and vaccines. Curr Drug Targets 2008, 9:921

In the latest VPH NoE strategy document (Hunter *et al.*, VPH Vision 2013) it was written: "age is the dominant risk factor for most complex diseases. The making of multiscale physiological models capturing the ageing process defines a very ambitious long-term theoretical – experimental research programme of vital importance to the VPH vision."

Ageing is a hurdle to overcome and its inclusion in personalised models for the Digital Patient is a challenge that multi-scale models will need to resolve. Already when merely considering the multifarious interconnections between ageing and lifestyle and genetic factors, one can appreciate the complexity of this dynamic process. The age factor is successfully used in epidemiological studies to specify, for example, the contact rate of the spread in an infectious disease, which summarises the infectious effectiveness of contacts between susceptible and infectious subjects. However, even for population/epidemiological studies where functional biological relationships between the different causes and effects of ageing in the model are not relevant, epidemic models that take into account the age structure of a population are very intricate.

One possibility is to identify genomic markers most closely associated with age and related disease traits. In the VPH-FET roadmap[1], it was highlighted that "[...] combining genomic, proteomic, metabolomic and environmental factors may provide insights into pathogenomic mechanisms and lead to novel therapeutic targets". In diseases precipitated by complex interplays of genetic predisposition and a broad spectrum of environmental and nutritional factors, the challenge is immense. In this context, epidemiological factors such as urbanicity, geographical distribution, migration behaviour, and maternal risk factors such as infections, malnutrition and adverse life events during pregnancy, have been suggested as being relevant to different extents. It is clear that a combination of different types of modelling paradigms will be necessary to establish the relationship between these factors and the interplay with genetic determinants, which thus far remains unknown. Integrated, system-based investigations are a promising approach to obtaining deeper insights into the disease aetiology and its management or cure.

In mechanistic-type models, the physiological aspects of ageing can be represented as time-dependent changes in relevant model parameters. On a population level, a number of such factors have been identified, including bone density in women, gradual reduction of renal function (i.e. falling GFR), reduced mobility (e.g., increased sitting-to-standing time), elevated pule arterial pressure, elevated TPR (total peripheral resistance), and left ventricular hypertrophy. As the mechanisms responsible for these age-related changes become elucidated, the corresponding details in the models can be adjusted accordingly, and when the mechanisms are unknown these changes will be reflected in appropriate phenomenological model parameters. However, ageing is perhaps a case where phenomenological models are easier to build (taking advantage of the wealth of observational data available) compared to the mechanistic ones, since mechanistic aspects of ageing are less well known.

1 https://www.biomedtown.org/biomed_town/VPHFET/reception/vphfet-publicrep/plfng_view

tioned above, a key point in this process is the validation of the models before actual clinical adoption can occur on a larger scale. Proof of the specificity and sensitivity of models in, for instance, diagnostic tools, is and will continue to be crucial to this adoption process. In the textbook developed by the VPH Network of Excellence (to be published by OUP), Viceconti and Graf draft a framework for pre-clinical and clinical model validation, as well as for clinical acceptance. While such a framework may appear complex and demanding, we believe it is only in this way that the natural resistance against computer simulations will be overcome, proving conclusively that the Digital Patient technologies are accurate, robust, and clinically effective.

4.2.7 An example of multiscale complexity: Ageing

4.3 Modelling different pathologies - exemplars

Patho-physiological phenomena must be interpreted from clustering of extracted features, time evolution, and multi-parameter analysis. For "black box" or data-driven models, this might be enough; an additional step of formulation of cause-effect relationships is needed for "mechanistic models". In any case, the lack of data covering decades hampers the effectiveness of most types of models. There are very few longitudinal studies available and this is one of the greatest challenges in modelling disease. Six examples in which modelling has been successfully used in clinical applications are described below in relative detail, but we also highlight areas in which gaps and unmet needs are evident. A comprehensive view of the six is presented in the table on the next page and descriptions follow below in the text.

4.3.1 Breast cancer

Multistage cancer models are widely used to model solid tumours that appear to develop through well-defined phenomenological stages, including initiation, pseudo-tumor-

Table: *Comparative overview of main features for 6 different pathologies*

Pathology	Comorbidities	Phenomenological modeling	Mechanistic modeling
Breast cancer	COPD; CHF; stroke	Tumor diameter growth; biopsies; histology; development of stage diagnosis	Cell invasiveness based on prognostic and diagnostic molecular markers
Osteoporosis	Several types of cancers (breast, prostate, multiple myelomas); endocrine unbalance; infections (HIV); therapies (HAART)	Bone mineral density; Wolff's law; development of Frax tool.	Molecule-to-cell, cell-to-tissue coupling models, for example osteocytes, hormones
Atherosclerosis	Inflammation; obesity; diabetes	Imaging: CT, MRI or US 3D+T with resolution of 1 mm per voxel; arterial elasticity; plaque biomechanics in general; restenosis after stenting	Proliferation and migration of vascular smooth muscle cells; plasma lipoproteins (LDL and HDL),
Cardiomyopathy	Obesity; diabetes; coronary artery disease; hypertension; infection	ECG patterns; abundance of longitudinal studies (Framingham[33], Dawber, Busselton)	Energy metabolism based on glycolysis; mitochondrial functionality; lactate production; ionic (sodium) currents; excitation/contraction of single cells
Dementia	Stroke and heart failure prediction tools predict dementia (Kaffashian[34])	Cognitive tests and memory; EEG patterns; MRI; brain mapping; network models of atrophy; use of longitudinal data	Amyloid plaques; neurofibrillary tangles; tau phosphorylation
Stroke	Hypertension; coronary disease and diabetes; the Charlson comorbidity	Cognitive tests and memory; performance; Charlson index; neuroimaging	Based on oxidative DNA damage and repair; vasoconstrictor such as endothelin-1

al and cancer transformation.[35] Here the histological analysis, screening, and clinical incidence data could be used to calibrate, validate and check the consistency of the several sources of evidence and define the stage of the cancer. The phenomenology of breast cancer disease is related to its aggressiveness, which stems from its rapid recurrence and metastasis positioning. Phenomenological models of breast cancer use a wide range of parameters related to imaging, pathology, basic research, clinical trials, clinical practice, genetic predisposition, and epidemiology. The most meaningful parameter set from these analyses could be wrapped to construct new phenomenological parameters to describe growth rhythms, growth delays, and time constants. This *modus operandi* introduces a vast simplification by turning a system with a large number of constituents specific to the used techniques into a limited number of effective degrees of freedom embedded in a few phenomenological parameters.[36] For example, in breast cancer, a diffuse redness provides evidence that inflammatory processes are involved in the pathogenesis of this disease, which is rare but the most aggressive form of breast cancer.

It is clear though that in order to understand the processes behind tumour growth and treatment, other (more mechanistic) approaches are required. For example, the Contra-Cancrum project[37] aimed at bringing together different levels of biocomplexity producing an integrated oncosimulator and validating it on two dedicated clinical studies concern-

35 see an example in Wai-yuan Tan, Leonid Hanin Handbook Of Cancer Models With Applications (Series in Mathematical Biology and Medicine) World Scientific Pub Co Inc; 1 edition (August 11, 2008)

36 Bastogne T, Samson A, Vallois P, Wantz-Mézières S, Pinel S, Bechet D, Barberi-Heyob M. Phenomenological modeling of tumor diameter growth based on a mixed effects model. J Theor Biol. 2010 Feb 7;262(3):544-52.)

37 http://www.contracanrum.eu

ing glioma and lung cancer. The project modelled and simulated cancer vs. normal tissue behaviour at different levels of biocomplexity, and also modelled a facet of the systemic circulation via pharmacokinetics, and synthesised models of hematological reactions to chemotherapy. [40,41]

One interesting proposition is to try harnessing the power of epidemiological studies in conjunction with a systemic mechanistic approach, as proposed by Sokhansanj and Wilson.[42] They describe a mathematical model that mimics the kinetics of base excision repair and thus permits them to investigate *in silico* the effects of genetic variation in this important DNA repair pathway. As written in [43] *"If one succeeds in constructing a mathematical model that reasonably represents the biochemical reality, the payoff is large. One can experiment with the model by increasing or decreasing inputs (corresponding, say, to changes in diet) or by raising or lowering activities of enzymes (corresponding to genetic polymorphisms), or eliminating entire reactions completely (corresponding to gene-knockout experiments). One can take apart and put back together the biochemical network piece by piece to determine how it works. In contrast to biological experiments, these in silico experiments are quick and inexpensive and, if done well, can give real insight into the genetic and molecular network".*

4.3.2 Osteoporosis

Bone is one of the most adaptable tissues in the body. Accurate phenotypic descriptions of human skeletal phenomena are starting to accumulate.[44] During adulthood, there is a stable equilibrium (homeostasis) with the formation of new bone by the osteoblasts and the removal of older bone tissue by the bone-resorbing osteoclasts. This homeostasis can be perturbed by aging (osteoporosis), infections (osteomyelitis[45]), changes in physical activity, or through metabolism. Due to the deposition of collagen in particular directions by osteoblasts, bone acquires anisotropic properties with an alignment of the principal directions of the bone (trabeculae) with the principal direction of stresses, known as Wolff's law. Hence there is a direct relationship between bone adaptation and mechanical loading. This sensitive equilibrium is broken at a later stage in life when the osteoblast activity is reduced, leading to osteoporosis and an increased fragility of bone. The osteoporosis case shows an excellent example of mechanistic modelling put to the service of the clinical community.

The mechanistic approach lends itself with relative ease to the understanding of osteoporosis; bone and muscle have been active and successful research strands in biomechanics for decades. Multiscale modelling and simulation approaches have tried to bridge the spatial and temporal gaps involved. For example: by detailed modelling of musculoskeletal anatomy and neuromotor control that define the daily loading spectrum, including paraphysiological overloading events; by modelling fracture events as they occur at the organ level and are influenced by the elasticity and geometry of bone, which leads directly to the tissue scale as bone elasticity and geometry are determined by tissue morphology and finally reaching the cell, as cell activity changes tissue morphology and composition over time. Some examples of this are found in[46,47].

Several types of phenomenological models have also been proposed, for example based on PDE solvers using histological and micro-CT image information[48], a topological osteoactivity metric, i.e., the resorption-formation steady-state is represented as a torus in multidimensional phase space[49], a process-algebraic specification (for example, the space-defined Shape Calculus), which provides an effective multiscale description of the process. The phenomenologi-

38 Thomas R. Dawber, M.D., Gilcin F. Meadors, M.D., M.P.H., and Felix E. Moore, Jr., National Heart Institute, National Institutes of Health, Public Health Service, Federal Security Agency, Washington, D. C., Epidemiological Approaches to Heart Disease: The Framingham Study Presented at a Joint Session of the Epidemiology, Health Officers, Medical Care, and Statistics Sections of the American Public Health Association, at the Seventy-eighth Annual Meeting in St. Louis, Mo., November 3, 1950

39 Kaffashian S, et al "Predicting cognitive decline: A dementia risk score vs the Framingham vascular risk scores" Neurology 2013; 80: 1300–1306.

40 A. Roniotis, K. Marias, V. Sakkalis, and G. Stamatakos "Mathematical guide for developing a heterogeneous, anisotropic and 3-dimensional glioma growth model using the diffusion equation", Information Technology Applications in Biomedicine (IEEE-ITAB 2009), Larnaca, Cyprus, 2009.

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42 Sokhansanj BA, Wilson DM. Estimating the impact of human base excision repair protein variants on the repair of oxidative DNA base damage. Cancer Epidemiol Biomarkers Prev 2006;15:1000–8

43 http://cebp.aacrjournals.org/content/15/5/827.full

44 see for example Groza T, Hunter J, Zankl A. Decomposing phenotype descriptions for the human skeletal phenome. Biomed Inform Insights. 2013;6:1-14. doi: 10.4137/BII.S10729. Epub 2013 Feb 4

45 Liò P, Paoletti N, Moni M.A., Atwell K, Merelli E. and Viceconti M, Modelling osteomyelitis, BMC Bioinformatics, 13: S12, doi:10.1186/1471-2105-13-S14-S12.

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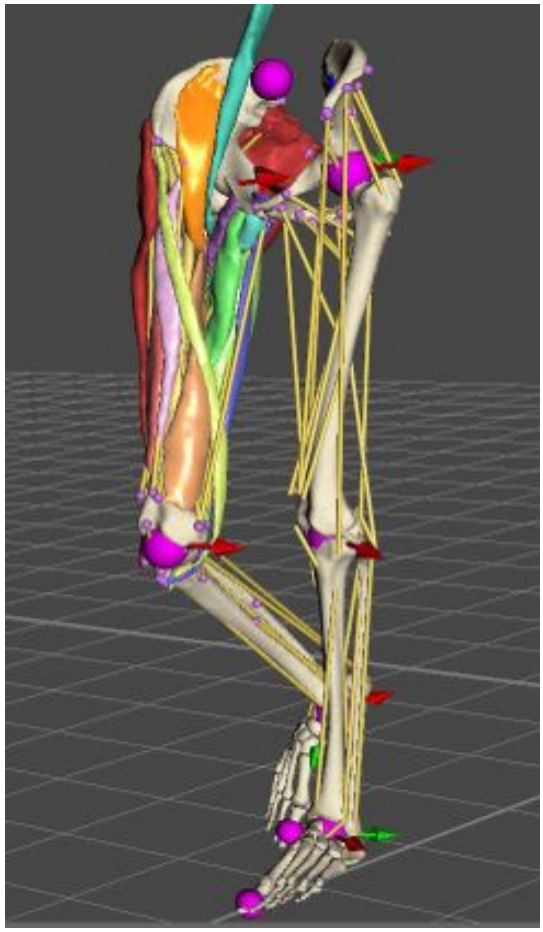
48 Viceconti, M., Clapworthy, G., Testi, D., Taddei, F., and McFarlane, N. (2011). Multimodal fusion of biomedical data at different temporal and dimensional scales. Comput Methods Programs Biomed., 102:227–237

49 Moroz A, Crane MC, Smith G, Wimpenny DI. Phenomenological model of bone remodeling cycle containing osteocyte regulation loop. Biosystems. 2006 Jun;84(3):183-90

cal approaches make use of abundant bone mineral density data in health and pathology (for example osteoporosis[50]).

One associated and interesting aspect of phenomenological modelling is its use in identifying the major reasons for osteoporotic fractures. While intensive work continues into evaluating bone loss and the aetiology of skeletal osteolysis throughout the ageing process, the single major cause for an osteoporotic fracture is the occurrence of falls. The accurate prediction of fracture risk can therefore only be achieved by observational studies that lead to an understanding of the factors that play a beneficial or detrimental role in modifying an individual's risk of fall. Fall risk assessment currently varies from questionnaire-based evaluation of health and medication factors to intensive laboratory measurements for quantification of gait and balance parameters[51]. However, most of these tools have been shown to discriminate poorly between fallers and non-fallers.[52,53] The best assessment tools currently achieve a sensitivity and specificity of around 75%.[54,55] In



Source: VPHOP

clinical assessments, the single best predictor for falls has been the existence of a previous fall.[56,57,58] While this increases the accuracy of fall risk assessment in retrospective studies where subjects have already fallen, identification of future fallers becomes challenging in prospective cases when a prognosis for a subject who has not yet fallen is required. In subjects with no previous falls, kinematic abnormalities during gait and balance seem to contain important information related to the likelihood of a future fall.[59] The successful identification and inclusion of such functional indices – including alance[60,61], temporal and spatial variability during gait[62,63] and muscle strength[64] – is now thought to contribute towards accurate predictions of fall risk when combined with established clinical parameters (e.g. medication, cognition), and may therefore allow improved stratification of elderly subjects in a clinical setting. Here, by investigating the functional movement and muscular control characteristics that differentiate subjects who are most susceptible to falling,

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51 Persad CC, Cook S, Giordani B: Assessing falls in the elderly: should we use simple screening tests or a comprehensive fall risk evaluation? European journal of physical and rehabilitation medicine 2010, 46(2):249-259

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observational studies are important in improving our understanding of the aetiology of falls, but may well play a key role pushing the boundaries for the early clinical identification and stratification of subjects at risk of falls.

It is noteworthy that the phenomenological modelling could in principle be applied to study the system: human body, sensor networks, prostheses, which could be tested and validated in a very effective way without a precise mechanistic model.

4.3.3 Atherosclerosis

Atherosclerosis is a multifactorial disease in which not only genetic, biochemical, and physiological factors play a role, but also environmental and life-style factors. This pathology is a prime example of complex processes acting along multiple biological, length and time scales. In this disease, lifestyle is particularly important and its interaction with genetic components can be subtle; for example, a single locus of lipoprotein A appears to identify patients at risk of aortic and mitral valve calcification.[65] Investigations regarding atherosclerosis have focused on various aspects of the disease to improve risk assessment for cardiovascular events, studying biomarkers related to the onset and progression of atherosclerosis, or applying experimental methods to investigate underlying disease mechanisms. Modelling in systems biology is also particularly active.[66,67] From a mechanical perspective, it is well known that the development of atherosclerotic plaque is most prevalent in regions of low shear stress. Computational investigations have considered certain aspects of the development of atherosclerosis connected to specific haemodynamic conditions. Their aim is to study possible hypotheses regarding the main processes of arterial pathogenesis. These models often use non-linear reaction-diffusion equations describing the transport and reaction of various species involved in the process.[68] Recently, a first version of a platform-based prediction of atherosclerosis was published.[69] It applies diffusion-reaction equations based on a patient-specific reconstruction of arterial segments and predicts plaque growth.

AZ/IS/S. Kaulitzki, M.Abilgaard, V. Yakochuk

However, time constraints – i.e. the disease may need a long time to develop – make mechanistic modelling difficult, and that is where statistical modelling often comes into play. There is a plethora of epidemiological studies and statistical modelling to predict risk linked to progression; for example, a recent study showed that sedentary participants had a 22% increased carotid atherosclerosis progression compared to active counterparts[70], and it is noteworthy that the statistical/epidemiological studies are the ones informing healthcare policy makers.[71] Modelling should make use of all data available by using the best modelling paradigms fit for each purpose and it is the integration of these that will allow making substantial progress. An interesting idea has been presented in[72], where hybrid mechanistic/data-driven approaches are proposed in order to overcome some of the limitations of mechanistic models via the use of machine learning (and vice-versa). The proposed framework attempts to develop a modelling workflow in which, instead of learning in the space of data, intelligent machines will learn in the space of mechanistic models. It is noteworthy that much of the data on atherosclerosis come from autopsies, since control data from a

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72 O.M. Doyle, K. Tsaneva-Atansaova, J. Harte, P. A. Tiffin, P. Tino and V. Díaz-Zuccarini, "Bridging Paradigms: Hybrid Mechanistic-Discriminative Predictive Models.", IEEE Transactions on Biomedical Engineering

> “Although dementia is the most studied neurological condition by the pharmaceutical industry, no efficient treatment is available and the mechanisms of the disease are not (fully) understood.
>
> Dr Hilkka Soininen, University of Eastern Finland

healthy population over long periods of time prove difficult to obtain. It would be ideal to consider phenomenological models as a way to augment the imaging information content. The challenge is to characterise the role of personalised modelling and how to integrate physiological, environmental, and lifestyle data.

4.3.4 *Cardiomyopathy*

Modelling techniques have been used with success in describing human anatomy, physiology, and disease. The use of novel technologies harnessing the power of mathematical models has progressed towards predictive cardiopatho/physiology from patient-specific measurements, for example[73] in order to improve diagnosis, treatment planning and delivery, and optimization of implantable devices by making cardiac models patient-specific using clinical measurements. Advanced cardiac models, for example[74], have been used as a starting point and used state-of-the-art clinical imaging to develop new and personalised models of individual cardiac physiology. There are interesting and promising results in this area, ranging from arrhythmias to myocardial deformation, cardiac wall motion, and patient-specific tissue information such as myocardial scar location.[75,76,77,78]

Current genome technologies may enable insights into personal behaviour and stress conditions that produce changes in DNA methylation in different tissues, like the heart.[79]

Challenges in phenomenological modelling could also look at medical and surgical interventions (for instance stents) and disease early predictors, as exemplified in[80] and making use of signal-based analyses. One challenge would be to consider phenomenological models to include comorbidities lie diabetes, as well as prior knowledge such as medication or medication history. This is reflected by the finding that patients that are scheduled for a peripheral artery intervention do much better if they are already on statins and aspirin.[81] Regular aspirin use is associated with an elevated risk for neovascular age-related macular degeneration.[82] Other factors that are difficult to include in a mechanistic assessment are, for example, ethnicity, gender, and lifestyle.

Source: PredictAD, VTT

73 www.euheart.eu
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4.3.5 Dementia

Dementia is not a single disease, but is rather an umbrella syndrome that includes many different forms.[83] All neurodegenerative diseases share a number of common distinctive pathological hallmarks, such as extensive neuronal death and clinical symptoms like compromised function in the affected brain regions. Although in many cases few proteins are found to have significantly different concentrations between healthy and diseased neurons, the basic mechanism of dementia is still unclear.[84] Effective pharmaceutical treatment of dementia is currently not available.

Mechanistic models can provide an essential and much needed platform for improved understanding of dementia. A clear exemplar is the case of vascular dementia, in which the use of a patient's anatomical and physiological characteristics and mechanistic models of plaque progression could lead to the development of powerful tools to help to elucidate the relationship between progression of disease in time, and cognitive impairment. There is also much to gain in better capturing the mechanistic complexities of the blood-brain barrier and its relationship to neural behaviour. Another compelling case is the role of detailed modelling and analysis of the microvasculature and its relationship with stroke and Alzheimer's disease, which has been recently addressed by.[85]

Mechanistic models based on molecular data are, however, challenged by results from epidemiological studies that point to lifestyle factors, such as poor diet and physical and cognitive inactivity. This is an area where phenomenological models could consider social parameters which are difficult to incorporate in mechanistic contexts; for example, (1) as a person-centric model highlighting the context of a patient's significant relationships; (2) as a disability approach, according to which people with dementia are people with cognitive disabilities; or (3) as a medical approach, in which people with dementia have a neurological disease. Lifestyle is very important, as shown by the finding that individuals with the highest levels of cardiorespiratory fitness during middle age were significantly less likely to develop dementia in their senior years.[86] Thus, introduction of physical activity can reduce the risk of cognitive impairment in old age. Metabolic syndrome and diabetes are also associated to dementia.[87]

4.3.6 Stroke

Stroke is yet another case in which modelling could offer much needed help. The rapid loss of brain function due to disturbances in the blood supply to the brain can be due to ischemia (lack of blood flow) caused by blockage (thrombosis, arterial embolism) or by a haemorrhage, which are all suited for rigorous analysis via *in silico* tools.[88] Stroke is one of the leading causes of death and acquired handicap. There is already work in the literature[89] developing physiology-based models for acute ischemic stroke. This is a case where most of the clinical trials have failed, contrasting with promising results during preclinical stages. This continuing discrepancy suggests some misconceptions in the understanding of acute ischemic stroke, and this is where modelling techniques can provide assistance for understanding its underlying mechanisms. One possible method for identifying the shortcomings of present-day approaches is to integrate all relevant knowledge into a single mathematical model and to subject that model to challenges via simulations with available experimental data.

Several phenomenological models have been proposed that account for stopping of the blood flow in some part of the brain (ischemia), reduced oxygen levels, and damage to cells.[90] Recent models have focused on studying the influence of spreading depression on the death of the cells; this is like a transient suppression of all neuronal activities spreading slowly across a large region of the brain.[91] Future models may take age into account: almost half of children with haemorrhagic stroke had seizures at presentation or within a week of onset.[92] Also lifestyle plays a key role. An

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> “Long-term health forecasting will play an important role in the efficient management of care in particular with chronic conditions, where the disease may change over a long period of time.”
>
> Clinical Scientist

exercise program such as *tai chi* that focuses specifically on balance was found to reduce the incidence of falls.[93] Phenomenological models should consider nutrition and cooking methods; for example, diets that are heavy in fried and salty foods could be the most dangerous in terms of stroke risk.

4.4 Timeline and impact

In this section, we try to summarise the long-, mid-, and short-term challenges for modelling in the Digital Patient framework. The challenges are ranked according to the developments that are required to meet them (short- / mid- / long-term) as well as by their impact (benefit for patients).

4.4.1 Short-term challenges

- Formalisation of model testing and validation strategies, determining how selection of testing strategies should be made independent of model development.
- To immediately strengthen collaboration between modellers and clinicians, and improve uptake and testing of models despite an on-going development process. A recommendation in this respect is to call for small focused projects that address early stages of the disease modelling process with mixed teams with the goal of early testing in small cohorts of patients.
- Encourage the development of hybrid paradigms in order to capitalise on the potential of modelling as a whole for personalised medicine.
- Development of relatively simple models (see examples provided in previous section for cardiovascular diseases and cancer) that address specific topics in patient studies, for the expansion of diagnostic methods and therapies in the clinic.
- Expansion of the set of models that can be applied clinically, with existing models applied in particular areas of diagnostics: models describing a small part of physiology, with a limited number of inputs and outputs, directed towards a specific disease or diagnostic method.

4.4.2 Mid term challenges

- Creation of online repositories to house disease- and patient-specific data, through which mechanistic model inputs may be linked to patient lifestyle factors (age, fitness, diet, etc.)
- Development of mechanistic models as tools to integrate data into structures that enable computation of their implications.
- Development and validation of customised models for specific pathologies, with patient-specific inputs and outputs.
- Development of hybrid strategies for the combined use of phenomenological and mechanistic models
- Development of mathematical formalisms for multiscale processes
- Automatic debugging and systematic testing tools for patient-specific models, possibly in combination of machine learning techniques and artificial intelligence

4.4.3 Long-term challenges

- Combination of specific models into a large-scale patient model encompassing larger, multifactorial pathologies such as heart failure, renal failure, etc.
- Personalisation of not only anatomical data but also the physiological/pathological processes taking place (multiscale) by linking model parameters to easily obtainable patient data, leading to an individual patient model rather than a statistical patient model.

4.5 Chapter summary/conclusions

Clinical utilization of models: reasons for optimism

In this chapter we have made an attempt to cover the mathematical modelling challenges that scientists and technologists will need to face in the short-, mid- and long-term to enable the realisation of the Digital Patient. The first one to be addressed is the *Selection of the most adequate mathematical modelling approach*. There is not a unique way of creating a model and a categorisation typically used to classify the mathematical models by the scientific community is distinguishing between phenomenological and mechanistic models. The first are built purely based on empirical observations of a phenomenon, while the second aim to represent the underlying mechanisms of a biomedical process. Making these models widely available in online semanti-

93 Taylor-Piliae, RE, et al “Stroke survivors in a 12-week Yang-style tai chi intervention have fewer falls” ISC 2013; Presentation W P362.

cally annotated repositories should enable the development of hybrid approaches able to customise and combine (even automatically) phenomenological and mechanistic models for use in the Digital Patient. The creation of such models also encompasses *the challenge of Personalising and extending them to cover multiple scales*, and including ageing is a representative example of this difficulty. Models are created using *real (and non-ideal) biomedical data sources* that commonly include incomplete entries, available in repositories that are non-standard, difficult to access or that lack interoperability features. This complicates even further the modelling process, because it needs to handle the uncertainty introduced by the often-incomplete input data and estimated parameters. As a result, any future model should come together with an estimated valid range of operation and a measure of confidence on the results.

Nevertheless, as already mentioned during the discussion of the *translation and clinical utilisation of models* challenge, despite the complexity of mathematical models of bodily functions, some have already **entered the clinical arena** in the form of software applications embedded in diagnostic or therapeutic devices. This indicates that in the short-term, **simple models** that cover a relatively small part of a pathology or process are *most likely to be adopted for clinical use* early on. Prior to actual clinical adoption on a larger scale, another key challenge especially relevant in the mid- and long-term is *Automating, generalising and formalising the process of model testing and validation*.

Concrete recommendations include the following:

1. Support the creation of online repositories to house and share disease- and patient-specific data and models to enhance collaboration within the VPH community, providing ubiquitous access

2. Prioritise the development of relatively simple models that address specific topics in patient studies, for the expansion of diagnostic methods and therapies in the clinic

3. Develop hybrid methods and strategies to automatically and seamlessly combine phenomenological and mechanistic models, exploiting the use of VPH ontologies and annotated online repositories containing well-documented and validated models

4. Develop surrogate modelling methods that make possible to replace computational demanding sub-models, typically large PDE models (partial differential equations models), with estimators developed on pre-computed solutions, to provide a fast estimate of the model outputs and an upper boundary of the estimation error

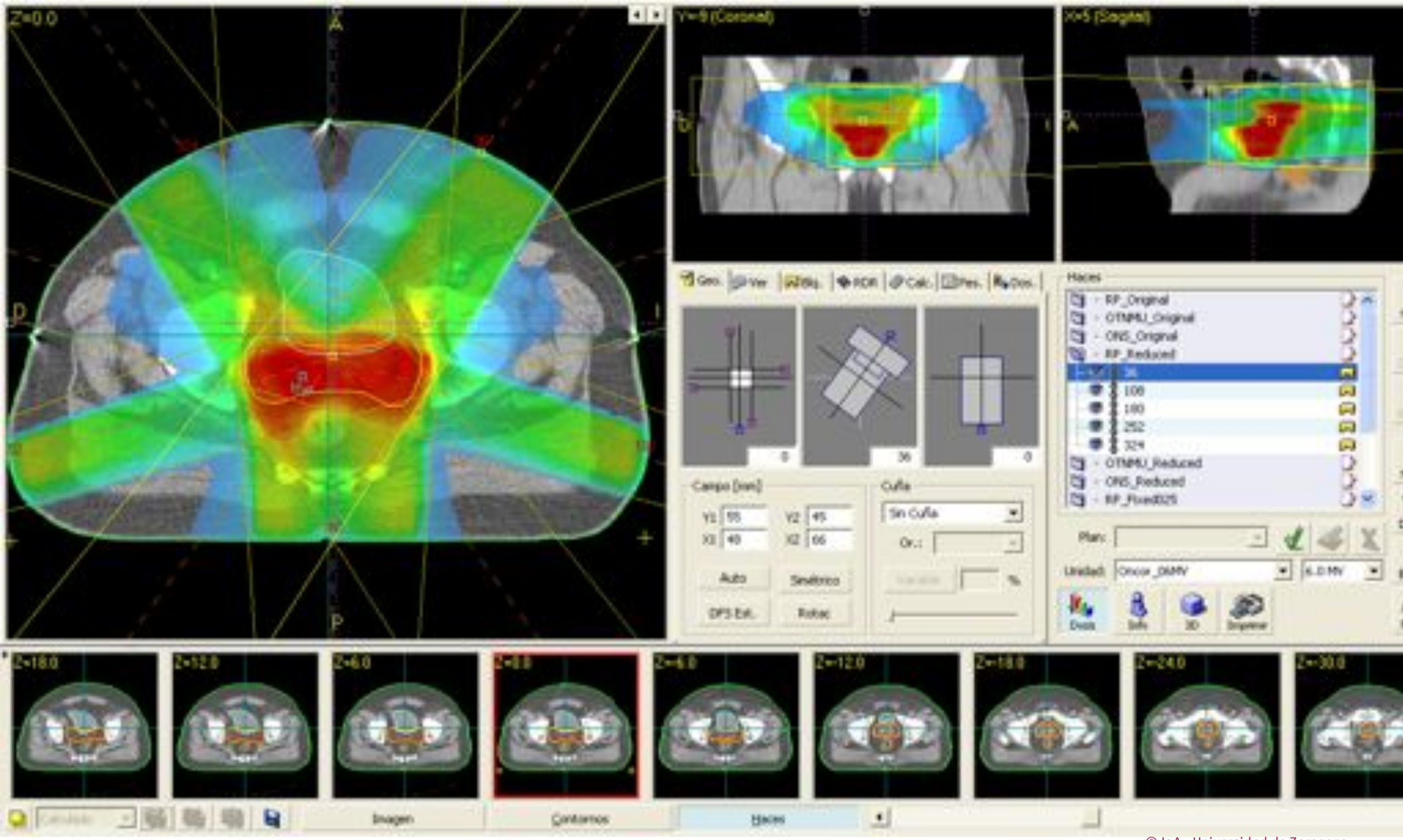
5. Develop integrative modelling frameworks that support the abduction cycle that applies inductive reasoning to observations to generate hypotheses on mechanistic relationships, verify these against reference observations, and where predictions are in good agreement with observations, incorporate this new mechanistic understanding into the inductive reasoning, so facilitating new discoveries

6. Develop fast numerical restart methods that make it possible to employ user exploration of the information space to re-run the model with different inputs at very low computational cost when compared to the first run

7. Personalise not only anatomical data but also the physiological/pathological processes taking place (multi-scale) by linking model parameters to easily obtainable patient data, leading to an individual patient model rather than a statistical patient model

8. Develop a theoretical framework for the analysis of scale separation, and general homogenisation and distribution strategies to define space-time relations across scales

9. Develop strategies to formalise and generalise the testing and validation of mathematical models, providing accurate and automatic estimations on the impact that incomplete data has in the personalised models



5. Clinical user interface

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5.1 General introduction

As a result of population ageing, healthcare and associated social welfare costs have in recent years grown exponentially and they will soon become unsustainable unless we change the way in which people are supported. In many cases, there is a need to shift medical care from institutions to the home environment. To this end, ICT tools are being used to reform the traditional ways in which medical data is recorded, tested, and analyzed, without compromising its quality. The Digital Patient framework will make it possible to set up new interactions between doctors and patients, and to maintain both the quality and intensity of treatment at a more sustainable cost. As such, it complies with the trend towards patient-centred healthcare and offers a pathway to enhance the self-awareness of citizens and to empower them to play a more significant role in their own health, which is regarded as an effective way of dealing with the increased challenges anticipated in future healthcare.

Giving patients an access to their own avatar means providing them with additional and/or more detailed information about their condition, treatment options and possible means to improve their lifestyle. This can contribute to an enhanced awareness of their health problems, and hence make the future healthcare system more efficient. It can also make it easier for patients to meet and talk with fellow patients suffering from similar diseases/conditions and to exchange experiences and hence raise their spirits collectively in the fight against the illness. Yet, the sustainability of healthcare systems remains largely dependent on the health professionals and in their ability to improve and optimise the clinical process, from prevention to rehabilitation via diagnosis, prognosis, treatment planning, treatment execution, and monitoring. From a clinical point of view, the Digital Patient framework will therefore make it possible to accompany individual patients throughout the entire clinical process and to concentrate on specific stages of this process on an individual basis.

European healthcare systems have a long and complex history of independent evolution in many different countries. As a result, the picture is highly fragmented with differences between member states, regions and even between hospitals within the same country, and information transmission is consequently often inefficient or unreliable, which has a strong impact on trust, safety and costs. Thus, from the perspective of the individual patient, maintaining a clinical record in a consistent manner is difficult and the problem is being exacerbated by the increased population movement within Europe. This situation poses as a threat to the provision of high quality healthcare services, and this is particularly true for the prediction and treatment of major and long-term diseases (e.g. cancer) where a consistent record of individual patients is of great importance. To this end, the Digital Patient framework and a universal individual avatar offer a coherent framework for information collection, access, sharing, and analysis.

Both citizens and health professionals are major actors in our healthcare system and section 2 of this chapter elaborates on the various categories of Digital Patient framework users. Section 3 elaborates on challenges and requirements of a clinical user interface, section 4 on the virtual interface of the framework, the patient avatar, section 5 on visual analytics, and section 6 concludes with research priorities.

5.2 Users

In line with the vision and strategy for the VPH[1], the Digital Patient should ultimately be viewed as a tool for citizens, thereby serving a healthcare system that does not only care for patients (i.e., diseased citizens) but also promote future health and wellbeing in healthy citizens by fostering the maintenance of a healthy lifestyle, by providing early symptoms notifications, and by allowing personal health forecasting.

"The vision of a "digital me" that contains all my healthcare information, safely managed for access by the various biomedical professionals with my approval, communicated with all my wearable and implanted technology to constantly monitor my health status and informing me, my family and friends, or my healthcare providers of alarming events, supporting the collaboration of various specialists around my complex systemic diseases, and used with all my data to predict the future development of my health in order to facilitate disease prevention and a fully self-aware lifestyle, is a powerful vision. But the challenges are huge."

Peter Hunter, *et al.* – A Vision and Strategy for the VPH[2]

However, tailoring the Digital Patient framework to accommodate the needs and interests of individual citizens and devising workflows to design interfaces and tools that are simple enough for medically and scientifically illiterate citizens is a long-term vision. By identifying translation to the clinic and clinical uptake in general as primary focuses, the Digital Patient framework is intended for clinicians and clinical researchers, and puts them at the very centre of the technological developments brought about by the research community, thereby adopting the priorities inherited from the VPH framework.

1 P. Hunter et al. A Vision and Strategy for the VPH http://www.imagwiki.nibib.nih.gov/mediawiki/images/c/cf/ VPH_vision_2011_23Dec2010.pdf
2 ibid.

5.3 Challenges and requirements

5.3.1 *Broad spectrum of users and functionalities*

Designing clinical user interfaces for a framework that is intended for clinicians and clinical researchers, i.e., all health professionals involved in the healthcare system, including physicians, radiologists, surgeons, intensive care specialists, nurses, administration, quality control and resource optimization officers, information technician, etc., and researchers, comes with a number of challenges, including:

- The diversity of professionals likely to interact with the system
- The constraints imposed by the ICT systems and the clinical and data workflows with witch the Digital Patient framework needs to be compatible. Simulations in particular are very time consuming and limitations associated with computational power impose restrictions on the achievable resolution and accuracy, which in turn can compromise reliability
- The numerous functionalities that the framework needs to offer. Those include the access and retrieval of heterogeneous information from individual or populations of patients (see Chapter 2), body-centric and multi-scale visualization of raw data and of simulated results (Patient Avatar, see section 4.3), multi-scale and multi-physics simulation and modeling tools (see Chapter 3), visually assisted data analysis (i.e. visual analytics, see section 4.4), and post-processing tools for the extraction of clinically meaningful information and for treatment planning, clinical decision support, and intervention support (augmented reality, see user interface examples below) for instance, for illustration, and for knowledge sharing and communication with fellows and patients. Existing tools serving those purposes are mostly developed in isolation, whereas a unified framework is needed, in which functional modules are fully compatible with each other.

User interfaces – examples

Augmented reality (AR) could be used for better visualization of a patient's anatomy during surgery to help guide surgeons, or a way to get medical history of a patient by examining them and seeing what areas have had medical supervision or diagnosis before by superimposing x-rays and other images over these specific areas. This technology could also be used for medical teaching, to help in providing medical care to remote locations or locations under duress (e.g., war or natural disaster). Additionally, AR could be used to address issues of patient compliance, for example, patients with chronic disease that needs to be managed pharmacologically in which case a "virtual nurse"/"virtual doctor" could help monitor the treatment by keeping these patients to the recommended dosages and on the right timetable.

Also, 'gaming' approaches, in much the same way that multi-player games work online could be used. This would allow access by different specialists at different locations. Each 'game' would be recorded and replayed if necessary. This would include; bringing up information that specialists deem necessary from the EHR, videos, conversations with patients, etc or adding professional 'knowledge' (information that the clinicians know and is not documented but that needs to be contextualised, written in mathematical form and displayed in a graphical manner). Automatic programming techniques might be needed in order to address this.

5.3.2 *Broad spectrum of devices and the purpose of application use*

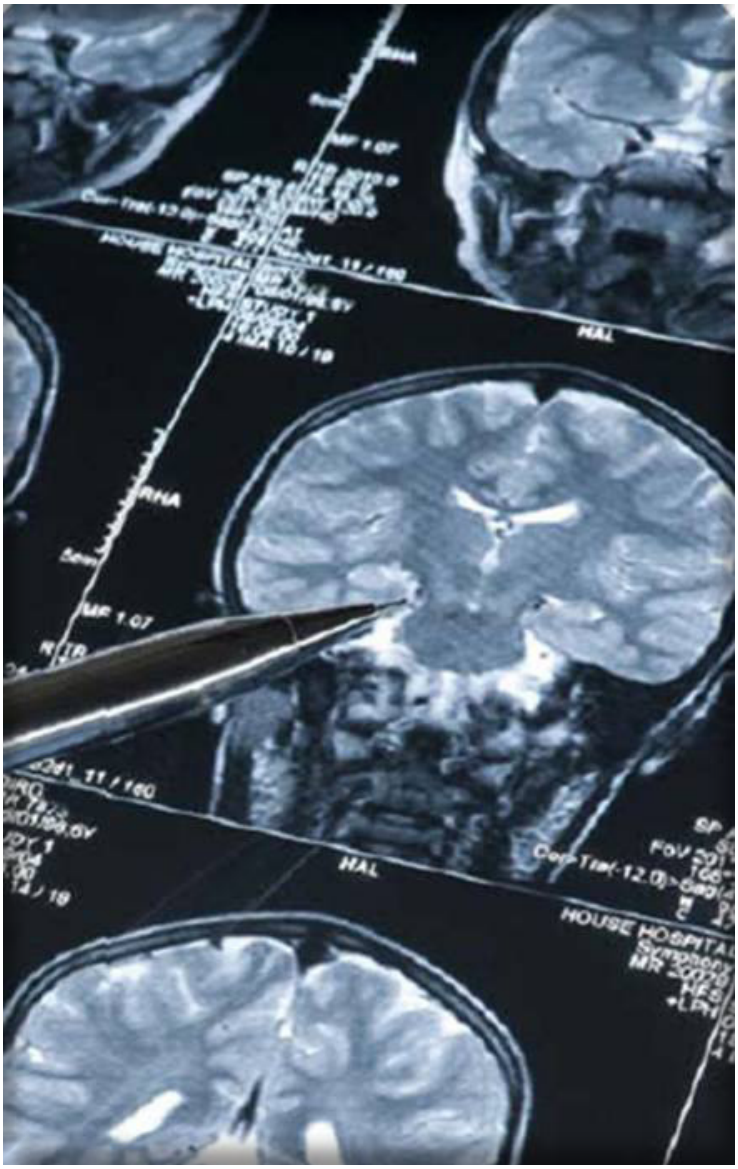
The devices used for running clinical applications differ with users, purpose of application, affordability, availability and use culture. Clinical user interface has to be customised to the electronic device on which the clinical application is going to run on. This includes desk stations and laptops, notebooks, tablets, ipads, smartphones, and in the future smart watches, smart glasses, etc. It is a challenge to accommodate the same amount of information and clinical functionalities, on screens with different sizes, technical functionalities and limitations.

Along with the electronic device, the user interface of the applications will have to differ according to the user needs. User needs in turn would also dictate the choice of devices used. The following is a spectrum of needs or purposes of the CUI:

- Educational purpose, delivering information knowledge to citizens
- Real-time feedback for diabetes patients with their sugar levels, hypertension patients with their blood pressure and heart rate, etc.
- Decision support, e.g., dose of warfarin in self-management of anticoagulation by patients, dose of insulin in diabetes, etc.
- Behavioural feedback for patients regarding continuation or discontinuation of exercise like running, depending on their heart rate and/or respiratory rate
- Clinic/hospital management including patient appointments, instigations, treatment and procedures
- Clinical Research studies with demographics, inclusion criteria, clinical assessments, images and statistical data

Clinical decision support systems (CDSS) are important tools to improve health care outcomes and reduce preventable medical adverse events. However, the effectiveness and success of CDSS depend on the ease and completeness of the Clinical user interface.

The ability to personalise the user interface to your needs



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could be an additional aspirational feature. If an individual user can modify the CUI, it can support one's specific job.

- Modify the home screen layout to only include data types that are relevant to you
- Choose to display only the columns you need in the exact order you need them, across most screens of the application
- Create queries and save them to run at any time.

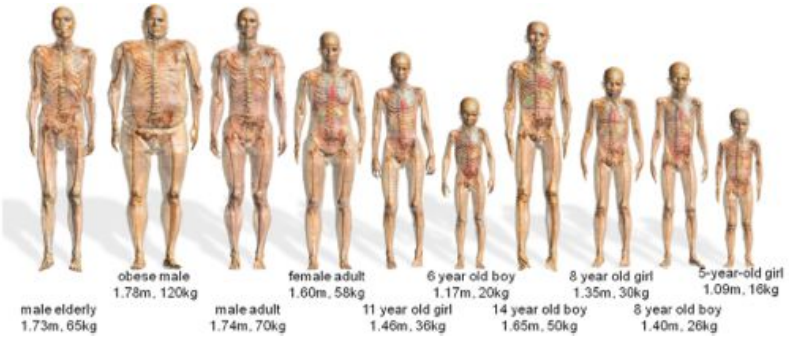
Thus, addressing these challenges and overcoming the obstacles they represent for the adoption of the Digital Patient framework by a heterogeneous population of users working in rigidly structured clinical set ups requires a thorough understanding of the user's identity, needs, and habits. This information will be best acquired by performing interviews with individual stakeholders prior to releasing a fully-functional interface and after given trial periods to assess efficacy and satisfaction. It is further contingent on minimising the required structural changes to existing systems and workflows, and minimizing the workload associated with required changes, devising intuitive graphical user interfaces, finding the right balance between automation and interactivity, reducing the risk of human error, providing automatically-generated reports that can serve several users in the clinical workflow, and either offering sufficient flexibility to accommodate individual user groups or institutions, or providing users or user populations with the ability to personalise their interface themselves.

Options for personalised interfaces could include the possibility to working with and displaying only particular types of data and applications, or the possibility to create queries and save them for later use. All the clinical integration work needs to be performed in close collaboration between the software developers and the clinical partners to guarantee that the results are optimised for clinical needs. This in turn requires the integration into the framework of feedback possibilities and a constant dialogue between stakeholders.

Use of clinical interfaces to interact with models of human physiology

The success of modelling and simulation projects often stands or falls based on the quality of the interfaces. This is particularly true for immersive acute care training simulations, where significant differences with clinical reality would greatly distract the trainees, and thereby most likely reduce both the quality of learning and transfer of learned skills from the simulated to the real environment.[1] In this context, trainee, instructor, and medical device interfaces are carefully designed.[2] Data from DP models could be presented to clinicians via these realistic interfaces, such as implemented in the Human Patient Simulator (HPSTM), commercialised by CAE Healthcare.

1 Van Meurs W: Modeling and Simulation in Biomedical Engineering: Applications in Cardiorespiratory Physiology. McGraw-Hill, 2011
2 Van Meurs WL, Good ML, Lampotang S. Functional anatomy of full-scale patient simulators. J Clin Monit 1997 Sep;13(5):317-24



Source: www.itis.ethz.ch/virtualpopulation

5.4 Avatar: a virtual integration of data and information

The Digital Patient framework will include a 4D individual-specific health avatar developed utilising modern ICT technology. This representation will serve as a portal for user-specific access to data, including long-term and consistent health status information of individual citizens, and for data analysis, knowledge discovery, and disease evolution and treatment efficacy forecasting by means of integrated predictive computer simulation models and other tools. Avatar literally means embodiment or manifestation and is a 4D personalised representation of individual patients developed utilising modern ICT technology.

This section builds upon the concept and use of the term avatar in two EC funded projects, **myhealthavatar**[3], a citizen centred avatar that promotes self-engagement of citizens, and **VPH-Share**[4], a safe online facility in which medical simulation developers can produce workflows - chains of processing tasks - to allow raw medical data to be refined into meaningful diagnostic and therapeutic information.

5.4.1 Health Avatars for citizens

As a general feature, any Digital Patient interface should allow access to the medical history of individual patients, to all the risk factors associated with the development of major diseases, and to all available data likely to serve the user's needs. Such an access obviously needs to be user-specific, such that any citizen can access his/her own data only, researchers can access and retrieve anonymised information relevant to their research projects, and health professionals can access and retrieve all the information likely to serve the purpose of informed decision making (decision), communication (explanation and presentation), prevention, planning, execution and assessment of treatments (execution), and knowledge integration and discovery (translation).

Access to extensive information will prove particularly useful for clinical decision-making as the risk, development, and treatment of many major diseases are affected by a great number of individual factors varying in time, ranging from genetic predispositions, to age, lifestyle, and environmental variables. Provided that the strong dynamic nature of these factors is accounted for and that their temporal variation is systematically recorded over the long term, these factors could be particularly useful in supporting individualised prediction and treatment. Moreover, the collection of such individual data across many individuals would result in comprehensive population-level information, which, in turn, would offer extremely valuable input to clinical research for new knowledge discovery. Given the increasing number of patients with or in the need for active and passive medical implants and the risks associated with exposing patients with implants to various imaging technologies (notably magnetic resonance imaging), available image data should be equally accessible and usable for segmentation and generation of meshed anatomical models, which in turn can be used with existing simulation technologies for personalised safety assessment. To date, creating realistic models including tissues and physiological functions on a routine basis remains unrealistic and considerable methodological developments will be needed. Once available, these functionalised models can be used for treatment planning (e.g., in radiotherapy) for instance and can be gradually enriched with novel data acquired on individual patients.

Hence clinical user interfaces of the health avatar should provide the necessary toolboxes and computing resources to support the access and retrieval of heterogeneous information from individual or populations of avatars, visually assisted data analysis (i.e. visual analytics, see section 4.5), multi-scale and multi-physics simulations, body-centric and multi-scale visualization of raw data and of simulated results for the extraction of clinically meaningful information such as symptoms' patterns, treatment success, drug response, self care guidelines, and risk factors, interactive treatment planning and information integration tools, and post-processing tools for illustration and communication. Clinical user interfaces need to be further refined to meet the needs of the various actors likely to interact with the Digital Patient in the clinic, which entails that certain levels of complexity are not required for all types of health professionals. A particular challenge associated with designing a clinical user interface comes with its integration into the established clinical ICT system and the clinical workflow. Both are likely to vary across institutions and the general acceptance of the Digital Patient framework in the clinical set up will be contingent on facilitating its integration and on devising user-friendly interfaces to ease adoption. An important step in the development of the Digital Patient framework and the clinical user interface is therefore to carry out interviews and identify the requirements associated with various healthcare systems.

3 http://www.myhealthavatar.eu
4 http://www.vph-share.eu

A simplified "user-friendly" interface designed for non-scientists should in turn facilitate individual data exploration, and self-motivated and user-centred data collection, while guaranteeing the necessary data integrity. The challenge associated with simplified user interfaces is the wide range of competences and levels of understanding in the population, which can most likely not be addressed in any systematic manner.

By functioning as a personalised metaphor, the 4D health avatar should bring explicit benefits that match the initiative of VPH, including personalised, predictive, and integrative treatment. It should also bring about healthcare cost reduction through individual self-monitoring, and maximised usage of biomedical research money through a facilitated access to individual and population-level data and a unique framework for merging greatly heterogeneous data, collected or generated using different models, organ systems, space-time scales and modalities.

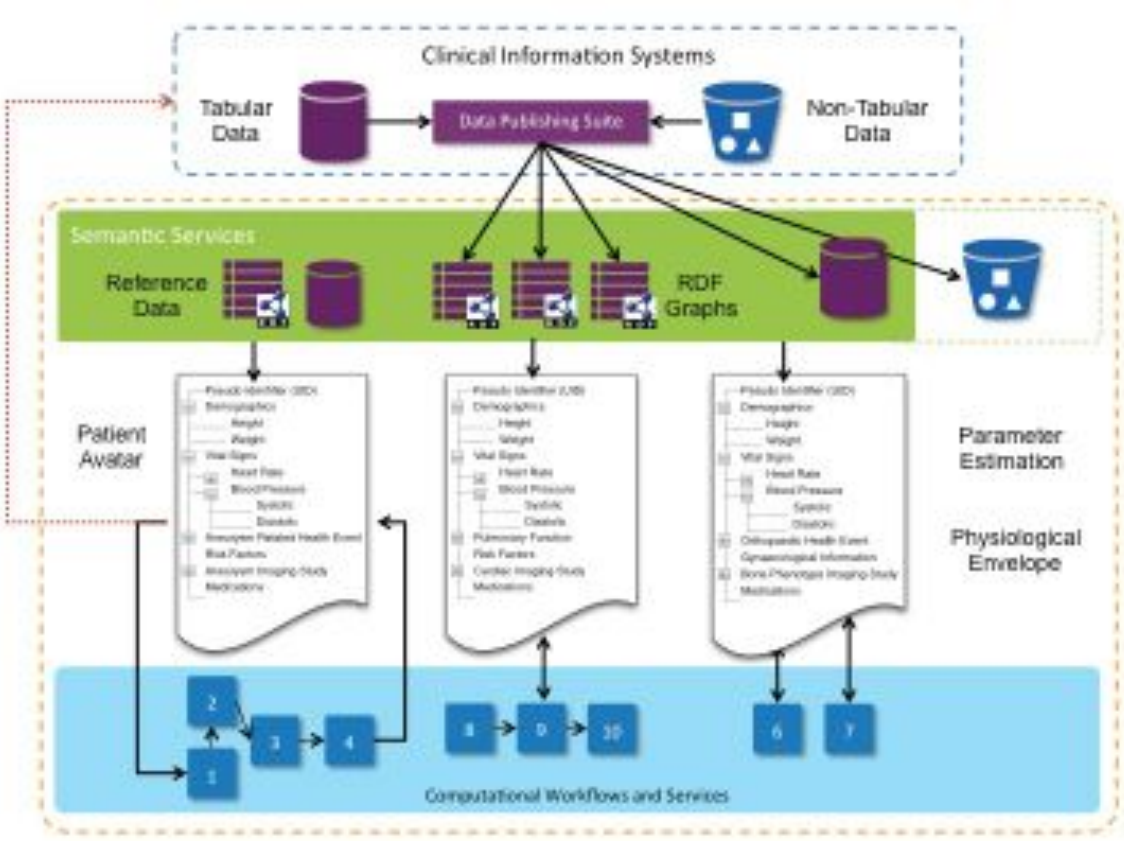
5.4.2 Patient Avatars for clinical research

A consensus body-centric and multi-scale digital representation of all health-related data that is available for a given individual is the Patient Avatar, a concept defined and promoted by the VPH-Share project as the general basis for the construction of each of the four VPH-Share flagship workflows[5].

A Patient Avatar embodies a strategy to catalogue every patient-health-related data item relevant for each of the four workflows (euHeart, @neurIST, VPHOP and Virolab) and to use it to help deduce relevant missing data items from all available VPH data sources and population data, providing appropriate average values and related variability and uncertainty inferred for a specific patient. It is a key strategy to help integrate available, but sometimes sparse, scattered and inconsistent clinical information within a personalised representation. The Patient Avatar requires a holistic and consistent view of the patient and therefore has a close relationship with and exploits the standards and technologies used to implement Electronic and Personal Health Records (EHRs and PHRs). The use of EHR standards also exemplifies the semantic aspects of the Patient Avatar as it imparts meaning to the sparse clinical data.

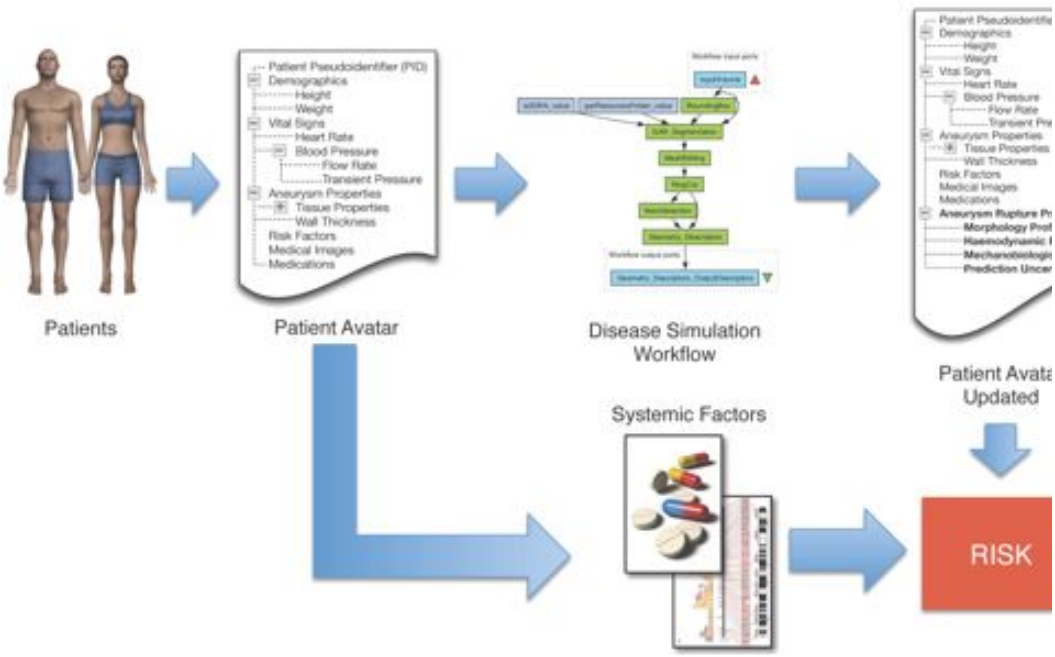
User interfaces and complex workflows: what is behind the Patient Avatar?

The potential integration of clinical, genetic, epidemiological, demographic and biological information with support from advanced computational and image processing techniques in conjunction with advanced user interfaces could transform research and the delivery of care. Digital extracts from such data and tool integration is of particular interest to all four workflows. In fact, all four workflows have already attempted to integrate clinical and workflow relevant information into their own respective pipeline internally, see the figure on the left. As part of the workflow development process, each workflow specifies not only a sequence of computational assemblies to process the clinical data, but also defines the input and output data using workflow archetypes specific to each individual workflow. This is essential information for the user interface. The Patient Av-



Clinical Data Integration and Publication Pipeline.
Source: VPH-Share

5 http://www.vph-share.eu



Computational Biomedical Modelling Workflow: From Patient to Risk Assessment.
Soure: VPH-Share

atar is an attempt to expose commonalities and specificities of such workflow archetypes into a global representation of a patient to help integrate and augment the data items with scattered external data, and allow workflows and other VPH projects interoperate.[6]

Deep integration and translation of mathematical and computational models into clinical practice for therapy planning can create new opportunities to gather workflow relevant clinical parameters from improved standard data acquisition protocol. A typical workflow, from the @neurIST project, which moves from the patient to disease event risk assessment via a disease simulation model, is shown in the figure above.

The disease simulation model is composed of multiple computational and/or mathematical models that represent the various aspects of the physiological process in general. Clinical data is represented as a Patient Avatar, which in turn is the combination of a common shared Patient Avatar archetype and a specific @neurIST *workflow archetype*. The model is tuned and executed using parameters derived from patient-specific data and population-level data represented to later inform and update the Patient Avatar with a risk profile.

Many of the parameters required for the simulation may not be part of standard data acquisition protocol and hence may need to be derived from literature and/or statistical models. Patient data are not usually single scalar quantities, but are often represented as a range of values measured at different times and states of the patient. The disease simulation model almost always represents an ideal generic case, where the variability and uncertainty of the patient data is not been taken into account. As part of the VPH-Share project, the Parameter Estimation and Physiological Envelope for Simulation and Model Interpretation tasks attempt to bridge this gap by introducing parameter estimation and uncertainty envelope libraries for simulation models.

Parameter Estimation and Physiological Envelope functions are part of the Patient Avatar and are external functions invoked by the disease simulation workflows to allow them to operate. They take as their starting points the data already in the Patient Avatar, and the derived results may be returned to the original Patient Avatar, with appropriate safeguards concerning their 'derived' nature, in a similar way as for simulation results. This also highlights a need for a Patient Avatar to be able to cope with uncertainty and importantly be differentiable into measured and derived at a scale that is perhaps actually a continuum - how close to reality is a measurement?

To be useful the parameter estimation process requires access to a large amount of literature, population data, and a large number of statistical models. An effective 'average' Patient Avatar is used to cluster the individual Patient Avatar population based on the specific phenotypes and extract that distribution (average and deviations) for use instead of the missing parameters. This can only be possible with deep integration of multiple sources of patient data within a single format, and hence the need for a Patient Avatar.

The use of holistic Patient Avatars with digital extracts from clinical EHR combined with averaged estimates from patient phenotypes could offer huge benefits for long-term clinical impact.[7] Some of these are outlined below:

6 Varma et al. VPH-Share D5.1 Patient Avatar Defined for Flagship Workflows. VPH-Share 2011 http://www.vph-share.eu/content/deliverables Retrieved 21 June 2013

7 Pelino et al. IT-enabled personalized healthcare. TechReport 2012. http://public.dhe.ibm.com/common/ssi/ ecm/en/gbe03299usen/

- Descriptive Use-Case: At this level, the Patient Avatar may simply be used as a *single point of truth* document to generate *standard* or *ad hoc* reports to help understand what happened and if needed *drill down* into the data for specific clarification
- Predictive Use-Case: At this level, predictive analytics can play a more significant role in facilitating clinical decision making by providing for example *alerts* for potential adverse drug interactions, *simulate* clinical trials on a virtual cohort of patients or even use the Patient Avatar to potentially *forecast* the diagnosis or prognosis by comparing an individual Patient Avatar with large populations. Within the scope of the VPH, the Patient Avatar could truly transform the predictive modelling capability in a clinical setting by offering patient identification, treatment planning and better management of outcomes
- Prescriptive Use-Case: The most challenging potential of the Patient Avatar is to help generate prescriptive clinical recommendations to help achieve the best outcome, even in lieu of constant variability not just in terms of patient status, but also new medical knowledge

Across all levels, success is highly dependent on the quality and completeness of the clinical data used as well as the sophistication of the methods, models, algorithms and techniques on which these analyses depend.

By functioning as a personalised metaphor, the 4D health avatar should bring explicit benefits that match the initiative of VPH, including personalised, predictive and integrative treatment. It should also bring about healthcare cost reduction through individual self-monitoring, and maximised usage of biomedical research money through a facilitated access to individual and population-level data and a unique framework for merging greatly heterogeneous data, collected or generated using different models, organ systems, space-time scales and modalities.

The Patient Avatar is a useful portal and a user-friendly entry point to the complex data, information, and knowledge available for individual patients. However, such an anatomical representation is not sufficient for all types of applications. For example reliable treatment planning or personalised safety assessment require highly detailed, image-based virtual patient models, enriched with tissue-specific and physiological information. The generation of such models necessitates segmentation and meshing of medical image data and can only be partly automated. Considerable methodological developments are needed for creating such models on a routine basis. Currently available models (e.g., Virtual Population models) are for instance used to quantify the risk associated with exposing patients with medical implants to prolonged magnetic resonance imaging. Given the increasing number of patients with or in the need for active and passive medical implants and the risks associated with exposing such patients to various imaging technologies and sources of electromagnetic exposure, the need for such models is only going to grow. It is further going to increase with the growing medical implant industry and the need for *in silico* experiments during product design, development, and certification.

GBE03299USEN.PDF Retrieved 21 June 2013.

5.5 Visual Analytics

Visual Analytics (VA) is an important way to graphically present data and information within a Digital Patient at various levels of details. It combines automated analysis techniques with interactive visualization for an effective understanding, reasoning and decision making on the basis of very large and complex data set.[8] As a major multi-disciplinary field, VA includes the science of analytical reasoning, interactive graphical representations, and interaction techniques, data representations and transformations, production, presentation and dissemination.

VA plays an important role in the interaction between users and the Digital Patient, allowing information comprehension and data analysis. Automatic data analysis has achieved great success in the last few decades. Visualization is effective in terms of helping domain experts to understand data by offering crucial visual information. However, due to the rapid evolution of data complexity, existing simulation and fully automatic data analysis is often not able to reach an optimal solution. It is found that a more effective approach can be to involve the power and versatility of human decision-making by integrating simulation and data analysis with interactive visualization.

Due to the complexity of clinical data and simulation results, it is extremely difficult to automatically find optimal solutions in clinical cases. Hence human knowledge is needed to achieve better solutions, and is provided manually by the users. The research question is how to facilitate the human-machine interaction and how to achieve a good balance between the level of automation and human intervention. A visual analytics system cannot be too demanding in terms of input (i.e. time & labour), but a higher level of automation may lead to unreliable results.

The effectiveness of visualization for clinical applications has already been demonstrated through many VPH projects. A distinctive feature of VPH is the handling of large,

8 D. Keim, J. Kohlhammer, G. Ellis and F. Mansmann, Mastering the information age: solving problems with Visual Analytics. Eurographics Association, 2010

complex and multiscale human data for clinical decision making. Often, the complexity of the clinical data and the diversity of the patient population suggest that many simulation and data analysis results can only serve as a reference to assist clinicians in making a final decision. To allow for effective involvement from the users, providing a faithful graphical representation of the data and good user interaction tools is important. To this end, VA fits well with the demands of the exploratory analysis from VPH as well as from the Digital Patient.

The task of VA for Digital Patient is to facilitate clinical decision-making and information access by providing users with integrated simulation, data analysis, and visualization tools to explore their results. Hence, the key research topics should include:

- Clinical data representation and management
- Analytical reasoning for clinical decision making
- High dimensional and complex data visualization
- System integration
- User interaction

A critical challenge in the representation of a Digital Patient is the size of the data set, as well as the level of complexity involved within the clinical cases. More specifically:

- Management of large data and models
- Visually controlled data mining to support the sound integration of user interaction for effective data mining
- New interaction techniques to support effective model/data exploration through user interaction, e.g. eye tracking, human gesture, touch screen etc. Special attention should be paid to interaction techniques for collaborative and distributed working environments
- Evaluation techniques to test the results of the above techniques.

Visualization techniques that are particularly suitable for the exploration of data and model relationships within a Digital Patient include the interactive visualization of very large models and data, multiscale visualization (in both the spatial and temporal scale), visualization of model and data uncertainty, and collaborative visualization. Whereas a lot of effort has already been invested into visualization techniques, much remains to be done. Visualization of high dimensional datasets and models for instance has been a research interest for many years in information visualization but many of the problems still remain largely unsolved and a convincing way to represent high dimensional information is still lacking. The visualization of multiscale data sets in turn has been successful in many cases, including Google Maps, human neural systems, etc, but much remains to be done in the biomedical area.

Finally, the limitation of classic human-computer interaction through the mouse and keyboard has already been generally recognised. However, many computer vision techniques, such as tracking human gestures and eyes, that are adopted in computer graphics and computer games to enable more “natural” ways of interacting with computers could be adapted to clinical applications. Multi-touch techniques, is another approach that has attracted a lot of research attention already and that can be further explored in the clinical context.

Evaluation is the key to clinical applications. To prove the effectiveness of VA, adequate evaluation will have to be carried out by users. The motivation of the evaluation would be to provide evidence that a VA can bring about improvements, to illustrate how visualization techniques have helped to highlight information which is not clearly visible in the original data; to illustrate why simulation and automatic data analysis have failed to achieve optimal solutions in these evaluated cases; and to exemplify how the iterative process of visualization, simulation, automatic data analysis and user interaction in visual analytics helps to achieve better results.

5.6 Summary and conclusions

In conclusion, it should be emphasised that currently working prototypes are available and allow the 3D exploration of large amounts of information on human anatomy, physiology and pathology, referred to an average subject (generic) in fixed time point (static).

Future research should prioritise:

1. Support for effective management of individualised data
2. The extension of existing tools to support time-varying, dynamic data, and support multiscale interactive visualization for data defined at different time scales (data defined across different spatial scales)
3. The development of efficient methodologies for the rapid generation of image-based functionalised anatomical models for safety assessment and treatment planning
4. Extensions to support novel human computer interaction and interactive visualization that allow the usage of large-scale data from heterogeneous sources for knowledge discovery
5. Extensions to support effective information retrieval
6. Extensions to support seamless interfacing with the existing healthcare systems under the criteria of clinical adaptability
7. Extensions to support sound evaluations of digital patient technologies.

6. Translation and adoption

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6.1 The central challenges

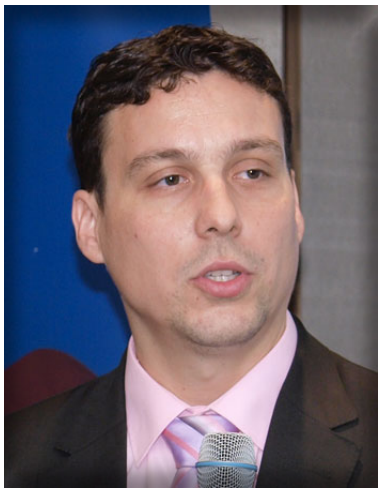
Certain topics arise repeatedly in almost every discussion of the focal issues and central concerns of today's health systems. Some of the most significant drivers and trends in healthcare have been identified as[1]:

- Demographic and social change (ageing of society and workforce; increasing life expectancy; changing family forms)
- Old and new disease threats (chronic diseases; environmental pollution; antibiotic resistance; modern living/ lifestyle diseases: depression, obesity, drug addiction)
- Rising health awareness and so-called consumerism
- Individualised/personalised medicine
- Growing ubiquity of health informatics and telemedicine[2]
- Understanding and exploitation of genomics, proteomics and other biomolecular sciences
- Other new medical technologies[3]
- Increasing costs of health and social care provision

These drivers and trends need to be reflected with key policy challenges across all European health systems. The opportunities and benefits offered by model-based *in silico* medicine should be realigned, to target solutions for these challenges.

The overarching aim of the Digital Patient is to facilitate and lead to improved health outcomes for citizens within Europe and beyond. In line with this ambition, and to investigate such a potential future, the task of translation and adoption is to explore possible future diffusion scenarios, their challenges and ways to mitigate those challenges. Estimates of potential clinical impact would enhance those diffusion scenarios.

It is important to emphasise that the use of mathematical and computational models in clinical practice is not a new phenomenon. Good examples of computational medical modelling have been around for over 50 years.[4] Early examples include models for the diagnosis of congenital heart disease[5] and the diagnosis of acute abdominal pain[6] which performed at least as well as clinical specialists. Some methods based on mathematical models have been in routine use for over 20 years, particularly in the management of cardiovascular disease risk.[7,8] What is new, are the benefits emerging from current ICT solutions; particularly in terms of speed and data handling capacity. Thus, the complexity of these models and the evidence supporting their use continues to grow.[9] Mathematical models and techniques have demonstrated a key role in policy making, including health-economic aspects; emergency planning and risk assessment; control-programme evaluation; and monitoring of surveillance data.



> "Exploring business models of healthcare adoption and of the delivery of new procedures is central to market translation"
>
> Miroslav Koncar, Oracle

The availability of new medical data and the development of new computational tools in medicine have also produced an increase in public media interest. The perception of the general public about the adoption of methods and techniques based on computational methods for health assessment is changing in a positive way. Recently, a new mathematical model for cancer treatment, based on a research project from the University of Maastricht, received wide media coverage. The model was claimed by the press to be "better than doctors"[10] as researchers found that it consistently outperformed experienced clinicians. However, news reports such as these, with an implication that computer prediction models will eventually replace doc-

1 World Economic Forum (2013). Sustainable Health Systems - Visions, Strategies, Critical Uncertainties and Scenarios.
2 http://www.ukbiobank.ac.uk/
3 For example, cf. http://www.nuffieldbioethics.org/neurotechnology

4 Ledley, LS, Lusted, LB (1959) "Reasoning foundations of medical diagnosis".Science;130;9-22
5 Warner HR, Toronto AF, Veasey LG, et al. (1961) "A mathematical approach to medical diagnosis: application to congenital heart disease". JAMA. 1961;177:75–81
6 Horrocks JC, McCann AP, Staniland JR, Leaper DJ, De Dombal FT. (1972) "Computer-aided diagnosis: description of an adaptable system, and operational experience with 2,034 cases". BMJ 1972 Apr1;2(5804):5–9
7 Tunstall-Pedoe H, (1991) "The Dundee coronary risk-disk for management of change in risk factors" BMJ. 1991 September 28; 303(6805):744-747
8 European Society of Cardiology (2012) "Score Risk Charts", accessible at http://www.escardio.org/communities/EACPR/toolbox/health-professionals/Pages/SCORE-Risk-Charts.aspx
9 Martin C, Vanderpump M, French J. (2004) "Description and validation of a Markov model of survival for individuals free of cardiovascular disease that uses Framingham risk factors" BMC Med Inform Decis Mak. 2004 May 24;4:6
10 Cf. "The Independent", April 2013, accessible at http://www.independent.co.uk/news/science/the-computer-will-see-you-now-the-cancer-prediction-software-thats-better-than-a-doctor-8583534.html

> “Next level of VPH research: not only improving diagnosis, treatment & prediction but also incorporate economic considerations: this would bring health systems on board.”
>
> Daniel Rüfenacht, Swiss Neuro Institute

tors, are potentially misleading. This is unlikely, and indeed unwelcome from the point of view of both doctor and patient, but we are already beginning to see a new generation of doctors who are happy to use computerised models routinely to support their decision-making.

All this activity is founded at a time when new business strategies for translational research are emerging within the healthcare industries. As discussed below, the changing landscape for pharmaceutical research is a good example in this context.

The business model for the pharmaceutical industry has been in a crisis since the early 2000's. With huge investments in research and development and very little output, companies have been forced to rethink their strategy. New translational research centres have been created in order to increase the collaboration with academia to turn new ideas from fundamental research into deliverable products.

Whilst it will take a little more time to see the effect of these new collaborations in terms of innovative drugs and treatments and economic results, the primary motivation of this new business model is to generate savings in investment within both the industry and the universities. A secondary aim is to encourage public and private researchers work together, irrespective of their somewhat different goals. As might be anticipated, this new approach brings not only benefits but also new concerns. Some areas of mathematical modelling in the pharmaceutical industry could be regarded as fundamental research and thus at risk of receiving less funding as the trend moves towards higher investment in applied research. Universities also have concerns about conflicts of interest for researchers working with industry[11], and regulations are needed to make sure that, for example, researchers will be able to publish their results, either positive or negative. Another risk of those important collaborations with the industry is that whole areas of pharmaceutical research might be put aside because of their low industrial output.[12]

Aside from its direct clinical application, the Digital Patient has a significant role to play in this new approach with the potential to help to turn early-stage innovations into new health products, advancing innovation to the point where it becomes attractive for further development by the medical industry or healthcare agencies. Mathematical models are already part of the R&D drug pipeline being an area continuously evolving in pharmaceutical companies. Areas such as Quantitative pharmacology (pharmacometrics) and Clinical pharmacology use population based modelling for the development of new therapeutics and novel areas as Systems pharmacology are trying to emerge as alternative approaches to translational medicine, combining computational and experimental methods.

Regulatory approvals for a New Drug Application (NDA) currently require specific mathematical analysis related to pharmacology studies (see the Modelling chapter of this Road Map for more details). A recent paper published by the European Federation of Pharmaceutical Industries and Associations (EFPIA) has highlighted the need to adapt regulatory frameworks to R&D advances and new therapies.[13] A central recommendation, particularly relevant to the Digital Patient, stresses the uptake and support of new trial designs and statistical methods to help reduce high failure rate of late-stage clinical trials. New approaches and methodologies based on the Digital Patient might become part of the proposed approval processes once these methods are validated and can be trusted by the Regulatory Agencies.

Irrespective of the exact target application, the central challenges to translation and adoption are the trustworthiness and the usefulness of DP solutions. These are addressed through validation: technology assessment (with different methodologies required for “validation” by engineers, by clinicians, and by policy-maker/economists) and clinical acceptance (i.e. adoption issues beyond clinical validation: workflow integration, clinical decision support systems (CDSS) and EHR integration, usability, etc).

The challenge for research into clinical decision support in the coming years is to build systems which are more than just reminder systems that animate simple guidelines. We

11 Commercial projects with Universities allowing industry to exploit global Intellectual Property yet with University rights for further R&D is a win-win. Adding clauses that further investment with the University if the ‘product’ is successful may continue a cyclical working synergetic partnership. Not always the best products get to market which is why companies need freedom-to-operate.

12 www.boston.france-science.org/2012/06/25

13 Forda, S.R., et al. (2013). “Priorities for improving drug research, development and regulation.” Nat Rev Drug Discov 12(4): 247-8.

should, instead, be seeking to realise the vision of personalised healthcare by creating systems that can deal with complexity, integrating multiple sources of information (and possibly creating new knowledge) in order to identify the appropriate course of action for an individual.

Clinical decision support systems: limitations and opportunities

Clinical decision support systems (CDSS) are usually defined as systems that make targeted knowledge available to clinicians in order to answer patient-specific queries, clinical decision support systems were first advocated as a solution to the increasing complexity of clinical medicine. It is therefore perhaps surprising that most contemporary implementations of decision support systems do not address complex problems. Rather most of the research effort has gone into systems designed to make the process of evidence-based practice tractable through the automated dissemination of consensus guidelines. There is good evidence that in certain settings such 'reminder' systems - if well integrated into existing clinical systems - can have an impact on clinical decision making and patient care and even improve outcomes. The goal is often to reduce physician error by repeatedly reminding the practitioner of what the guideline says is best practice in a given situation, or to alert the prescriber to possible contraindications for a drug.

There are clear limits to the effectiveness of this kind of intervention: repeated alerts are overridden without attention, guidelines deal only with 'typical' presentations and since most patient are elderly and most elderly people have multiple co-morbidities, management must often be tailored. The limitations of the current approach can be seen in the limited success that such decision support systems have had.

The challenge for research into clinical decision support in the coming years is to build systems which are more than just reminder systems that animate simple guidelines. We should, instead, be seeking to realise the vision of personalised healthcare by creating systems that can deal with complexity, integrating multiple sources of information (and possibly creating new knowledge) in order to identify the appropriate course of action for an individual.

Validation is the main enabler for translation. The current paucity of evidence of clinical efficacy, cost benefits and time saving has been highlighted as a challenge to translation and implementation. Validation is a prerequisite for the acceptance of any new technology by clinicians and health care providers alike. There are other more technical challenges to successful translation, such as availability of large banks of data, data quality and integrity, storage, information and knowledge management, acquisition of prospective data and access. These are discussed in previous chapters of this Roadmap.

The availability of data for model validation can be a problem for the Digital Patient. On one hand, sharing data is not a natural process in industry or even, as is often the case, in academia. Industry is resistant to publishing their data due to confidentiality issues, and some academic groups prefer to keep their data to themselves (in order to maintain their competitive advantage). On the other hand, some models require data that is not readily available, not easily measured and requires additional investment of resources (money, equipment, people, time, etc) that industry, hospitals or academic departments are not willing (or able) to fund. Sharing of any pre-existing data would be invaluable in this context.

Healthcare professionals will require objective evidence of rigorous validation as a pivotal component of the pathway to the adoption of DP technology in clinical settings. This translational research gap requires urgent attention.

In order to translate conceptual prototypes of the Digital Patient that are effective and fit for clinical purpose, each patho-physiological modelling component will require user-friendly interfaces that can be tailored for prevention, diagnosis, prognosis, treatment planning, and/or monitoring purposes.

The Digital Patient, as a new research agenda that aims to interact with clinical users and deliver simulation results, must be proven to be clinically useful and demonstrated to be effective. To this end, health technologies are usually subjected to experimentation, refinement, and increasingly realistic testing,[14] which, in the case of VPH technologies, means to clinical testing (i.e. clinical trials). The testing for correctness ranges from technical capability assessment (verification, sensitivity, validation), to accuracy assessments (prediction uncertainty), and efficacy and clinical effectiveness assessment.

The set of effectiveness and safety metrics should also include subjective indicators that capture the user experience; user cohorts must be stratified to represent realistic and relevant clinical scenarios (e.g. trainees, senior users with low IT exposure, etc.) as well as stratified for different patient scenarios.

14 http://www.techwhiteboard.com/tech-research-levels/

> “Successful R&D is right from the start linked with the embracing of exploitation strategies, impact analyses and validation”
>
> Dirk Colaert, Agfa Healthcare

6.2 Drivers to translation and implementation

6.2.1 Enabling implementation with a common data dictionary and shared language specification

A key enabler of implementation in the hospital setting is the defined specification of the model in a shared language specification. For example, the Data Mining Group (DMG) propagates a specification language called the Predictive Model Markup Language (PMML), which is an XML-based markup language providing a way for applications to define models (e.g. a logistic regression model) and to share those models between PMML-compliant applications. Whatever the specification language used, an important part of the specification should be dedicated to the “data dictionary”. The data dictionary will enable the clinician to apply, and understand, the model within the specific clinical settings. Variable settings will drive the clinician’s use of the model to enable him/her to use the specific model with confidence. For this reason, it is essential that each variable is clearly defined in terms of its type and acceptable range (for example the variable name “blood glucose” may refer to the fasting blood glucose level, measured as a continuous variable, and has the unit mg/dL). The definition of the variables will be dependent on both the user and the clinical scenario. For example, the model should contain domain-specific factors (e.g. for a model in geriatrics one may expect variables covering co-morbidity, pre-morbid cognitive and functional status). There should not be abrupt risk changes in the model due to the use of thresholds to categorise continuous data (for example one should refrain from categorising ages in e.g. the categories 35-39 and 40-45 because the risk for a patient who is 39 years of age would not be expected to undergo an abrupt change when they turn 40).

In addition, the model should provide the specifications needed for interaction with its environment, and any application that uses the model, in order to obtain values of the variables (for example with digital patient records). To this end it is important to specify the communication standards (such as HL7 or Web Standards) that are expected by the application to communicate with other components in the clinical environment.

In conclusion, enabling implementation will necessitate concurrent feedback between the development phase and the future users to define the clinical values in the clinical settings.

6.2.2 Implementation, statistical and clinical safety validation

The model should undergo a thorough statistical validation. It is not usually sufficient to rely on internal validation alone but rather, the behaviour of the model must be demonstrated for prospective data (temporal validation) and for data collected from other centres (external validation). Performance criteria used to assess the predictive abilities of a model (such as discrimination, accuracy, calibration etc) must be in line with the intended use of the model. Purposes such as benchmarking, screening, decision making etc imply different performance aspects.

Many predictive models rely upon input parameters for a given patient that originate from a range of different sources, including: electronic health records, laboratory and radiology information systems, alongside direct data input by the clinician during a consultation with the patient, and in future data provided by the patient directly or via personal health systems and other monitoring devices. With this in mind, a number of factors must be considered at the development stage in order to secure acquisition of reliable data. For reliable computation, objective, rather than subjective, variables are preferred, for example, blood glucose levels are measured by a laboratory or a near-patient device (objective input) but the Glasgow Coma Scale used in the ICU setting might be scored differently by two clinicians (subjective). Applications that use predictive models should ensure that the data are always checked during operation of the model. Specifically, the application should establish

that the variable values it obtains are credible and refer to measurements from a known source and a known context (in the case of the blood glucose example, is the measurement obtaining during fasting or non-fasting?). Values of blood glucose levels above a certain threshold should be considered inadmissible. Similarly, is the measurement valid? In the ICU setting, repeated respiratory measurement with very low variability of tidal volume could mean that the measurements are inaccurate. In such cases the application should refrain from providing advice and/or alert the user that advice cannot be given (and why).[15]

Systems that store or capture new patient data might fail, become temporarily unavailable, or contain data errors. For clinicians and patients to trust the results offered by Digital Patient models and simulations evidence is required for how the models respond in the event of missing data or, to data values that seem inconsistent with the overall clinical picture and thus might be incorrect. Models might also be reliant upon other up-to-date knowledge that is not patient-specific (for example instrument calibration, reference ranges etc.) and that might be temporarily inaccessible or has not been updated. These are only examples of possible sources of failure, and a comprehensive risk assessment needs to be performed before models and the components that use them are evaluated.

Many risk mitigations can be managed through the DP software itself (e.g. checking the date of reported calibration information), or by the software raising an alert to the clinician or patient user (e.g. if a data source is missing, or if a current data value is very different to previous equivalent values and there might be a data entry error), or by the software declaring an inability to perform a computation because critical values are missing. Safety testing of DP predictive/simulation software must include safety cases that verify the behaviour of the system in such circumstances.

Since the Digital Patient vision implies the combination and probable collaboration of multiple models, safety testing needs to consider the interactions between components as well as each component individually.

Open publication about the safe behaviour of such components, as evidenced by certification, is a prerequisite to establishing clinical utility validation.

6.2.3 Clinical utility validation

Fundamental to the vision of the DP are the scientific and methodological challenges posed by the correctness and accuracy of the developed predictive models in biomedical research. Developers and users are rightly concerned with whether a model and its results are "correct". The correctness needs conceptualisation – in a highly interdisciplinary field of science that is at the crossroads between biological, medical, physical and engineering sciences.

This challenge not only affects scientific quality and the definition thereof, but it has highest relevance for clinical acceptance and adoption, and entails political and economic consequences. Clinicians have expressed their concerns that some VPH ideas are "too virtual", caused by a methodological gap between clinical research standards and physics-based approaches to model validation.

There is currently a lack of a common understanding, and semantics, between the physical and the medical world about what is meant by "model validation". Ignorance of this potential for misunderstanding has become a serious inhibitor for advancing VPH technologies into clinical deployment. In the absence of robust and clinically acceptable evaluation, assurances given by a VPH developer are likely to disillusion clinicians, while funding agencies may be misguided about the maturity of a model through weak evaluation criteria. Presently, the most advanced VPH technologies can be better interpreted as delivering pre-clinically validated models, i.e. some form of prototype demonstration with the use of real patient data, but not clinical validation suitable for a clinical environment and real patient use, which can only be achieved with prospective clinical trials.

> "Digital Health solutions would come from the collaboration of industry, science, and society"
> Hans Hofstraat, Philips Research

Furthermore, even if a model is evidenced as being safe (i.e. that it always provides the intended outputs, if it should), further validation is needed to confirm that these outputs provide appropriate recommendations to patients. Pilot studies can be used to test recommendations against established practice (i.e. mirroring, but not influencing, established practice). Similar validation experiments might also be performed using large clinical databases (EHRs) containing relevant patients with outcomes that are already known. Larger scale (e.g. controlled) studies will later be used to demonstrate the relative effectiveness of novel DP predictions and recommendations over existing practice. Such studies might also be used to develop quantified evidence of the clinical outcome (i.e. clinical benefits). Full Health Technology Assessment (HTA), including cost effectiveness, is eventually desirable to stimulate a trusted mar-

15 Minne, L., et al. (2011). "Prognostic models for predicting mortality in elderly ICU patients: a systematic review." Intensive Care Med 37(8): 1258-68.

ket for the wide scale deployment of digital patient innovations. Here, it may be necessary to formulate new approaches as current methodologies may not be readily applicable to these new technologies. Liaison may be advisable with regulatory authorities to agree the most suitable evidence required for formal approval.

The added value of a Digital Patient combination (fusion) of models – greater than each of the models individually – will also need to be established.

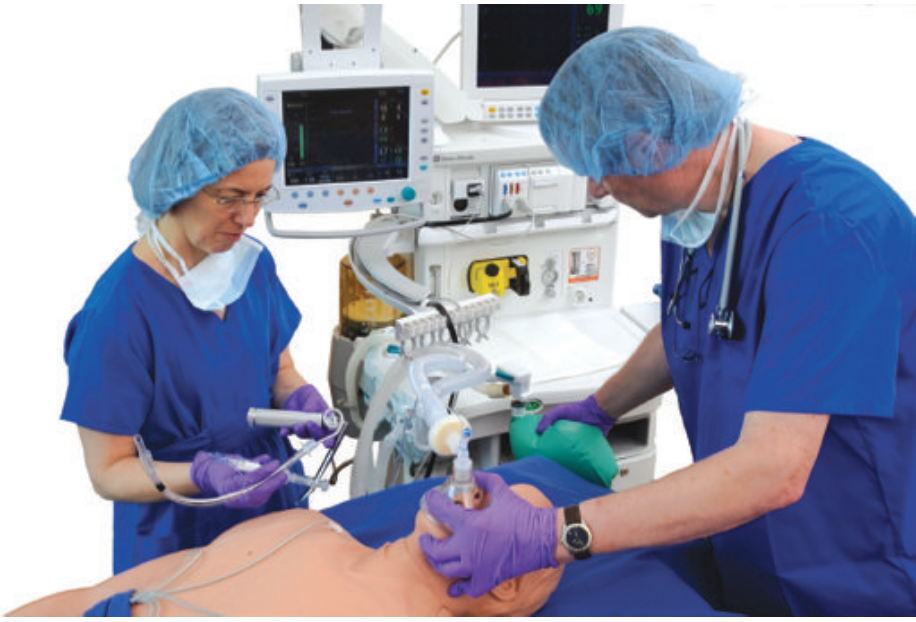
Validated outcomes need to be shared, transparent with clearly defined clinical performance indicators including cost-benefits, hence sustaining the "momentum" through the whole implementation cycle of the new technology. Strengthening open access repositories with protocols, case studies and success stories, costs-benefit analyses and continuous reports of outcomes at national and at European levels could be implemented to facilitate translation based on acceptance. There is value in facilitating a pan-European agreement on validation metrics, to enable comparisons between studies and solutions.

The European Innovation Partnership on Active and Healthy Aging (EIP AHA)[16] is an example of how stakeholders can communicate, identify barriers and mobilise instruments, share best practice and support deployment. The EIP AHA is able to achieve critical mass to facilitate scaling and multiplying innovative ICT solutions in health care systems to bridge gaps and speed up the innovation process. The EIP AHA goals will "enable citizens to live longer independently in good health (increasing Healthy Life Years by 2 by 2020, Quality of Life, Efficiency gains". Such a platform offers a unique chance to sustain public and private collaboration and high level political commitment.

6.2.4 Verification, validation, technology assessment

The validation methodology of physics-based simulation models can be summarised as:

- *'Model validation'*, which is the process of demonstrating that the model matches experimental reality - normally carried out by the author of the model as part of the scientific publishing process.
- *'Model verification'*, which is the process of ensuring that the claimed model outputs can be achieved for the specified inputs (model, parameters, data) - i.e. someone other than the model developer can verify that the model behaves as expected (even if the model bears no relation to reality - i.e. that need not have been validated).



Induction of anaesthesia on the CAE Healthcare Human Patient Simulator (HPS™).
Source: CAE Healthcare

New health technologies are usually subjected to experimentation, refinement, and increasingly realistic testing which, in the case of VPH technologies, refers to clinical testing. The testing for correctness ranges from:

- the technical capability assessment (verification, sensitivity, validation),
- via accuracy (prediction uncertainty),
- to efficacy and clinical effectiveness assessment.

The challenge of validating multi-model simulations poses an additional challenge to validation methodology. This key element for the Digital Patient contains the concept of integrative reasoning, where new knowledge is produced by composing models into a new integrative model. However, there are challenges with this: how can the models be applied as a whole integrated tool, when they are produced in isolation and at a specific level/organ site? How can the validity of basic models be translated into validity of the combination of models, i.e. a hypermodel?

Validation, assessment and healthcare milestones

A research-roadmap-driven taxonomy with a deployment perspective should provide an initial structure for identifying the technology readiness level of a technology, and the assessment approaches deemed appropriate and applicable at the various development and innovation stages:

- verification and physics-based validation of simulation models relate to their technical merit (is it feasible, does it "work"?),
- a socio-economic assessment perspective facilitates

16 European Innovation Partnership on Active and Healthy Ageing, COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL "Taking forward the Strategic Implementation Plan of the European Innovation Partnership on Active and Healthy Ageing" COM/2012/083 final, accessible at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2012:0083:FIN:EN:HTML

the development and testing of clinical application scenarios,
- For evidence-informed implementation and diffusion decisions, the assessment taxonomy should further be complemented by:
- clinical efficacy assessment,
- clinical validation,
- dynamic benefit-cost modelling, reflecting value-propositions for key stakeholders involved,
- development of successful exploitation plans and business models.

In general, the challenges behind scaling up the adoption of the Digital Patient will very much focus on generating evidence of its economic benefits; for example, only a clinical business case will lead eventually an to industrial business case (e.g. vendor adoption, procurement). For proving clinical impact of disruptive technologies such as the Digital Patient, efficacy assessments and clinical validation need to be complemented by cost-benefit modelling of care pathways in routine clinical settings (who benefits? who pays?) Health Technology Assessment (HTA) approaches might be adapted for this, reflecting value-propositions for key stakeholders and market segments, allowing for business planning. Clinical investigations and trial design eventually needs to also comply with the EU medical device regulation(s) for high-risk devices.

The underlying general inhibitor is that many health technology product developments (as is the case with VPH) are typically driven by engineering milestones (prototyping, technical validation, etc), and not healthcare milestones (clinical indications, target product profile, stakeholder analysis, care pathway analysis, business planning, patient safety, reimbursement).

6.2.5 Distributed access (federation, cloud computing)

The health context is changing and with it data exchange is exponentially expanding, because hospitals need to cooperate to provide the best health care to patients with complex co-morbidities. Clinical care increasingly relies upon the integration of digitised patient information derived from multiple care settings and systems (e.g. hospital and GP). Many health services are nowadays looking to cloud computing as an easily accessible means to use data more efficiently in hospitals, and to implement data-sharing at a regional level. Cloud computing can also provide value for training. Socio-technical challenges for the acceptable use of cloud solutions include: data protection, privacy issues, and legal issues. In practice, local and regional differences in accessing ICT services need to be taken into account. A hospital or regional level federation of existing services may at times be preferable to fully external cloud solutions.

6.2.6 Simplification and usability

Models and computational tools should be friendly and relevant for the user. The user should be confident in trusting the models and the models should help to answer the relevant clinical/medical questions the user has.

In the various clinical scenarios, the common goal is to re-

Verification and validation (V&V) of VPH models can possibly be informed by similar work in the somewhat more constrained context of models of human physiology and pharmacology for educational simulation. Building on a basic V&V strategy for organ and organ system level models of human physiology,[1] recent work[2,3,4] is expected to quickly lead to a systematic validation approach that explicitly refers to educational goals, makes use of real tracings whenever appropriate, and provides recommendations for blinding expert validators to - or informing them about - underlying simulated conditions and/or the use of real tracings.

An opportunity to test and assess DP technology prior to clinical tests provides the Human Patient Simulator (HPSTM), commercialised by CAE Healthcare, Montréal, Canada. It was developed at the University of Florida to train anaesthesia residents in basic skills and emergency procedures.[5] Its potential to be used in studies assessing clinical procedures and technologies was recognised early on, for example to assess the influence of pulse oximetry on the time to diagnosis of critical incidents in anaesthesia[6] or to assess a new plastic optical fiber stylet for human tracheal intubation.[7] Similarly, spin-off DP technologies, such as tools for clinical decision support, could first be tested on the HPSTM bench top, before their testing and application in the real clinical environment.

1 Van Meurs W: Modeling and Simulation in Biomedical Engineering: Applications in Cardiorespiratory Physiology. McGraw-Hill, 2011
2 Bastos LF, Lobo MF, van Meurs WL, Ayres-de-Campos D: An intrauterine pressure generator for educational simulation of labour and delivery, Med Eng Phys. 2010 Sep;32(7):740-5
3 Bastos LF, van Meurs W, Ayres-de-Campos D: A model for educational simulation of the evolution of uterine contractions during labor, Comput Methods Programs Biomed. 2012 Aug;107(2):242-7
4 Lobo MF, Bastos LF, van Meurs WL, Ayres-de-Campos D: A model for educational simulation of the effect of oxytocin on uterine contractions, Med Eng Phys. 2013; 35: 524-531
5 Good ML, Gravenstein JS. Anesthesia simulators and training devices. Int Anesthesiol Clin 1989; 27(3):161-168
6 Lampotang S, Gravenstein JS, Euliano TY, van Meurs WL, Good ML, Kubilis P, Westhorpe R. Influence of pulse oximetry on time to diagnosis of critical incidents in anesthesia: A pilot study using a full-scale patient simulator. J Clin Monit Comput 1998 Jul;14(5):313-21
7 Gravenstein D, Melker RJ, Lampotang S: Clinical assessment of a plastic optical fiber stylet for human tracheal intubation. Anesthesiology. 1999 Sep;91(3):648-53

use data from different sources and platforms, enrich the models, and enable rapid decision support analysis (for example, the case of treating patients with acute coronary syndrome in the acute setting of the Accident and Emergency Department). This requires simple user interfaces and the training of the users. Usability of the tools is proposed as a driver for translation: to make the Digital Patient "simple" to use. Predictive models should be easily generated from the model and predictions should be obtained in an understandable fashion (''black box'' models may not be readily acceptable).

Funding can support further development in parallel to clinical validation such as for example visualisation interface (cf. the H2020 Societal Challenges, eHealth Action Plan 2012-2020).

Other drivers such as funding and education can be identified to facilitate translation.

6.2.7 Clinician and patient education

ICT based education is also seen as a driver for translation and implementation. Education curricula for healthcare professionals vary widely between Member States. Skill gaps still remain to be addressed, and are not restricted to physicians but career development is needed for all healthcare professionals who will support the uptake of the VPH technologies, including database managers and hospital administrators.

It is expected that the Erasmus for all programmes in H2020 will allow the enforcement of the European Research Area. At a time of budget constraints, such an international mobility programme requires attention from the European Commission. Skilled researchers are needed for the implementation and sustainability of the Digital Patient agenda. "Digital healthcare professional teams" must be addressed within standard education curricula towards 2020.

Patient education will also be important: the expert inputs to DISCIPULUS have indicated that downstream Digital Patient developments should increasingly be directed at patients. Patient advocacy groups identify patients participation in R&D as an important driver to patients empowerment. To this end the European Patients' Academy on Therapeutic Innovation" (EUPATI) funded under the Innovative Medicine Initiative (IMI) programme, has identified specific areas of work towards patients education and training that will allow effective participatory involvement of patients in the whole R&D process involved in clinical trials.

6.2.8 Sharing best practice

Innovations in eHealth, such as the Digital Patient, cannot be directly absorbed into an unchanged clinical workflow and healthcare service model. The DP can and should result in altered care pathways, new interactions between care team members and with patients, possibly altered utilisation of existing resources and may impact on treatment costs.

The successful translation of the Digital Patient will be the re-design of health service models – at times perhaps only at a micro level – that yield best value from specific DP solutions. In the longer term, learning from each other's best practices can support validation and translation, leading to acceptance with success stories. Hospitals also need support and expertise with the development of business plans for the implementation and use of eHealth technologies.

Currently, there is no standard framework for business plans addressing innovative eHealth technology in the clinic. Funding concerning business plans should also be provided in line with the implementation of research projects in Horizon 2020. More broadly, it is important to note the need for political incentives at regional and national levels in the vision of eHealth to enable preparedness and acceptance of the technology.

6.2.9 Measuring clinical impact

In order to render the clinical scenarios of the Digital Patient well-developed, useful and realistic, it will be necessary to provide at least rough estimates of their potential socio-economic impact, and in particular their clinical benefits. The major stakeholders to be considered will be citizens/patients, healthcare providers, health insurers and public payers, and society at large. The latter represents societal value beliefs which are particularly relevant in a field such as health.

Any health or clinical impact assessment will usually have a distinct purpose. This could be to inform decision-making in the context of a specific health RTD, health policy, health (system) management, or health service delivery issue. Here policy is understood to also concern issues at the concrete implementation level of an individual person or organisation, not only at the societal level.

In principle, the assessment may concern only the technology under consideration; however, given the fact that health service provision demonstrates a level of maturity, it is common practice for the assessment to concern two (or more) competing technologies.

For clinical impact scenarios, the comparator used for DP workflows is the current standard of care or patient management. Issues to be considered are how traditional and

new (DP-enabled) clinical care pathways and their comparative outcomes can be assessed. Any scenario will also need to reflect the specificities relating to deployment of the respective DP-related workflow and, eventually, the level of clinical readiness of its technology, or, in other terms, its maturity for application at whatever level of routine healthcare.

In order to observe an impact, there must be a direct or indirect causal relationship between an input (research effort; medical intervention; ...), and an output (new simulation model; improvement of health; ...) or result, facilitated by the technology and its property(ies), e.g. usability.

Clinical impact and health-related outcomes may refer to factors and variables such as:

- Primary and secondary endpoints of medical and clinical trials, for example, changes in mortality (death rate) or morbidity (disease rate), length of stay in hospital, visits to physicians/outpatient clinics or hospitals avoided, quality of life of patients, etc.

Other benefits may include:

- reduced period of bed-rest at home for patients, reduced readmission rates due to the avoidance of complications and side effects, fewer drugs to take, less care to be provided by community nurses, family carers and neighbours, fewer side -effects experienced, and so on.

Further clinical impacts may relate to:

- Organisational and change management aspects
- Human resource implications, knowledge & education needs
- Efforts for application (convenience/ease of use; costs for introduction of new technology)

6.3 Exemplary clinical challenge

The exemplary clinical challenge described below focuses on osteoporosis fracture risk decision support:

Present standard of care

A key challenge for clinicians working in the field of osteoporosis and treating patients has been the identification of those (potential) patients with a high absolute risk of fracture, and how to base their treatment decisions on reliable predictors of the probable impact of different prevention and treatment options. The widely applied forecast model, the WHO-supported FRAX tool, is based on population data alone; it demonstrates a high failure rate in terms of correctly predicting the fracture risk for a particular patient, i.e. it has a rather low sensitivity level. It misses a lot of patients who should have been identified as needing therapeutic intervention to avoid fractures, i.e. its specificity level is also quite low. In terms of the provision of decision support, when selecting prevention and treatment options, the FRAX tool does not provide much support either.

Furthermore, at the present time there are no agreed-upon European or global evidence-based guidelines to support clinicians in their daily decision making. Only guidance documents (e.g. from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) are available. When undertaking clinical trials to test new drugs or other treatment options in this area the usual clinical outcome measure is whether or not a patient suffers a fracture within a given time period. This leads to rather lengthy, costly and inefficient clinical trial set-ups.

Expected value-added of VPH-OP decision support

In contrast to this state of affairs, the advantage and key value proposition of the VPHOP approach (virtual physiological human for osteoporotic patients; www.vphop.eu), if successfully and clinically validated, is that – by integrating all information available on the specific patient – it becomes possible to improve general knowledge about, and predictive capability of, decision support tools based on population observations, and to target them to the specific needs of the individual patient. This will lead to a practical way of realising the provision of truly personalised medicine and means that:

1. Every clinical decision taken will be based on knowledge about the specific person being treated rather than just the "average" human being or a given population. The patient's gender, age, phenotype, lifestyle, etc. is known and integrated into the overall decision making process. This will increase the precision of the diagnosis considerably as well as ensuring the appropriateness of the clinical treatment.

2. Initially, during its early development phase, VPHOP technology is based primarily on population-based predictions. As the knowledge base increases, and the tool is applied to more and more patients, it becomes possible to add patient-specific information. Based on this and the experience gained, an early estimate of fracture risk for a specific patient can be obtained before more advanced and costly examinations are undertaken. Thus it becomes possible to improve early selection of those patients at higher risk, to avoid unnecessary interventions for patients at low, or no, risk, and to arrive at more precise predictions for the higher risk patients. All of this, once incorporated in the full application, will make it possible to reduce both under- and over-diagnosis and treatment, with all the associated benefits for patients as well as significant positive effects on the

cost and efficacy of our healthcare systems.

3. Furthermore, at an early (diagnostic) stage of the impending disease, preventive interventions will not only be possible, but they can also be expected to lead to a high rate of success due to the early and correct identification of citizens in need of those preventive interventions.

4. For those patients identified as having an immediate high absolute risk of fracture, the various treatment options available can be simulated, thus making it possible to base the final decision regarding the future clinical process on highly specific, personalised evidence.

In summary, the VPHOP technology will allow for improved identification of osteoporosis patients with a considerable to high present or future risk of fracture, whilst at the same time, supporting decision making on both the probable success of preventive measures and on the optimal treatment path if indicated. It can be expected that the additional costs which such a sophisticated Clinical Decision Support System will incur will be more than offset by savings in treatment and long-term care costs, not to mention an increased quality of life, and life expectancy, for those patients affected by this disease.

6.4 Summary and Conclusions

The area of translation requires the development or the adaptation of formal processes for verification, sensitivity analysis, validation (including clinical trials), risk-benefit and cost-benefit analyses, and, ultimately, leading to product certification. Reference to the pharmaceutical and medical device industries provides guidance on suitable methodological approaches but further developments will be required.

1. Input is required from regulators to define the full translational path from verification to certification for different types of Digital Patient solutions. This will, by necessity, be a two way process as regulatory experts will need to be familiarised with the VPH concepts and the DP landscape.

2. Health Technology Assessment methodologies must be adapted and adopted to compare VPH solutions with current standard of care.

3. It is unlikely that current conceptual prototypes, developed as proofs of concept, can be effective for direct clinical translation. It will be necessary to re-engineer current prototypes for each specific clinical task, re-engineering the user interface to specific prevention, diagnosis, prognosis, treatment planning, and monitoring purposes

4. Sets of metrics are required including both objective indicators, and subjective indicators that capture the user experience; user cohorts must be stratified to represent realistic and relevant clinical scenarios (e.g. trainees, senior users with low IT exposure, etc.). Clusters of descriptors for patient analyses will have to be revised based upon novel hypotheses generated through VPH technologies

5. Health economic and business models must be developed placing the DP within the hospital, clinic or surgery.

6. There will be a significant demand for education and training. Training programmes will be required to provide technicians with a strong underpinning knowledge base. In early and mid-term stages of translation, training will be needed for clinical end users in principles of the VPH.

7. Clinical scenarios

Nephroblastoma

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7.1 Clinical scenarios and technological challenges

To illustrate the potential of Digital Patient technology (once developed, validated and adopted as outlined in the previous chapters) we present three exemplary clinical scenarios developed by leading clinical specialists with the support of VPH researchers. The starting point is current practice and challenges in meeting patient and clinical needs today, followed by a story of how diagnosis, treatment and prediction may look in the future and what technological challenges need to be addressed in order to realise the future scenarios.

7.1.1 Nephroblastoma (Wilms tumour)

The patient's view:

Bill had just had his 6th birthday when his mother and I began to notice that he wasn't really 100%. Then we saw that his tummy seemed rather swollen. It wasn't because he was eating too much, because he actually seemed to have lost a bit of his appetite. Sometimes he said he just didn't feel like eating, even his favourite food – sausages and chips, which was very unusual for him. We just knew that something wasn't right and we took him to see the doctor. The doctor sent Bill for some scans and he was diagnosed with nephroblastoma (Wilms tumour). Bill started treatment straight away and then had some surgery.

The story now: The doctor's view

Bill, a 6 year old boy, is diagnosed with nephroblastoma (Wilms tumour) based on clinical and MRI tomographic examinations. Since Bill lives in Europe, his paediatric oncologist decides to preoperatively treat him with a chemotherapeutic scheme according to the prevailing SIOP (International Society of Paediatric Oncology) clinical trial protocol which follows the upfront chemotherapy principle. The paediatric oncologist hopes that Bill's tumour will shrink considerably so as to facilitate its subsequent surgical excision. However, following the completion of the preoperative chemotherapeutic scheme, MRI shows that no significant shrinkage of the tumour has occurred. Surgery takes place under tumour size conditions much similar to the ones observed right after diagnosis. The side effects of ineffective preoperative chemotherapy as well as the invaluable time lost are obvious.

What could happen in 2023

Nephroblastoma diagnosis is based on clinical, latest technology multi-structural and multi-functional tomographic examinations, molecular biological tests revealing and grossly quantifying tumour histology and additional specific molecular tests. By exploiting the data generated by these tests, a detailed multiscale profile of the tumour is created. All generated data is appropriately pre-processed and fed into a validated multiscale hyper-model based "Oncosimulator." The paediatric oncologist runs a number of experiments *in silico* (= on the computer) simulating the most likely response of the tumour to the most relevant candidate chemotherapy schemes. The quantitative outcomes of the simulations predict that preoperative chemotherapy is unable to lead to any considerable tumour shrinkage. The paediatric oncologist decides to immediately proceed to the surgical excision of the tumour and administer chemotherapy postoperatively following a treatment protocol similar to the National Wilms Tumor Study (NWTS) protocol currently prevailing in the USA, which follows the upfront surgery principle. Both the unnecessary side effects of ineffective preoperative chemotherapy and the loss of time are avoided.

Prof Norbert Graf, University of Saarland

Certain core technologies mentioned in this scenario are already available in some raw form. Therefore, the challenges are related to the development of the missing technologies, the integration, the clinical adaptation and the validation of cancer hypermodels and hypermodel based oncosimulators and the subsequent deployment of the latter. For the sake of generality the following developments refer to cancer in general whereas nephroblastoma specific procedures are clearly indicated.

1. Multiscale data to be exploited

- Multi-structural and multi-functional tomographic imaging data at the macroscopic level allowing for detailed structural and functional segmentations of the tumour and the broader anatomic region of interest
- Blood plasma protein analysis revealing and quantifying tumour histology (antigen-antibody, miRNA) especially in cases where pre-treatment biopsy is to be avoided (e.g. in the nephroblastoma case)
- Quantitative histological data pertaining to the structure (actual size, morphology etc.) of tumour cells, their mitotic potential and their metabolic and cycling status
- Cell culture data providing inter alia a quantification of the stemness/clonogenicity and the differentiation degree of tumour cells
- Whole tumour and normal tissue genome data
- Omics data (proteomics, metabolomics, etc.)
- Special clinically validated molecular biomarker data

pertaining to the tumour under consideration

2. Multiscale data storage and retrieval

- Highly automated storage of pseudonymised multiscale data in multifunctional clinical trial oriented databases
- Highly automated retrieval of multiscale data from such "intelligent" databases

3. Cancer hypermodels and dedicated oncosimulators

- Extensions of already existing cancer models and oncosimulators so as to include modules dealing with detailed modelling of specific critical biomechanisms. The tumour cell fate during treatment as foreseen by interacting molecular pathways is a characteristic example.
- Development of multi-modeller hypermodels and oncosimulators so as to integrate and exploit the globally distributed cancer modelling expertise to the fullest

4. Multiscale data preprocessing

- Highly automated preprocessing of the multiscale data to be subsequently used by the oncosimulators. Semiautomatic and automatic structural and functional segmentation of tomographic images and value initialization of the related molecular pathways constitute two representative examples of this process
- Automated storage of the preprocessed data in dedicated "intelligent" databases
- Automated feeding of the preprocessed data into the oncosimulator

5. Technological integration of in silico oncology components into a single platform

- Integration of all the previous *in silico* oncology components into a single platform. The platform should possess the potential for its dynamic restructuring depending on the particular needs of any given application (e.g. sensitivity analysis experimentation, generic discovery oriented *in silico* experimentation, patient individualised clinical *in silico* experimentation)
- Development of "clinician friendly" platform portals and applications (apps)

6. Multi-resource simulation execution

- Depending on the accuracy sought, execution of cancer hypermodels should be possible on various computing facilities with markedly differing capabilities ranging from standard personal computers/laptops to large super-clusters and latest technology cloud infrastructures
- In order to account for the unavoidable stochasticity and inaccuracies in the estimated input model parameter values, treatment response simulations should be executed for a large ensemble of possible instances of the virtual patient corresponding to his or her real counterpart. *In silico* predictions should be based on a statistical analysis of the simulated responses of all ensemble members (virtual patient instances.) This may dictate a very large number of parallel simulation executions and therefore appropriate resources.
- Internal optimization and parallelization of hypermodel and oncosimulator codes. Use of appropriate resources in order to accelerate the code execution for each separate virtual patient instance i.e. each member of the corresponding statistical ensemble. The clinically acceptable overall execution time should be of the order of a few minutes or less.

7. Clinical adaptation and validation of hypermodels and dedicated oncosimulators

- Provision of large numbers of pertinent and trustable multiscale data sets each one covering at least the molecular, the cellular, the tissue, the system and the organism level of the human biological constitution.
- Design and execution of prospective clinical trials in order to assess and validate hypermodel based multiscale oncosimulators
- Involvement of multiple clinical centres in both large scale retrospective and prospective clinical trials aiming at validating and assessing oncosimulators. Special clinical trial protocols to be jointly developed and agreed upon by all participating centres.

8. Pre-commercialization of oncosimulators

- Provided that both retrospective and prospective large scale clinical validation prove the capability of oncosimulators to reliably predict the treatment outcome within acceptable deviation bounds for particular tumour types, pre-commercial versions of dedicated validated oncosimulators (pilots) are to be developed.
- Introduction of pilot oncosimulators into specially controlled clinical environments and long term study and optimization of their behaviour.

Certification of the oncosimulator needs to be performed according to the Medical Device Directives

7.1.2 Osteoporosis: osteoporotic fracture

The patient's view

Mrs Jones writes: "I had to go out to buy some medicine for my husband who was ill and in bed. Yesterday it had been snowing a lot and during the night it had frozen hard. The pavement had not been properly cleared of ice and was very slippery. On the way back home, I slipped and fell on my wrist. Being only 65, I was very disappointed when an X ray showed that my wrist was broken because I have always been a very active and sporty person and am reasonably healthy. I thought my bones would be strong as I have never smoked and I rarely drink alcohol, just a little wine at parties. The only illness I have is that I suffer from asthma, which I have had since childhood. I'm slim and have a pretty good figure for my age. I have been menopausal since the age of 50 and I have not taken any hormone replacement therapy."

The story now: The doctor's view

A 65 year old female patient came to the emergency ward with a classic history of wrist fracture after a slip on an icy pavement. She is fit and healthy and is a non-smoker. Her anthropometric values were: weight 51 kg, height 1.60m, BMI 20 kg/m. The fracture was set with a cast and the patient went home with an appointment for review at the fracture clinic, without any further prescription or recommendation. The fracture healed nicely, and the patient returned to her normal life. Two years later she tripped in the garden, falling on her side very gently but, despite the relatively low impact, she experienced a femoral neck fracture. She lay in the garden until her son found her the next day, and called an ambulance. The traumatic experience left her into a state of confusion that never entirely disappeared; she had to have major surgery where her hip was replaced with an artificial joint. Over the following 3 years she experienced 2 vertebral fractures, produced by minor trauma or incorrect movements. The second of these resulted in her being immobilised in bed for 6 weeks, during which time she developed respiratory complications that were fatal.

For those patients who are fortunate enough to live in a location with an osteoporosis referral centre

A 65 year old female patient came to the emergency ward with a classic history of wrist fracture after a slip on an icy pavement. She is a non-smoker and fit and healthy. Her anthropometric values were: weight 51 kg, height 1.60m, BMI 20 kg/m. The fracture was set in a cast and the patient went home with a referral to her family doctor for possible osteoporosis. She was given an appointment at the osteoporosis clinic, where she was examined using a DXA bone densitometer. Before the visit, a nurse interviewed her, collecting all the data required by the FRAX risk indicator, which is based on epidemiological data. DXA and FRAX data suggested she was of medium risk, for which no clear guidelines exist. The specialist, in the light of this data, and keeping in mind cost-reduction pressures, decided she was not in need of pharmacological treatment. The fracture healed nicely, and the patient returned to her normal life. Two years later she tripped in the garden, falling on her side very gently but, despite the relatively low impact, she experienced a femoral neck fracture. She lay in the garden until her son found her the next day, and called an ambulance. The traumatic experience left her into a state of confusion that never entirely disappeared; she had to have major surgery where her hip was replaced with an artificial joint. She started pharmacological treatment for osteoporosis, but in spite of this she suffered 2 vertebral fractures in the subsequent 3 years, produced by minor trauma or incorrect movements. The second one immobilised her in bed for 6 weeks, during which she developed respiratory complications that were fatal.

What could happen in 2018

Mrs Jones' wrist fracture was set in a cast and the patient went home with a referral to her family doctor for possible osteoporosis. She was given an appointment at the osteoporosis clinic, where she was examined with a DXA bone densitometer. Before the visit, a nurse interviewed her, collecting all the data required by the FRAX risk indicator, which is based on epidemiological data. DXA and FRAX data suggested she was of medium risk, for which no clear guidelines exist. During the visit the specialist decided to request an individualised prediction of the risk of fracture; for this purpose he supplied the patient with a wearable sensor, and asked her to perform a few exercises such as walking in a straight line, sitting down and then standing up. All recorded data were digitally transferred to the doctor's computer, and from there sent (after proper anonymisation and encryption), together with the imaging and clinical data, to an external simulation service. The next day the simulation specialist read the individualised risk report, which suggested mild bone fragility, but this was coupled with a significant risk of falling. The specialist wrote an email to the family doctor, recommending vitamin D prophylaxis, a physical activity program specifically targeted to improve balance, a two year sequential drug program and an annual review.

Most of the core technologies described in this scenario are already available in some raw form. Thus, the challenges are more related to integration and deployment:

1. **Incomplete information: DXA is a 2D imaging modality, but to be accurate, personalised models need to be 3D**

- Develop ultra-low dose 3D imaging (target < 50 µSv)
- Develop protocols that combine one high dose 3D imag-

ing exam with subsequent low dose 3D imaging exams
- Develop image modelling methods to generate 3D models from a small set of 2D projections

2. Propensity to fall: so far the instrumental information provides moderately accurate predictors of the propensity to fall

- More accurate and extensively validated stability protocols
- Better understanding of the overloading scenario (fractures not associated with a fall)
- Explore combination of imaging information and sensors information, especially to quantify muscle tonicity and strength

3. Automation: current individualised modelling protocols require at least eight hours of a skilled operator to transform the input data into a reliable prediction of the risk of bone fracture

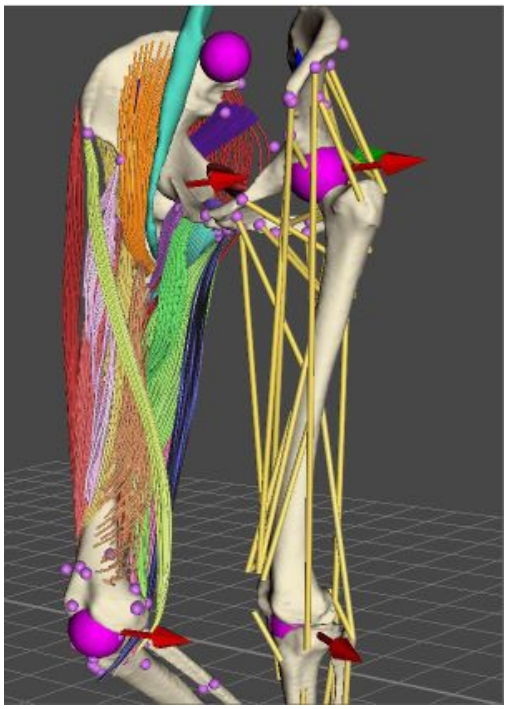
- Fully validated automated segmentation and meshing for hip, spine, wrist and ankle
- Development and assessment of meshless methods for direct image-to-model conversion

4. More efficient stochastic modelling: current methods require some CPU hours per patient, primarily because of the rudimentary Monte Carlo methods used

- Develop Markov-chain Monte Carlo or Bayesian Networks methods to speed up the calculation
- Explore other approaches based on uncertainty propagation embedded into the modelling methods

5. Clinical assessment: so far all assessments have been done retrospectively, using non-optimised input data

- Expand pre-clinical and clinical research in the modelling of the effect of existing pharmacological treatments, so that they can be more effectively accounted for in individualised predictions
- Conduct some large scale multicentric prospective clinical trials to assess the predictive accuracy of individualised models in comparison to the current standard of care based on epidemiology models



Source: VPHOP

What could happen in 2023

All of Mrs Jones' activity data are automatically transmitted via her mobile phone using new m-health interoperability standards, to her secure on-line account. Here a Personal Health Forecasting (PHF) program continuously updates her health predictions and provides feedback, again via her mobile phone. The PHF system also monitors local weather forecasts using the GPS coordinates from her phone. This means that when Mrs Jones has to go out on an icy day the phone reminds her to put on the anti-slip footwear she was advised to buy on-line when her stability index started to decline. During her walk she slips, but the footwear helps her to regain stability and a possible fracture is avoided. Her phone sensor records the quasi-fall, and recommends a new stability assessment. As a result, Mrs Jones is advised to sign on at a local Tai Chi class, which helps the elderly regain stability. Her nephews think that this is very amusing, and call her 'Kung-Fu Granny'.

1. Reliable activity monitoring: most activity monitors currently available present moderate accuracy when used on low-intensity activity profile typical of the elderly.

- Develop new multimodal monitors that combine accelerometric, gyroscopic, gravimetric and GPS sensors to more effectively discriminate activities
- Develop miniaturised, skin-attached sensors that can be worn under the clothes comfortably, allowing reliable recording
- Develop accurate monitoring and detection algorithms that provide statistics on physical activity but also raise alarms for events that suggest increased risk of falling
- Explore the use of individualised models to improve the sensitivity and the accuracy of wearable sensors, as well as for the interpretation of sensors outputs

2. Personal Health Forecasting

- Develop Personal Health Forecasting models that continuously and automatically process data arriving from all sources in addition to logging information in the EHR, and also return predictions and recommendations directly to the patient
- Develop computational methods for efficient re-run of solved models when only a few input parameters change
- Develop fully encrypted and pseudo-anonymised data

models that ensure high levels of security and total flexibility on the location of the digital resources in the cloud
- Develop and validate dedicated user interfaces for osteoporosis patients, which return useful and educative information, inducing a positive effect on lifestyle, and reducing the environmental determinant of the risk of fracture

3. Digital Prevention: the effect of prevention activities is difficult to prove

- Use VPH approaches to accurately quantify the compliance and the effects of prevention programs for each participant in the cohort
- Develop infostructures that make it possible to run such studies on cohorts of thousands efficiently and with moderate costs

7.1.3 Atherosclerosis: acute coronary syndrome

The patient's view

"I've worked as a gardener all my life and am fit, although I did smoke when I was younger. My parents both died in their early sixties from heart disease and I've been slightly concerned that it might happen to me. Six years ago, I went to see my GP about a throat infection. My blood pressure was high and she put me on tablets to control it. I also developed diabetes and started taking metformin . Two years ago I started to feel heaviness in my chest when I did heavy work. My GP referred me to the hospital and I saw a specialist who said I might have angina. To help make the diagnosis, I had a test where they took my heart tracing while I walked fast on a treadmill. Unfortunately, this wasn't normal and so I had an angiogram. The consultant put a tube into my groin and some dye into the coronary arteries in my heart. They told me I had some 'furring up' of the arteries and put a stent into one of them to help keep it open. He told me that this was probably the cause of my pains and after this the pains disappeared. I was fine until this week when the pains came back. I took time off work but it got worse, they started occurring even when I was walking around the house. Then the pain became really bad and I started to get pins and needles in my arms. When I started to feel sweaty and cold I called an ambulance. In A&E they told me I was having a heart attack. The Cardiologist told me that I needed an emergency angiogram. One of my arteries was completely blocked and this was the cause of my heart attack. They used another stent to keep the artery open and the pain went away immediately. I recovered on the ward but the doctors said that the prognosis was positive because they got to me quickly. I was put on a few more pills and told I could go home in a couple of days if everything was okay."

The story now: The doctor's view

Mr Green presented to A&E with severe central chest pain radiating down his arms. He had several risk factors for coronary heart disease: smoking, hypertension, hypercholesterolaemia and a family history of coronary artery disease. Subsequently, he was found to have a TaqIB polymorphism for the cholesteryl ester transfer protein (CETP) . In addition, he already had a personal history of coronary artery disease having been diagnosed with angina several years ago. His symptoms improved significantly after he had Percutaneous Coronary Intervention (PCI or 'stenting') two years ago. However, the combination of the above risk factors with the nature of his severe pain made myocardial infarction the most likely diagnosis. The diagnosis was confirmed when an ECG was performed. It demonstrated elevation of the ST segments in the parts which represent the front of the heart. This indicated that a major coronary artery had been totally blocked by a blood clot, the usual cause for a heart attack. Urgent intervention was necessary and the emergency primary PCI team were called in. They performed an angiogram, identified the blocked artery and stented it open. Good flow returned down the artery and the heart attack was aborted – an excellent result. We did spot some more disease and even some partial blockages but we did not deal with these during the emergency procedure. Mr Green did well on the ward and made a good recovery. We prescribed him some more medications including clopidogrel which will help to keep the stent open. He was seen by the cardiac rehabilitation nurses and discharged two days later.

What could happen in 2018?

We saw Mr Green in a follow up clinic six weeks after his procedure to decide what to do with the remaining disease. The Medical Physics Department helped us out by virtually reconstructing his coronary artery anatomy on a computer using his angiogram pictures. This 3 dimensional model (Digital Patient, DP) clearly demonstrated the partial blockages and the areas which had been opened. The DP allowed us to simulate the blood pressure and flows down the artery. It revealed that while one of the partial blockages would not require intervention, the other one was significant and would require PCI. The DP really helped here because it saved the patient from unnecessary tests along with the time and cost that this entails for both the patient and the health service. A further advantage was that it allowed the cardiologists to 'virtually stent' the coronary arteries on the computer before performing the procedure on the patient. This facility allowed the doctors to assess the physiological impact of various stenting approaches prior to implementing them. Prior to this technology, the cardiologist would have had to make a judgement about which was best and just 'go for it' without being able to assess the impact. You cannot take a stent back – they only go in! This makes the virtual stenting tool a very helpful resource indeed. We are pleased to report that Mr Green has had his procedure and

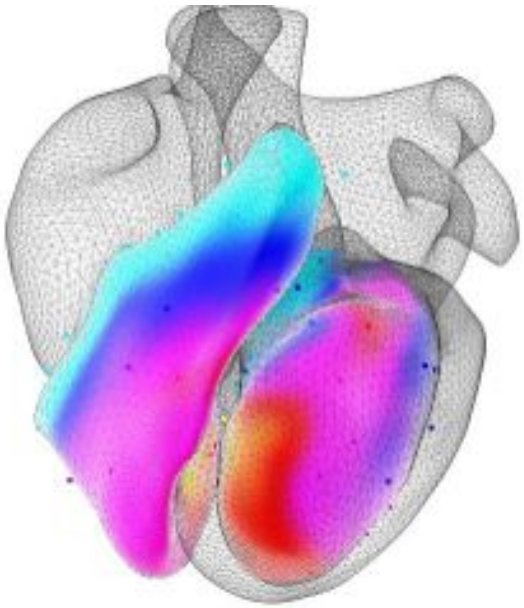
the partial blockage which the computer model highlighted as a problem has now been sorted out with another stent.

Technological challenges

In this scenario the emphasis is on the diagnosis and treatment of the coronary disease focusing on the evaluation and restoration of blood flow through the diseased arterial segments. The core technology that supports this clinical scenario is already available. Nevertheless there are specific challenges that need to be met to see the benefits of the simulation technology in the clinic. The essential IT and engineering components of the scenario are infrastructure, analysis methods and model personalisation. Furthermore, the importance of validation and clinical evaluation must not be underestimated.

1. Infrastructure

- Gather information from what are currently separate systems in most hospitals to build a comprehensive representation of the digital patient on which the model can operate. This scenario requires angiographic image data from, ECG data, possibly Doppler ultrasound data, demographic data, LABS data and individual clinical observations from the patient record.
- Define operational architecture. Virtual machines operating in a cloud environment show great promise, partly because this approach is applicable for smaller scale simulations but readily extensible if and when the need for more computationally-challenging models is demonstrated.
- Elaborate private cloud applications, operating on local resource behind the hospital firewalls. A private cloud operating close to catheterisation laboratory might be the ideal platform for this scenario.
- Elaborate public cloud operations, security issues, pseudonymisation, licensing issues, billing models. When this scenario is rolled out to smaller hospitals (after 2018) a pay-per-use model might be an attractive option.
- Emphasis on easy-to-use modelling environment for clinical use. In this scenario the environment should facilitate communication between physicist and clinician.
- Flexible work flow engine for local customisation and integration, and ultimately for development of new work flows.



Source: Eurobioimaging

2. Analysis methods

- Further improvements of segmentation methods, particularly for four-dimensional reconstructions and especially for arterial systems in which diameter changes might be small but very important in terms of physiological significance, interpretation and diagnosis. This scenario requires effective segmentation of the coronary arteries from a range of modalities.
- Closer integration of segmentation and solution of engineering equations (equilibrium, conservation).
- Further development of data assimilation methods for integration of sparse and/or approximate medical image data into comprehensive engineering simulations.
- Development and implementation of parameter fitting/optimisation methods for inference of boundary conditions for numerical models from softer data and observations in the patient clinical record. For this scenario a critical issue is the representation of the impedance of the vasculature, including microvasculature, distal to the imaged segments.
- New methods for fast solution of haemodynamics in arterial systems: use of lower dimensional models and/or precomputed solutions, response surfaces, mathematical decompositions, parameterisation, interpolation. All of these hold promise for the current scenario. For this scenario the target is personalised solutions for diagnostic purposes in less than ten minutes.
- Development of methods to represent physiological and measurement uncertainty, and to run and to manage an appropriate range of simulations for personalised diagnosis. In this scenario we would wish to characterise the local physiology over the physiological envelope of the individual.

3. Model personalisation

- Fast and effective segmentation of patient image (see 2a). For the current scenario 4D segmentation and effective segmentation of plaque are important issues.
- Personalisation of boundary conditions, possibly in the form of parameterised lower-dimensional models (see 2d).
- Simulation of interventional procedures. For this scenario the operator should be able to study the effect

on local physiology of several candidate interventions (placement of stents, multiple stents ...).

4. Validation and clinical evaluation

- Clinical trials to prove the effectiveness of Fractional Flow Reserve, a physiological measure of great relevance to this scenario (the first computational implementations, already available in the community, seek to replace the (costly and uncomfortable) invasive measurement of this quantity with a computed measurement) include low thousands of patients. Similar numbers of validated simulation studies must be performed to give the clinical community confidence in these measures.
- Multi-centre clinical evaluation will be required.

EHR integration note

In this patient's case, in each of the time points documented, the principal information needed from Mr Green's EHR is recently collected and quite detailed cardiovascular examination and investigation findings. The virtual physiological modelling algorithms seem primarily to require, as input parameters, observational data collected from these, and not much historic information. The success of the modelling will be critically dependent upon how comprehensive there underpinning researches for the wide diversity of persons: different ages, vascular elasticity, body size, and the presence of other conditions that may influence plaque formation. The development of the predictive models, on the other hand, may have required many other parameters from the EHR of previous patients, both in order to include and in order to rule out their predictive value.

What could happen in 2023?

When Mr Green arrived in A&E, several images of his heart were taken non-invasively. These were used to build a virtual model of his heart, as part of his digital patient model.

The heart model automatically integrated appropriate data from Mr Green's healthcare record including previous scans, blood tests (including appropriate elements of his genetic profile) and physiological parameters. This provided the patient and doctors with a comprehensive evaluation of his heart function, coronary arterial physiology and a truly personalised assessment. Doctors used this assessment to diagnose the acute problem and plan intervention based predictions /simulations specific to the patient, not based on population averages. The assessment quickly identified the problem as an acute myocardial infarction with focal myocardial impairment but with salvageable myocardium. Urgent PCI was therefore indicated. The virtual stenting module allowed patient-specific arterial segments to be trialled with various stent models and deployment pressures and visualisation of the resulting parameters like stenosis widening, stent alignment with the vessel and contact pressure between stent and vessel wall. The cardiologist could also proceed to perform a blood flow analysis of the coronary tree prior to and after intervention and visualise the changes to the blood flow in all the branches including perfusion rates, resulting pressure drop and shear stress mapping. The cardiologist used this virtual stenting tool to simulate the physiological impact of alternative strategies. The integrated, personalised assessment also identified that Mr Green had a rare problem affecting his platelet function, increasing his risk of stent thrombosis and recurrent heart attack. The post procedure prescription was altered accordingly.

When Mr Green returned to clinic six weeks later, data was also downloaded from his stent. These data were automatically integrated into his heart model. The updated digital patient model provided an individualised model of plaque progression, based on his anatomical details (thus, it automatically extracted Mr Green's images from the hospital database) and launched simulations with different scenarios (cholesterol levels, blood pressure, stress levels, etc.) according to the clinician's guidance. The extent to which alterations in blood pressure and LDL cholesterol influence likely plaque progression are also incorporated. It also contains a personalised simulation of the response to statins and can therefore increase the information available to Mr Green and his clinicians to support them in making informed treatment choices. Mr Green's simulations demonstrated the likely patterns of plaque progression according to the prescribed treatment. The model also demonstrated that although other areas of coronary disease may impair blood flow, in this case (taking into consideration multiple other parameters such as activity levels, kidney function and flow through the implanted stent) only one segment was likely to progress to significance over the next decade. Doctors therefore scheduled a further procedure to deal with this. Doctors were also able to use the simulations to minimise the possibility of plaque growth in other regions with medical therapies targeting LDL cholesterol, elevated blood pressure and inflammation.

The personalised simulation also identified a separate, otherwise occult problem with his leg arteries. It demonstrated to Mr Green that he is likely to progress to ischaemia if he doesn't change his lifestyle and follow the advice from his clinician. The personalised model of Mr Green showed the plaque progression in his case may be quite fast, likely occluding his superficial femoral and distal arteries in less than 5 years. He needs to react to his problem quickly since this would impact his quality of life and livelihood. The simulation also showed that high dose statins and risk factor modification would at least defer this problem. He knows that without these changes, he may require surgery.

Technological challenges continued

For this specific scenario we might anticipate that in 2023 there will be stronger integration between the local physiology and the systemic physiology of the patient, so that the wider effects of the disease and of potential interventions can be simulated. It might be that this will see a reduction in invasive interventions when it is fully understood that local improvements might not always be effective in the context of this individual patient. There are special challenges for cardiovascular physiology in terms of multi-scale, multi-science modelling, and we anticipate that a major improvement will be in the integration of physics with biology models so that the evolution of disease, with and without intervention, can be predicted effectively. This is a much greater challenge than the diagnostic and acute intervention scenario achievable in 2018. It will require a much stronger integration of population models, epidemiology and systems biology with accurate models of anatomy and physiology. Integration of molecular and genetic information and biological pathways into the physics-based simulations will bring new levels of accuracy and prognostic capacity, as well as developing new, mechanistic, insight into pathophysiological processes. The first steps in this process are under way, but there is a long way to go.

In 2023 we might anticipate a more pervasive environment in which the physiological envelope of the patient is more accurately represented by continuous measurement of activity. The underpinning technologies include improvements in and wider adoption of sensing technology in the home environment:

1. Monitoring

- Develop new multimodal monitors that combine accelerometric, gyroscopic, gravimetric and GPS sensors to more effectively monitor the patient's activity
- Develop accurate monitoring algorithms that provide statistics on physical activity
- Integrated sensors in the device to monitor drug delivery (in the case of a drug-eluting stent) and flow through the stented artery
- Develop accurate algorithms that provide data on stent patency

2. Personal Health Forecasting

- Develop Personal Health Forecasting models that continuously and automatically process data arriving from all sources and return predictions and recommendations directly to the patient, in addition of logging information in the EHR
- Develop fully encrypted and pseudo-anonymised data models that ensure high levels of security and total flexibility on the location of the digital resources in the cloud

3. Develop and validate dedicated user interfaces for coronary disease patients, which return educative information on the predicted long-term outcome, inducing a positive influence on life style

These technologies, combined with the developments overviewed in the previous paragraph, will bring new opportunities in Personal Health Forecasting and in Digital Prevention.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DISCIPULUS
What are the Scientific and
Technological Challenges
we need to overcome to

8. Conclusions and recommendations

8.1 A historical perspective: looking back and time for assessment

In 2005 a small group of European researchers met in Barcelona to discuss the need that was emerging within multiple segments of applied biomedical research, namely to better understand physiological processes in living organisms, particularly human beings. In order for such processes to be effectively explained, mechanistic hypotheses are required to explain and integrate observations made at radically different scales of both time and space, across cell to organ systems, and across the traditional sectors of biomedical knowledge (biology, physiology, medicine, biochemistry, physics, etc.). It was consensus that the only way to cope with the underlying complexity, that this integrative approach required, was to use computer models to capture the mechanistic knowledge generated at each scale and to combine such models into new types of hyper or integrative simulation models. But in order to make this vision a reality, it was first necessary to develop a framework of methods and technologies that would make it possible to investigate the human body using an integrative approach such as this. The research community called this framework the *Virtual Physiological Human* (VPH).[1]

This scientific concept has attracted, to date, approximately €200m of funding from the European Commission (primarily in the ICT for Health section of FP7), with additional support emerging from funding bodies within individual member states. By 2010 a small number of the research projects inspired by this vision had already reached completion, but the first batch of projects funded under VPH-specific calls ended only recently. Many projects are still running, and those funded in Calls 9 and 10 will complete in 2017. The ten year horizon underlying the 2007 VPH Research roadmap[2] published by the STEP consortium is only at the half-way stage of its development.

Ample has happened over these years to allow a first, preliminary reflection of what has already been achieved. Evidence confirms that the VPH initiative is and will continue to be a success, both in the research and development domain and in the field of applied medicine.

One measure of success is that the VPH initiative has been acknowledged, worldwide, as a recognised endeavour that targets key diseases, major organ systems across many space-time scales.[3] It has been estimated that today, in Europe alone, there are over 2000 researchers that have selected development of the VPH as their primary research topic.[4] By now, VPH-researchers constitute an established European and global community working towards the systematic use of simulation models to better understand and explain life processes, including diseases, and predictive models to improve and personalise healthcare services. This community has come together on numerous occasions to provide a voice for those who are convinced that, within modern healthcare, quality of care is intimately and firmly facilitated by and linked to technological progress. The interdisciplinary cooperation of physicians, engineers, biologists, clinical professionals and other scientists has opened up new possibilities in medical diagnosis and treatment, as well as disease prevention and rehabilitation.

The Digital Patient concept presents an innovative domain for R&D efforts offering significant clinical and commercial potential. It will play a key role within EU innovation policy as it is aligned with all of its three main priorities – excellent science, industrial leadership, and societal challenges.[5]

In the light of current challenges facing European healthcare systems, in particular the pressure of multi-morbidity, demographic change and spiralling costs, it is crucially important that the potential of technological innovation for the benefit of the individual patient is fully utilised and exploited.

An exciting future is envisaged where the 'Digital Patient' has a key role to play.

> *"A scientist ... is usually expected not to write on any topic of which he is not a master... We are only now beginning to acquire reliable material for welding together the sum total of all that is known into a whole [but] it has become next to impossible for a single mind fully to command more than a small specialised portion... I can see no other escape from this dilemma than that some of us should venture to embark on a synthesis of facts and theories, albeit with second-hand and incomplete knowledge ...and at the risk of making fools of ourselves"*
>
> from the preface to ***Erwin Schrödinger***'s *'What is Life'*

1 http://vph-institute.org/documents/public-repository/ec-vph-white-paper2005nov.pdf
2 http://vph-institute.org/documents/public-repository/STEP%20vph_roadmap_printed_3.pdf
3 http://vph-institute.org/documents/public-repository/IMAG_Futures_Report.pdf

4 Hunter P, Coveney PV, de Bono B, Díaz V, Fenner J, Frangi AF, Harris P, Hose R, Kohl P, Lawford P, McCormack K, Mendes M, Omholt S, Quarteroni A, Skår J, Tegner J, Randall Thomas S, Tollis I, Tsamardinos I, van Beek JH, Viceconti M. A vision and strategy for the virtual physiological human in 2010 and beyond. Philos Trans A Math Phys Eng Sci. 2010 Jun 13;368(1920):2595-614.
5 Horizon 2020 - The Framework Programme for Research and Innovation. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. COM(2011)808, Brussels, 30.11.2011, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2011:0808:FIN:en:PDF

The primary aim of this Roadmap is to provide insight and guidance on targets for future research and innovation initiatives and to identify the gaps where further developments and investment will be critical to ensuring the success and widespread uptake of Digital Patient applications by healthcare professionals when seeing patients.

In order to further progress and implement the Digital Patient vision, we need to provide a balanced overview maintaining a clear perspective of the many positive achievements to-date and those challenges that remain unsolved. This is developed in the sections that follow.

8.2 VPH is ICT, Health, FET

One of the greatest assets of areas of research such as the VPH is their multi and trans-disciplinary natures. VPH and the Digital Patient define a research strategy that bridges disciplinary boundaries to create a holistic approach. The VPH initiative is focused on scientific challenges that cross the boundaries of many disciplines, having successfully translated concepts or methods that were originally developed in discrete branches of knowledge (such as engineering, mathematics, physics) into medicine and ultimately to the greater understanding of health and disease. This is no mean feat and it is testimony to the energy and stamina of the VPH community that ceaselessly communicates with other disciplines in order to solve what initially appear to be intractable problems.

Interestingly, this also leads to a major obstacle that has come to light in this area that is the problem of adapting a research initiative that cuts across traditional partitions of research domains to the somewhat artificial, albeit necessary, walls imposed by funding agencies in order to contain and define their remit. As the Digital Patient moves towards maturity, some of the emerging requirements for support will, without doubt, extend beyond its current positioning within the eHealth objectives of the 7th Framework programme, which has been consistent with the technological remit of current projects. In order to speed up the adoption of VPH technologies, it will, in the future, be necessary to conduct more clinically focused research. At this juncture it is also important to mention that some of these technologies are not mature for clinical translation just yet. It is first necessary to fully understand, develop and harness fundamental technological and biomedical problems. Joint developments in both clinical and computational research are of outmost importance to properly refine and validate the VPH tools that will shape the future of *in silico* medicine.

In this regard, the promise of the H2020 programme where Health research and ICT for Health research are much more closely organised, can only be welcomed. Nevertheless, to further develop this field, ***in silico* medicine must be recognised as a Grand Challenge,** where fundamental research in biomedical science, mathematical and computational methods, bioengineering, and computer science must coexist with more applied and translational research.

8.3 Efficacy evidence

Only a few VPH projects have been completed so far, and of these, only a sub-set[6] was able to model a significant number of real patients and make clinically-relevant predictions on their health status. However it is important to note that all of these have an important clinical component and all of them have brought their results to the clinic in a way that has created clinical awareness of VPH research. Moreover, clinicians have enthusiastically supported and welcomed VPH research, as evidenced by the large number of clinicians attending the DISCIPULUS 2nd Consultation Meeting in Barcelona, November 2012.

In the few cases where efficacy results are already available there is a concrete improvement in health outcome measures. However, this improvement comes at a cost: there is an increase in complexity that the current VPH modelling procedures impose on medical research as well as practice. There are three dimensions to this that are explored briefly below.

The first is that VPH research was prematurely positioned as translational from the very outset. Individualised multiscale modelling of human patho-physiology is a Grand Challenge and there are some hard-core aspects such as (to cite just a few); homogenisation (translation of properties across scales), combinatory explosion of computational complexity, hard coupling across scales, uncertainty modelling – all of which require further fundamental research to be undertaken. Research on these fundamental aspects must run in parallel to more applied research.

The second is linked to the generation and access to patient and health information and data. In many cases the stumbling block is not the modelling method as such but rather a lack of patient and other data of sufficient quality, extension and resolution, to properly inform the model. In most cases, due to ethical and financial constraints, VPH projects have been designed based on input from routine clinical imaging or sensing data sources and files, with which VPH modellers have to 'make do'. This approach presents numerous drawbacks. Imaging and sensing for research and modelling purposes are often substantially different from those done for routine clinical use. Imaging and sensing technologies move from a mere generator of visual patterns, that a trained clinician can interpret, more and more

6 VPH NoE Newsletter, No. 4, July 2011.

towards measurement instruments that are used to quantify a number of physical properties of the human body and its organs. Protocols for measurements and data sequences generated must be optimised for modelling purposes in order to be truly effective.

The feedback we have received from stakeholders (especially clinicians and patient representatives) suggests that the historic focus of VPH research on secondary care specialist decisions is only one of the possible opportunities. We identified considerable interest in supporting patients with lifestyle and self-management simulations and predictions, and guiding generalists on how to manage complex care in the community, and when to escalate treatment to specialists. Rehabilitation following a major illness event or procedure was also identified as a potential service that predictive modelling and simulation could contribute to.

These novel areas of attention for the Digital Patient will require further basic research in the development of suitable models. They will also require access to richer, more diverse and more longitudinal electronic health record information than has often been required for specialist models. International investments in electronic health record and interoperability standards, in clinician friendly interfaces and patient friendly mobile applications will hopefully contribute to the availability of relevant personal data for the research and eventual deployment of such new models. However, we know that progress towards high quality and complete health records is slow, and the Digital Patient / VPH community should add its weight to efforts being made across healthcare and research stakeholders to invest in methods to improve the quality of EHRs. At present, parallel development of VPH models and clinical trials and studies, both focussed on the development of prediction-based ICT platforms, is of major importance to achieve model-compatible clinical data and/or clinical-compatible model formalisms.

The third dimension of this problem is related to the engineering challenge of setting up a data processing pipeline that transforms a large amount of heterogeneous data for an individual patient into an individualised model, flexible enough to be used on a large number of patients. In itself the engineering problem is not insurmountable. Nevertheless, it becomes an issue when we try to tackle in parallel the development of the modelling methods themselves.

“Although it seems science fiction, the Digital Patient is not only a real possibility, it will happen. It is not a matter of if, but when. And what a difference the DP will make in healthcare! It is almost impossible to understand all the repercussions in science, medical practice and healthcare. It will have a profound societal impact”

Vanessa Díaz, UCL

As mentioned earlier in this chapter, to date there is little experience of real-life application of VPH models at the clinical coalface to support patient care decisions on a significant scale. Since model formulations are now reaching maturity, there is an urgent need for clinical studies to validate the safety and relevance of the models in the context of real life care decisions. Such clinical trials are mandatory in order to give assurance to the clinical professions and to health services that these simulations and projections can be used in a trustworthy way. Such studies should also highlight improvements in care pathways that can be introduced because of the knowledge delivered through Digital Patient technologies.

An important step towards gaining clinician trust in the reliability and medico-legal acceptability of modelling based support and guidance could be to arrange interviews and small scale workshops with clinical professional associations and possibly with health insurers. These activities could help to clarify the extent of the clinical trial like evidence that would be needed to allow these technologies to become accepted.

Regarding validation of simulation models and evidence on their efficacy of improving healthcare, **we recommend that in Horizon 2020 three distinct types of projects should be funded:**

- those that focus on modelling methods and the further development of integrative models, including targeting their pre-clinical or retrospective validation;
- those that focus on engineering the large scale deployment of established modelling methods (as well as diffusion of models and applications following their clinical validation and assessment, see next point) and
- those that conduct clinical assessment studies (*in silico* and by way of clinical trials) to determine the safety, efficacy, efficiency and benefits of these models and resulting decision support tools for patients and the healthcare system as a whole.

For the latter we recommend that continuity and further refinement of those projects supported by FP7 calls, which have already produced VPH platform-dedicated clinical data, are sought.

It is strongly advised to not require projects to develop all of these aspects simultaneously – it would be detrimental because it would overburden them.

8.4 The clinician at the centre of the Digital Patient vision

Early in the development of the vision, VPH technology was described as a fully automated process, typically embedded within imaging workstations, which would provide push button answers to the clinical users. In reality, this vision was rapidly challenged on two fronts. First, because of their inherent complexity, many VPH models require support from an experienced technician. Technical input is necessary, not only to pre-process the data, but also to provide essential quality assurance checks. Second, for many projects, VPH solutions were designed from the outset to return to the clinical user an all-inclusive answer intended to be immediately used to make a clinical decision. It took time to realise that clinical experts are trained to aggregate heterogeneous information, exploring it to extract patterns even when information is very noisy or incomplete; these are tasks that computers will always find very difficult to complete.

Convergence can be achieved on these two fronts by (1) accepting that VPH technologies are complex, requiring a new generation of hospital technicians specifically trained to use them and (2) by developing the Digital Patient in such a way that the technicians can prepare the data and models to the point of an exploratory analysis where the clinical expert can integrate the simulation results into his/her clinical reasoning and extract the maximum advantage from them. In other words, when approaching the stage of implementing VPH models into clinical workflows, **we must put the clinical professional at the centre of the process.**

8.5 The future and the digital patient: a grand challenge for H2020

The new research challenge addressed in this Roadmap, the *Digital Patient*, aims primarily to address the final shortcoming of the VPH initiative emerging from these first years. **The Digital Patient represents a new research agenda that positions the clinical user and its interaction with the simulation results at the centre as a new paradigm for clinical decision support.** This Grand Challenge articulates specific recommendations for each area of scientific and technological challenges identified during consultation with a wide range of stakeholders.

The recommendations that **DISCIPULUS** has gathered on behalf of the VPH community for the realisation of the Digital Patient, in the areas specified are as follows:

8.5.1 Area: Generation of data for model construction, validation and application

The generation, standardisation, validation, integration and homologation of data have been identified by the wider VPH community to be of outmost importance for realising the Digital Patient vision. The following main application areas require targeted support:

1. Construction and validation of data-driven prediction models of clear biomedical relevance
2. Application of data-driven prediction models within primary and secondary healthcare
3. Construction and validation of causal and predictive models of clear biomedical relevance
4. Application of causal models within primary and secondary healthcare
5. Multidimensional phenotypic data analysis to uncover new important patterns that can serve as inspiration source for statistical and causal models

Research and innovation should focus on:

- Exploration of suitable existing and possible new sources of information - development of new acquisition methods, devices and technological tools, use of longitudinal data; both across the disease time course and the life-span, including data on comorbidities, etc.
- Development and adoption of acquisition methods and technology to determine genotype and measure high level phenotypes: anatomical data obtained from next generation image modalities such as MRI, CT and US (ultrasound), new imaging and sensing technologies for acquisition of data in more physiological conditions such as standing, moving, exercising; new (wearable, multimodal) sensors and sensor data analysis to obtain functional data, also during daily life (point of life), lab-on-a-chip devices to obtain biomarker and gene-expression data, new phenomics technology
- Development and homologation of next generation acquisition methods (data independent from the acquisition system, the acquisition method, or the acquisition source)
- Exploitation and initiation of new developments in data formatting and data processing to enable enhanced data provision: advanced ICT solutions to preferably automatically collect and format the data and provide it to the Digital Patient for use and sharing. This includes denoising and dimensionality reduction of the raw data and of the extracted feature space; data formatted in a predefined standardised and certified way (provided patient consent about the level usage is embedded) for

research purposes

8.5.2 Area: Biomedical information management

Biomedical information management is a complex multi-faceted problem including challenges such as the collection and sharing of data, the standardization of data collection and the question of ontology, the dimensionality reduction, the question of security and privacy, computer and storage infrastructure needed to store enormous amounts of data retrievable rapidly, safely and from everywhere. These facets are interdependent and interact with each other which renders biomedical information management extremely demanding. We recommend to:

1. Develop patient-centred authorisation mechanisms that allow automatic requests for secondary use of clinical data after collection and anonymisation

2. Develop methods to compute k-anonymity[7] for anonymised secondary use databases of clinical data when combined with any other information available on the Internet

3. Strengthen the efforts to develop dynamic semantic mediation strategies that allow clinical specialists to participate in multicentric data collection with clinical data available in their research warehouses, employing easy-to-use procedures to define the semantic mapping between the local warehouse structure and the collection ontology

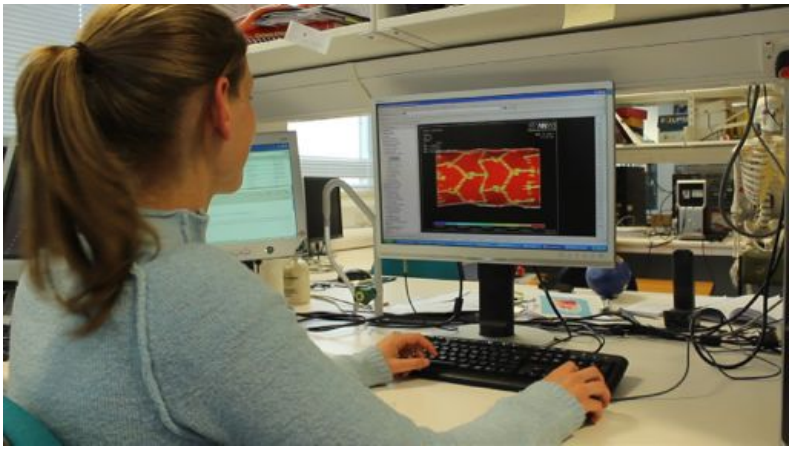
4. Develop automatic extraction of quantified phenotypical disease traits, and use these as similarity metrics to retrieve cases comparable to the one at hand from within the warehouse

5. Develop new innovative storage and computing services that enable data intensive analysis of biomedical big data preserved economically over long term

8.5.3 Area: Mathematical modelling for the Digital Patient

The Digital Patient relies on the power of predictive modelling to be able to progress into a "medical avatar" as its final realisation. In fact, it can be argued that modelling is at the core and the most fundamental element of the Digital Patient as it is able to seize observations, data and explanations to formulate them and/or capture them in a mathematical and numerical form, in order to achieve the goal of explanatory/predictive medicine. It is the extraordinary and compelling power of multiscale predictive models that will help achieving the goals of the Digital Patient. Within this context, the areas that have been identified as priorities in modelling are:

1. Support the creation of online repositories to house and share disease- and patient-specific data and models to enhance collaboration within the VPH community, providing ubiquitous access (in compliance with data protection, privacy and confidentiality rules)



2. Prioritise the development of relatively simple models that address specific topics in patient studies, for the expansion of diagnostic methods and therapies in the clinic

3. Develop hybrid methods and strategies to automatically and seamlessly combine phenomenological and mechanistic models, exploiting the use of VPH ontologies and annotated online repositories containing well-documented and validated models

4. Develop surrogate modelling methods that make possible to replace computational demanding sub-models, typically large PDE models (partial differential equation models), with estimators developed on pre-computed solutions, to provide a fast estimate of the model outputs and an upper boundary of the estimation error

5. Develop integrative modelling frameworks that support the abduction cycle that applies inductive reasoning to observations to generate hypotheses on mechanistic relationships, verify these against reference observations, and where predictions are in good agreement with observations, incorporate this new mechanistic understanding into the inductive reasoning, so facilitating new discovers

6. Personalise not only anatomical data but also the physiological/pathological processes taking place (multi-scale) by linking model parameters to easily obtainable

7 http://dataprivacylab.org/dataprivacy/projects/kanonymity/

patient data, leading to an individual patient model rather than a statistical patient model

7. Develop fast numerical restart methods that make it possible to employ user exploration of the information space to re-run the model with different inputs at very low computational cost when compared to the first run

8. Develop a theoretical framework for the analysis of scale separation, and general homogenisation and distribution strategies to define space-time relations across scales

9. Develop strategies to formalise and generalise the testing and validation of mathematical models, providing accurate and automatic estimations on the impact that incomplete data has in the personalised models

8.5.4 Area: Clinical user interface

Currently working prototypes are available and allow the 3D exploration of large amounts of information on human anatomy, physiology and pathology, referred to an average subject (generic) in fixed time point (static). Future research should prioritise:

1. Support for effective management of individualised data

2. The extension of existing tools to support time-varying, dynamic data, and support multiscale interactive visualization for data defined at different time scales (data defined across different spatial scales)

3. The development of efficient methodologies for the rapid generation of image-based functionalised anatomical models for safety assessment and treatment planning

4. Extensions to support novel human computer interaction and interactive visualization that allow the usage of large-scale data from heterogeneous sources for knowledge discovery

5. Extensions to support effective information retrieval

6. Extensions to support seamless interfacing with the existing healthcare systems under the criteria of clinical adaptability

7. Extensions to support sound evaluations of digital patient technologies

8.5.5 Area: Translation and adoption

The area of translation requires the development or the adaptation of formal processes for verification, sensitivity analysis, validation (including clinical trials), risk-benefit and cost-benefit analyses, and, ultimately, leading to product certification. Reference to the pharmaceutical and medical device industries provides guidance on suitable methodological approaches but further developments will be required.

1. Input is required from regulators to define the full translational path from verification to certification for different types of Digital Patient solutions. This will, by necessity, be a two way process as regulatory experts will need to be familiarised with the VPH concepts and the DP landscape

2. Health Technology Assessment methodologies must be adapted and adopted to compare VPH solutions with current standard of care

3. It is unlikely that current conceptual prototypes, developed as proofs of concept, can be effective for direct clinical translation. It will be necessary to re-engineer current prototypes for each specific clinical task, re-engineering the user interface to specific prevention, diagnosis, prognosis, treatment planning, and monitoring purposes

4. Sets of metrics are required including both objective indicators, and subjective indicators that capture the user experience; user cohorts must be stratified to represent realistic and relevant clinical scenarios (e.g. trainees, senior users with low IT exposure, etc.). Clusters of descriptors for patient analyses will have to be revised based upon novel hypotheses generated through VPH/DP technologies

5. Health economic and business models must be developed to identify and validate the business case of implementing a specific clinical application for each group of relevant stakeholders, placing the DP within the hospital, clinic or surgery context, as well as for the health system as a whole

6. There will be a significant demand for education and training. Training programmes will be required to provide technicians with a strong underpinning knowledge base. In early and mid-term stages of translation, training in principles of the respective VPH model/DP solution will be needed for clinical end users

8.6 Digital Patient recommendations for Horizon 2020:

The upcoming European Union Horizon 2020 Framework Programme for Research and Innovation foresees as one of its core objectives to further the health and wellbeing of European citizens. In line with this, the Digital Patient Initiative inquires into novel applications combining the power of advanced, computer-supported modelling and simulation of human organs and diseases with the innovation thrust of clinical professionals to progress rapidly towards a more individualised, predictive and preventive medicine, particularly in light of the increasing number of multi-morbid and elderly patients. Great benefits in terms of quality of life and quality of care for patients, better selection of treatment options, and more efficient healthcare provision will be forthcoming.

On the basis of the recommendations included in this roadmap and the maturity levels identified, the following objectives for H2020 can be formulated:

Interactive health analytics (Maturity Level #1): Allow for novel tools to facilitate individualised knowledge fusion

1. In support of integrative biomedical information management, foster the development of solutions based on open source components for the replication of heterogeneous clinical databases (containing, e.g., still and moving images, biosignals, lab exams, clinical reports, clinical genomics, etc.) and of patient and other health (system) data collected outside the hospital (point of care, GPs, home, telemedicine) into a research repository, with automatic anonymisation and, fully in line with European Data Protection regulations, exposure outside the hospital for secondary use in clinical research. Proposed solutions should make possible the federation of multiple repositories, including semantic mediation, into regional or national resources for clinical and health system research.

2. To improve usability and usage, initiate the further improvement of user interfaces that provide explorative capabilities over large and heterogeneous collections of clinical databases. Invest in the combination of scientific information and data visualisation techniques to create interactive environments tailored for specific families of diseases, which allow the search for similar cases, the comparison of multiple cases across heterogeneous information, and the interactive exploration of high-dimensional datasets such as those produced by VPH simulations.

3. To allow for big health data analytics, it is necessary to develop advanced algorithms and methods for the automatic or semi-automatic efficient analysis of large collections of heterogeneous and long-preserved clinical data. This requires advanced storage systems that can execute restricted computation modules (storlets) in the storage close to the data. Priority should be given to approaches that combine heterogeneous information sources.

Individualised wellbeing and healthcare management (Maturity Level #2): Provide for improved clinical applications fully supporting individualised care:

1. Applications for individualised healthcare require modelling solutions to support clinical decision processes (from prevention to diagnosis, prognosis, treatment, rehabilitation, and monitoring) integrating and exploring subject-specific information across scales (from the molecule to the organism). VPH research allows constructing and validating such prediction models and integrating them into highly useable clinical decision support tools. These are at the core of personalised medicine as proposed by the Digital Patient. To support these modelling-based applications, solutions should include technologies to automate data extraction relevant to the health challenge at hand. Also, these solutions must provide for effective exploratory clinical interfaces in order to ease the clinical decision-making process.

2. Efficacy and effectiveness studies of individualised care tools and work flows are needed to speed up clinical acceptance and diffusion of such applications. Clinical studies and trials on prospective or retrospective cohorts aimed to investigate the differences in efficacy, effectiveness and efficiency of individualised care approaches based on VPH technologies developed in previous projects should be supported. Priority should be given to approaches that use VPH-style simulation to integrate information across scales. This research should also explore the development and accuracy of mathematically efficient models replacing computational demanding sub-models with estimators developed on pre-computed solutions and error estimators.

3. Research should be aimed particularly at those individualised computer simulation models/applications that have the prospect of improving treatment and thereby reducing the burden of the most important diseases in Europe based on the 2010 Global Burden of Disease study.[8] In term of Disability-Adjusted Life Years (DALY), these are cardiovascular and respiratory diseases (ischemic heart disease, stroke, COPD, vascular dementia, other cardio-circulatory), musculo-skeletal diseases (lower back pain, neck pain, falls, other musculoskel-

8 http://www.ncbi.nlm.nih.gov/pubmed/23245608

etal), cancer (lung, colorectal, breast), neurological (Alzheimer) and metabolic (diabetes) diseases, and on those diseases that have a considerable burden in term of quality life years lost due to disability (YLD), such as obesity, depression, chronic kidney and urinary disease, all forms of arthritis, etc. Such individualised computer simulations should deal with uncertainty and should work on strategies to formalise and generalise testing and validation of these models, providing estimations on the impact that incomplete data has in the personalised model. Furthermore, an extension and integration of such models towards dealing with multimorbidity is urgently required, because such patients are by far the most costly ones when compared to those suffering from only one or two diseases.

Patient Avatar (Maturity Level #3): Develop novel, advanced modes of visualisation of medical conditions and implementation of Digital Patient solutions for both clinicians and patients

1. Integrative interactive visualisation in healthcare is a most promising new area of application facilitated by technical progress in both hard- and software. Development of model-based prototypes that provide testable proof of concept for clinical use using realistic and relevant clinical scenarios should be supported. These prototypes should include interactive user interfaces specifically designed for the clinical exploration of large, heterogeneous, high-density collection of information. These should also develop tools that allow for an easy to understand visualisation of uncertainty in the Digital Patient output. Studies should include experiments to quantify the effectiveness of the proposed interfaces and tools, over cohorts of expert and in-training medical professionals as well as patients.

2. Development of methods for real-time interactive simulation is urgently needed. These are computational methods that allow generating computer predictions of VPH-style hypermodels as part of an interactive session, involving, e.g., different specialists, a clinician and a patient, etc. These may include pre-computing strategies, surrogate modelling approaches, or brute-force hardware/solver optimisation for drastic speed-ups.

3. To allow for a better assessment of alternative exploration strategies and decision support when investing in Digital Patient applications, policy makers, health system managers as well as clinicians need better data on the impact of the new technology and the respective "business" case. This requires the development of novel health technology assessment methodologies, cost-benefit approaches and exploration planning tools adapted for Digital Patient solutions.

4. The rapid diffusion of Digital Patient solutions will demand their clinical assessment and economic evaluation against the current standard of care in realistic scenarios and routine application contexts.

“We are on a journey but we are not doing it quickly enough. In my view, we need to move quicker. We need enthusiasts from engineering and the government to get it going. Uptake will improve as the products improve.”

(Consultant Surgeon)

9. Annex I - Bibliography

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Aligned standards + Interoperability
Computational Storage < Infrastructure cloud
High speed networks
Automated Curation
Open world assumption
Centralised / Federated Balance
Information Security
Privacy
Dimensional reduction [key parameters Relevance]
(Accessibility – usability)
Intelligent algorithms – high scale – personal scale
Explicitness + transparency
LEARN FROM OTHER SECTORS
Dirk
Automated ontology
Extensible standards
Reliable risk assessments
Blanca
Inf. security + privacy
Nora
Computing infrastructure
Debora
Data collection + integration
Magda
Natural Language
Darnah

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Wirix-Speetjens	Roel	Materialise	BE	Industry
Wood	Steven	STHT	UK	Clinical
Yaro	Abubakar	Annals of Tropical Medicine & Public Health	GH	Industry
Zachow	Stephan	MXL	DE	Academia
Zadpoor	Amir A.	Delft University of Technology	NL	Academia
Zary	Nabil	Karolinska Institute	SE	Clinical

11. Annex III - VPH projects

Acronym	Title	Website	Short description	Start Date	Duration	Specialisation
@neurist	Integrated Biomedical Informatics for the Management of Cerebral Aneurysms	www.aneurist.org	AneurIST is focussed on cerebral aneurysms and provides an integrated decision support system to assess the risk of aneurysm rupture in patients and to optimise their treatments.	01 January 2006	48months	Cardiovascular
ACGT	Advancing Clinico-Genomic Trials on Cancer	acgt.ercim.org	ACGT will develop a bio-medical GRID infrastructure supporting seamless mediation services for sharing clinical and genomic expertise. Such interactions will allow joint clinico-genomic trials and help finding quicker and efficient routes to identifying patients' individual characteristics that make one treatment more appropriate than another.	01 February 2006	48months	Genetics
Action-Grid	International cooperative action on grid computing and biomedical informatics between the European Union, Latin America, the Western Balkans and North Africa	www.action-grid.eu	The project aims to exchange research results and foster collaborations in Nanoinformatics, Grid technologies and Biomedical Informatics among Latin America, the Western Balkans, North Africa and the European Union (EU). One of its main aims is to deliver a White Paper that will provide input to the European Commission in developing a future agenda in R&D in these areas.	01 August 2008	18months	Information Technology
AirPROM	Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling	www.airprom.european-lung-foundation.org/	AirPROM aims to bridge the gaps in our clinical management of airways disease, by providing validated models that predict disease progression and response to treatment.	01 March 2011	60months	Respiratory

ARCH	Patient specific image-based computational modelling for improvement of short- and long-term outcome of vascular access in patient on hemodialysis therapy	www.vph-arch.eu	The ARCH project aims at developing image-based computational modelling tools for surgical planning and management of vascular access, the surgical arterio-venous shunt used to connect patient circulation to artificial kidney, a critical component of renal replacement therapy.	01 June 2008	36months	Cardiovascular
ARTreat	Multi-level patient-specific artery and atherogenesis model for outcome prediction, decision support treatment, and virtual hand-on training	www.artreat.org	ARTreat aims at developing a patient-specific computational model of the cardiovascular system, which will be used to improve the quality of prediction for the atherosclerosis progression and propagation into lifethreatening events that need to be treated accordingly.	01 September 2008	53months	Cardiovascular
ASSIST	Association Studies Assisted by Inference and Semantic Technologies	www.assist.iti.gr	ASSIST aims to provide medical researchers of cervical cancer with an integrated environment that will virtually unify multiple patient record repositories, physically located at different laboratories, clinics and/or hospitals.	01 January 2006	36months	Information Technology
CHIC	Computational Horizons In Cancer: Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology	www.chic-vph.eu	CHIC proposes the development of a suite of tools, services and secure infrastructure that will support accessibility and reusability of VPH mathematical and computational hypermodels. Cancer hypermodels to be collaboratively developed by the consortium cancer modellers will provide the framework and the testbed for the development of the CHIC technologies. Clinical adaptation and partial clinical validation of hypermodels and hypermodel oncosimulators will be undertaken.	1 April 2013	48months	Oncology and Information Technology
CONTRA CANCRUM	Clinically oriented translational cancer multilevel modelling	www.contracancrum.eu	The ContraCancrum project aims at developing a composite multilevel platform for simulating malignant tumour development and tumour and normal tissue response to therapeutic modalities and treatment schedules in order to optimise the disease treatment procedure in the patient's individualised context.	01 August 2008	36months	Oncology

DISCIPULUS	Digitally Integrated Scientific Data for Patients and Populations in User-Specific Simulations Research area	www.digital-patient.net	Discipulus has been set to produce a research roadmap for the realisation of the Digital Patient, an initiative to provide an integrative, sustainable approach to using patient information and computational models in the clinic.	01 October 2011	18months	VPH Planning & Promotion
DR THERAPAT	The Digital Radiation Therapy Patient	www.drtherapat.eu	DR THERAPAT's aim is to create the Digital Radiation Therapy Patient platform. This platform will integrate available knowledge on tumor imaging, image analysis and interpretation, radiobiological models and radiation therapy planning into a coherent, reusable, multi-scale digital representation. Radiation therapy was chosen as the application to prove the integration of those concepts since inherently imaging plays a major role in radiation therapy planning and delivery, so the imaging information is available as input for various models, and the delivery process is relatively well understood, making the model validation easier compared to e.g. chemotherapy.	01 February 2013	36 months	Oncology
euHeart	Integrated cardiac care using patient specific cardiovascular modelling	www.euheart.eu	The euHeart project aims to use patient-specific cardiovascular modelling as biophysically-based integration framework to improve the diagnosis, planning, and treatment of cardiovascular disease and to reduce the allied healthcare costs.	01 June 2008	48months	Cardiovascular
EuResist	Integration of viral genomics with clinical data to predict response to anti-HIV treatment	www.euresist.org	The EuResist project aims to develop a European integrated system for the clinical management of antiretroviral drug resistance. The system will predict patient reactions to antiretroviral treatments for HIV, thus helping clinicians to select the most appropriate drugs and drug combinations for any given HIV genetic variant.	01 January 2006	30months	Multidisciplinary

FUSIMO	Patient specific modelling and simulation of focused ultrasound in moving organs	www.fusimo.eu	FUSIMO aims at developing a model for focused ultrasound surgery in moving organs, such as the liver. With support in planning of the intervention, monitoring of the treatment progress, as well as by assessing the therapy outcome, focused ultrasound can become a safe und successful non-invasive procedure for tissue ablation in moving abdominal organs.	01 January 2011	36months	Multidisciplinary
GO-SMART	A Generic Open-end Simulation Environment for Minimally Invasive Cancer Treatment	NA	The Go-Smart project will build a generic open-source software simulation environment for planning of image guided percutaneous Minimally Invasive Cancer Treatment (MICT).	1 April 2013	36months	Oncology
GRANATUM	A Social Collaborative Working Space Semantically Interlinking Biomedical Researchers, Knowledge And Data For The Design And Execution Of In-Silico Models And Experiments In Cancer Chemoprevention	www.granatum.org	The vision of the GRANATUM project is to bridge the information, knowledge and collaboration gap among biomedical researchers in Europe (at least) ensuring that the biomedical scientific community has homogenised, integrated access to the globally available information and data resources needed to perform complex cancer chemoprevention experiments and conduct studies on large-scale datasets.	01 February 2011	30months	Information Technology
HAMAM	Highly accurate breast cancer diagnosis through integration of biological knowledge, novel imaging modalities, and modelling	www.hamam-project.org	HAMAM will tackle the challenge of early detection and accurate diagnosis of breast cancer by integrating available multi-modal images and patient information on a single clinical workstation. Based on knowledge gained from a large multi-disciplinary database, populated within the scope of this project, suspicious breast tissue will be characterised and classified.	01 August 2008	36months	Oncology
Health-e-Child	NA	www.health-e-child.org	The Health-e-Child project aims at developing an integrated healthcare platform for European paediatrics, providing seamless integration of traditional and emerging sources of biomedical information.	01 February 2006	48months	Information Technology

I-Know	Integrating Information from Molecule to Man: Knowledge Discovery Accelerates Drug Development and Personalised Treatment in Acute Stroke	cfin.au.dk	I-Know is a knowledge discovery IT -based tool designed to aid early stroke diagnosis, stroke treatment, drug development and identification of risk factors as targets in disease prevention for the benefit of European industry and citizens.	01 May 2006	36months	Multidisciplinary
ImmunoGrid	The European Virtual Human Immune System Project	www.immunogrid.org	The project will focus on establishing an infrastructure for the simulation of the immune system that integrates processes at molecular, cellular, and organ levels. It will be designed for applications that support clinical outcomes such as design of vaccines and immunotherapies and optimization of immunization protocols.	01 February 2006	36months	Infection & Immunology
IMPPACT	Image-based multiscale physiological planning for ablation cancer treatment	www.imppact.eu	IMPPACT develops an intervention planning system for Radiofrequency Ablation of malignant liver tumours accounting for patient specific physiological factors. Validation is performed at multiple levels through comparison of simulation and treatment results gathered in animal studies and during patient treatment.	01 August 2008	36months	Oncology
INBIOMEDvision	Promoting and Monitoring Biomedical Informatics in Europe	www.inbiomedvision.eu	INBIOMEDvision is a Coordination and Support Action that aims to promote Biomedical Informatics by means of the permanent monitoring of the scientific state-of-the-art and the identification of common grounds and potential synergies between current Bioinformatics and Medical Informatics approaches.	01 February 2011	24months	VPH Planning & Promotion
INTEGRATE	Driving Excellence in Integrative Cancer Research through Innovative Biomedical Infrastructures	www.fp7-integrate.eu	Synergy between clinical research and the VPH community will speed up the development and validation of multiscale predictive models in breast cancer - an area in which modelling significantly lags behind due to high variability in molecular/genetic and tissue level characteristics –, improve patient outcomes and reduce costs. INTEGRATE will enable this through a dynamic environment, collaboration tools and secure access to comprehensive datasets.	01 February 2011	36months	Multidisciplinary

LHDL	The Living Human Digital Library	www.livinghuman.org	Every hospital, every research laboratory in Europe has a wealth of biomedical data locked-up somewhere that, if shared with other experts, could dramatically improve healthcare practice as well as the development of better biomedical products. LHDL finally makes it possible to share biomedical data in an easy, controlled, safe, and financially viable way.	01 February 2006	36months	Information Technology
MD-Paedigree	Model-Driven European Paediatric Digital Repository	www.md-paedigree.eu	MD-Paedigree aims to validate and bring to maturity patient-specific computer-based of various paediatric diseases, making them readily available not only in the form of sustainable models and simulations but also as newly defined workflows for personalised, predictive medicine at the point of care.	01 March 2013	48months	Multidisciplinary
MISSION-T2D	Multiscale Immune System Simulator for the ONset of Type 2 Diabetes integrating genetic, metabolic and nutritional data	www.mission-t2d.eu	Development and validation of an integrated, multilevel patient-specific model for the simulation and prediction of metabolic and inflammatory processes in the onset and progress of the type 2 diabetes (T2D).	01 March 2013	36months	Multidisciplinary
MOSAIC	MOdels and Simulation techniques for discovering diAbetes Influence faCtors	NA	MOSAIC will address two very specific aspects linked to the prediction of risk of developing diabetes (type 2 and gestational) and complications associated to diabetes. These objectives respond to a widely recognised problem related to diabetes management and have the potential to have a major impact in the way diabetes is currently diagnosed and followed in Europe.	01 January 2013	40months	Diabet
MSV	Multiscale Spatiotemporal Visualisation: Development of an Open-Source Software Library for the Interactive Visualisation of Multiscale Biomedical Data,	www.msv-project.eu	MSV aims to define an interactive visualisation paradigm for biomedical multiscale data, to validate it on the large collections produced by the VPH projects, and to develop a concrete implementation as an open-source extension to the Visualization Tool Kit.	01 January 2010	36months	Information Technology

MULTI-KNOWLEDGE	Creating new knowledge in networks of medical research	www.multiknowledge.eu	The MULTI-KNOWLEDGE Project aims to integrate different biomedical information from heterogeneous sources (clinical, laboratory and metabolic) with data on gene and protein expression provided by new high throughput technologies in a system committed to cardiovascular risk profiling.	01 January 2006	26months	Information Technology
MYHEALTHAVATAR	A Demonstration of 4D Digital Avatar Infrastructure for Access of Complete Patient Information	NA	MyHealth Avatar is an attempt at a proof of concept for the digital representation of patient health status.	01 March 2013	36months	Information Technology
MySPINE	Functional prognosis simulation of patient-specific spinal treatment for clinical use	www.myspineproject.eu	MySpineaims to create a clinical predictive tool that will help to determine the best treatment for low back pain by providing clinicians with patient-specific biomechanical and mechano-biological analysis	01 March 2011	36months	Multidisciplinary
NeoMARK	ICT enabled prediction of cancer reoccurrence	www.neomark.eu/portal/	NeoMark Virtual Physiological Human (VPH) approach integrating heterogeneous data collected with different techniques and in-silico representation, modelling and prediction of biological phenomena linked to the disease evolution, will improve significantly the management of oral cancers.	01 June 2008	36months	Oncology
NMS Physiome	Personalised models of the neuro-musculoskeletal system	www.nmsphysiome.eu/	NMS Physiome aims to integrate communities, technologies and services developed in two large research projects: VPHOP (Osteoporotic Virtual Physiological Human) funded by the European Commission, and SIMBIOS (Center for Physics-based Simulation of Biological Structures) funded by the US National Institutes of Health.	01 January 2010	36months	Muscular-Skeletal
PASSPORT	Patient specific simulation and preoperative realistic training for liver surgery	www.passport-liver.eu	PASSPORT aims at developing a dynamic liver modelling, which thanks to a preoperative surgical planning simulator, will allow to predict a surgery's feasibility and thus increase the rate of surgical treatment so as to save patients suffering from liver pathologies.	01 June 2008	36months	Surgery

p-medicine	From data sharing and integration via VPH models to personalised medicine	www.p-medicine.eu	The p-medicine project aims at developing a secure IT infrastructure, innovative tools, and VPH models for decision support to accelerate the progression and implementation of personalised medicine. All services, models and tools are clinically driven.	01 February 2011	48months	Information Technology
preDICT	Computational prediction of drug cardiac toxicity	www.vph-predict.eu	The preDiCT project will model and ultimately predict the impact of pharmaceutical compounds on the heart's rhythm using computer simulation. Using this information, the project hopes to identify new biomarkers which will provide more reliable indication of harmful drug side effects.	01 June 2008	36months	Multidisciplinary
PredictAD	From patient data to personalised healthcare in Alzheimer's Disease	www.predictad.eu	PREDICTAD aims to develop an objective tool for enabling earlier diagnosis of Alzheimer's disease. Biomarkers derived from various data sources of patient monitoring, such as neuropsychological tests, medical imaging, electrical brain activity measurements and blood samples will be studied and combined.	01 June 2008	36months	Neuology
RADICAL	Road mapping technology for enhancing security to protect medical and genetic data	www.radicalhealth.eu	RADICAL aims at approaching coherently, studying in depth and revealing scientifically, the beyond the state-of the art research and policy roadmap for security and privacy enhancement in VPH, taking into consideration technology advancements, business and societal needs, ethics and challenges that should be addressed and answered.	01 July 2008	24months	Information Technology
RICORDO	Interoperable anatomy and physiology	www.ricordo.eu	RICORDO is focused on the study and design of a multiscale ontological framework in support of the VPH community to improve the interoperability amongst its Data and Modelling resources.	01 February 2010	24months	Information Technology
RT3S	Real Time Simulation for Safer vascular Stenting	NA	The RT3S project aim to develop and validate a sophisticated patient-specific, probabilistic model of the fatigue-fracture of a stent, integrated in a computer-aided surgery planning application, implemented to run in real-time during the surgical planning, so as to provide advice of the risk of stent rupture while the surgeon is planning the operation.	01 January 2011	36months	Cardiovascular

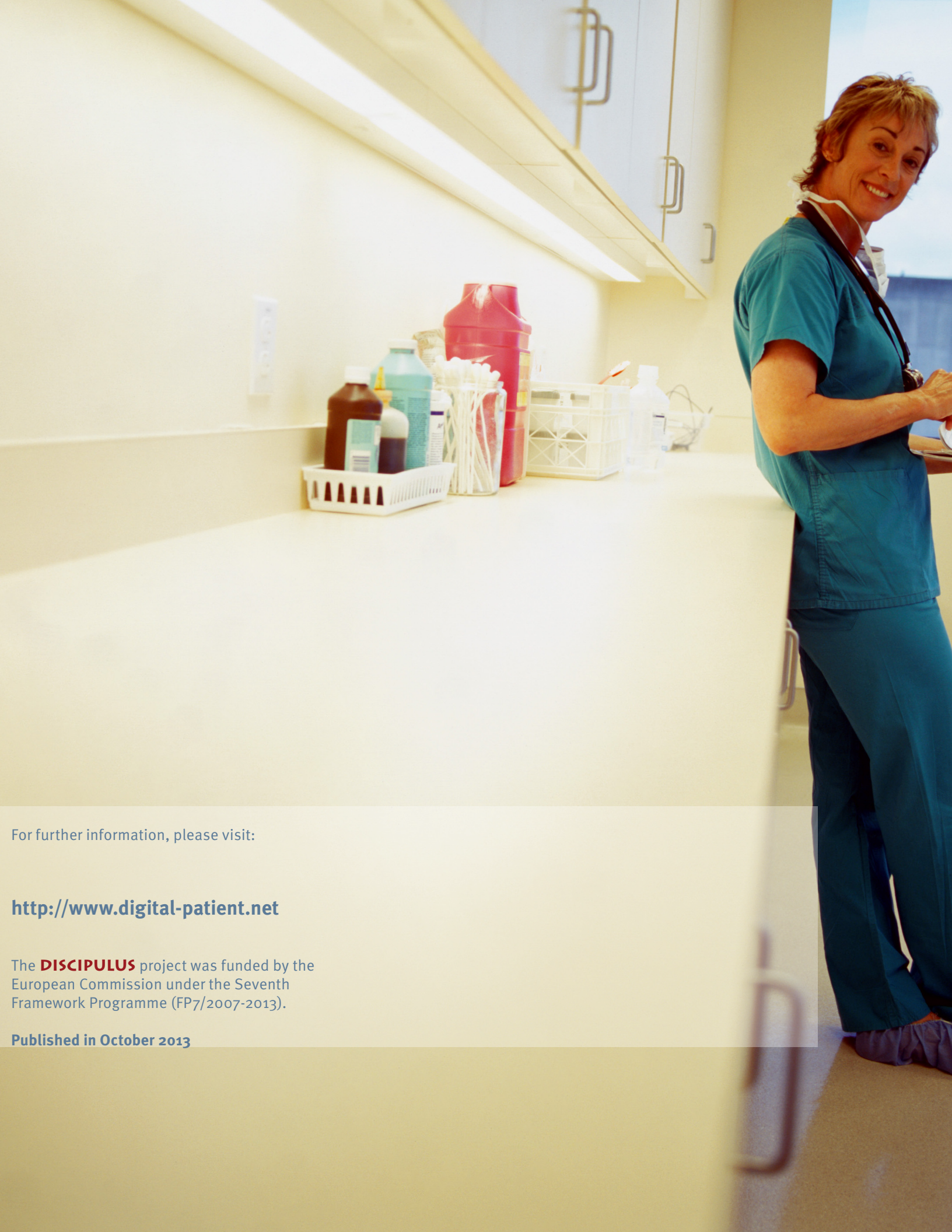
Sealife	A Semantic Grid Browser for the Life Sciences applied to the study of Infectious Diseases	www.biotec.tu-dresden.de/sealife	How can the researcher in the lab benefit from this new infra-structure to science? A technology is needed to transparently bring such services to the desks of the scientists. Sealife will develop a browser, which will link the existing Web to the currently emerging eScience infrastructure.	1 April 2006	36months	Information Technology
Share	Supporting and structuring Healthgrid Activities and Research in Europe	initiative.healthgrid.org	SHARE aims to define a roadmap for future healthgrid research, highlighting opportunities, obstacles and potential bottlenecks.	01 January 2006	26months	VPH Planning & Promotion
SIFEM	Semantic Infostructure interlinking an open source Finite Element tool and libraries with a model repository for the multi-scale Modelling and 3d visualization of the inner-ear	NA	SIFEM focuses on the development of a Semantic Infostructure interlinking an open source Finite Element Tool with existing data, models and new knowledge for the multi-scale modelling of the inner-ear with regard to the sensorineural hearing loss.	01 February 2013	36months	Information Technology
Sim-e-Child	Grid-Enabled Platform for Simulations in Paediatric Cardiology Toward the Personalised Virtual Child Heart	www.sim-e-child.org		01 January 2010	30months	Information Technology
STEP	A Strategy for the Euro-Physiome	www.europhysiome.org	STEP was a Coordination Action that sought to coordinate European activity relating to the physiome – a description of human physiology that will span multiple levels from the whole body down through the organs to the cells and beneath in an integrated manner.	01 January 2006	14months	VPH Planning & Promotion
SYNERGY-COPD	Supporting highly adaptive Network enterprise collaboration through semantically enabled knowledge services	www.Synergy-COPD.eu	The Synergy-COPD project develops a simulation environment and a decision-support system aiming at enabling the deployment of systems medicine. The Synergy-COPD system focuses on patients with chronic obstructive pulmonary disease (COPD), which is a major public health problem and a complex, heterogeneous and multi-component disease.	01 February 2012	36months	Respiratory

TBIcare	Evidence based Diagnostic and Treatment Planning Solution for Traumatic Brain Injuries	www.tbicare.eu	TBIcare will provide an objective and evidence based solution for management of traumatic brain injury by improving diagnostics and treatment decisions for an individual patient. It does this by analysing and combining a wide range of biomarkers. It will provide clinical decision-making assistance and improved outcome.	01 February 2011	36months	Neurology
THROMBUS	A quantitative model of thrombosis in intracranial aneurysms	www.thrombus-vph.eu	Cerebral aneurysms are undesired local deformations of the wall of a brain vessel whose rupture can be lethal. The natural repair of an aneurysm is through a thrombosis process. The problem addressed in THROMBUS is to propose a multi-scale simulation model to predict how cerebral aneurysms may occlude after the insertion of a stent.	01 February 2011	36months	Cardiovascular
TUMOR	Transatlantic TUmour MOdel Repositories	www.tumor-project.eu	TUMOR aims at implementing a EU cancer model/data repository, and developing/providing specific tools and methods for the collection, curation, validation and customization of existing EU and US cancer models, by linking the most significant relevant EU VPH projects on cancer modelling (ContraCancrum, ACGT), and the US project (CViT).	1 April 2010	36months	Oncology
VIGOR++	Virtual GastrOintestinal tRact	www.vigorpp.eu	VIGOR++ aims to improve detection and accurate assessment of Crohn's disease, an autoimmune condition with 700,000 diagnosed cases across Europe. By combining advances in image analysis, modelling and interactive visualisation VIGOR++ will create a personalised model of the gastrointestinal tract reducing the need for frequent and often invasive examinations.	01 February 2011	36months	Gastrology
VIROLAB	A Virtual Laboratory for Decision Support in Viral Disease Treatment	www.virolab.org	ViroLab enables easy access to distributed resources as well as the sharing, processing, and analysis of virological, immunological, clinical and experimental data.	01 March 2006	36months	Infection & Immunology
VPH2	Virtual pathological heart of the virtual physiological human	www.vph2.eu	VPH2 aims to develop a patient-specific computational modelling of the heart to assist cardiologists/ cardiac surgeons in defining the severity and extent of disease in patients with post-ischemic Left Ventricular Dysfunction (LVD), with or without ischemic mitral regurgitation (IMR).	01 July 2008	36months	Cardiovascular

VPH-DARE@IT	VPH Dementia Research Enabled by IT	NA	The DementiA Research Enabled by IT project responds to the European Parliament's 2011 resolution for a European Initiative on Alzheimer's disease and other dementias, and the EU Year of the Brain 2014 Initiative. It delivers the first patient-specific predictive models for early differential diagnosis of dementias and their evolution.	1 April 2013	48months	Dementia
VPH-FET	Future and Emerging Technologies for the Virtual Physiological Human	www.biomedtown.org/biomed_town/VPHFET	VPH- FET is a Support Action designed to identify Future & Emerging Technologies (FET) that can support VPH into the future and to establish VPH as a viable and acknowledged area for "blue sky" research within the EC Framework Programme. Thus, if it achieves its aims, VPH-FET will create a dedicated funding stream for VPH within the Future and Emerging Technologies Programme in FP7 and open up considerable opportunities for the expansion and diversification of VPH research.	01 September 2010	12months	Multidisciplinary
VPH-NoE Exemplar Project 1	A multi-organ Core Model of arterial pressure and body fluids homeostasis	NA	NA	Within the NoE	12months	Multidisciplinary
VPH-NoE Exemplar Project 10	Environment for Sexually Transmitted Infection Modeling	NA	NA	Within the NoE	12months	Infection & Immunology
VPH-NoE Exemplar Project 11	Vascular Tissue Modeling Environment (VTME)	NA	NA	Within the NoE	12months	Multidisciplinary
VPH-NoE Exemplar Project 2	Integrated multi-level modelling of the musculoskeletal system	NA	NA	Within the NoE	12months	Muscular-Skeletal
VPH-NoE Exemplar Project 3	The Vertical and Horizontal Atherome (WHAM)	NA	NA	Within the NoE	12months	Multidisciplinary
VPH-NoE Exemplar Project 4	Multi-scale simulation and prediction of the drug safety problems related with hERG	NA	NA	Within the NoE	12months	Muliple

VPH-NoE Exemplar Project 5	Digital Patient Working Group: Modelling and visualising brain function and pathophysiology	NA	NA	Within the NoE	12months	Neurology
VPH-NoE Exemplar Project 6	Establishing ontology-based methods for the VPH ToolKit to improve interoperability between data and models: the Guyton case study	NA	NA	Within the NoE	12months	Multidisciplinary
VPH-NoE Exemplar Project 7	CIGENE: Integrating genetic theory and genomic data with multiscale models in a population context	NA	NA	Within the NoE	12months	Genetics
VPH-NoE Exemplar Project 8	USFD: The NoE, Infrastructure and the Challenge of Call6	NA	NA	Within the NoE	12months	Information Technology
VPH-NoE Exemplar Project 9	VIP for VPH : Execution of medical image simulation workflows on DEISA through workflow interoperability between the Virtual Imaging Platform and the VPH toolkit	NA	NA	Within the NoE	12months	Multidisciplinary
VPHOP	Osteoporotic Virtual Physiological Human	www.vphop.org	VPHOP aims to develop, validate and deploy to pilot clinical studies the next generation of technology for predicting the risk of fracture in patients with low bone mass and assisting clinicians in prognosis and treatment planning (both pharmacological and interventional).	01 August 2008	48months	Muscular-Skeletal
VPH-PRISM	Virtual Physiological Human: Personalised Predictive Breast Cancer Therapy Through Integrated Tissue Micro-Structure Modelling	NA	VPH-PRISM will provide a proof of concept for multidisciplinary model based discovery of environment-tissue interactions, quantitative drug efficacy assessment, surgery planning, and treatment outcome prediction at early and advanced stages of breast cancer.	01 March 2013	36months	Oncology

VPH-Share	Virtual Physiological Human: Sharing for Healthcare - A Research Environment	www.vph-share.eu	VPH-Share is building a safe, online facility in which medical simulation developers can produce workflows - chains of processing tasks - to allow raw medical data to be refined into meaningful diagnostic and therapeutic information.	01 March 2011	48months	Multidisciplinary



For further information, please visit:

http://www.digital-patient.net

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