TOWARDS THE VIRTUAL PHYSIOLOGICAL HUMAN: THE LIVING HUMAN PROJECT

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1. ABSTRACT

One limitation of western medicine is that specialisation causes the medical professional to focus on specific parts of the human body, which tends to result in the systemic nature of our physiology being overlooked. This is a cultural, educational, but also a technological and an organisational problem. Everything, from the cost model of healthcare to medical imaging technology, is organised around this partitioning of the human body.

One possible answer to this limitation is the creation of the human Physiome. The *physiome* is the quantitative and integrated description of the functional behaviour of the physiological state of an individual or species. The physiome describes the physiological dynamics of the normal intact organism and is built upon information and structure (genome, proteome, and morphome).

The Physiome Project is a worldwide effort to define the physiome through the development of databases and models, which will facilitate the understanding of the integrative function of cells, organs, and organisms. The Project is focused on compiling and providing a central repository of databases, linking experimental information and computational models from many laboratories into a single, self-consistent framework. It is evident that this ambitious objective poses a number of technological challenges. Some fundamental contributions in this direction may come from the development of the so-called Virtual Physiological Human (VPH). The VPH is an organised collection of computational frameworks and ICT-based tools for the multilevel modelling and simulation of human anatomy and physiology. Once sufficiently developed, the VPH will provide an essential technological infrastructure to the Physiome Project, to pathology-specific initiatives in translational research, and to vertical solutions for the biomedical industry. The present paper describes a first attempt to transform the VPH concept into reality: the Living Human Project.

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2. INTRODUCTION

The Living Human Project (LHP) aims to create an *in silico* model of the human musculoskeletal apparatus which can predict how mechanical forces are exchanged internally and externally at any dimensional scale from the whole body down to the protein level. This ambitious goal is being pursued through the following steps:

- creation of a community of researchers interested in the project and in the idea of exchanging information, data and models to create a collectively owned resource
- development and implementation of a specialised infrastructure, called the Living Human Digital Library, which makes it possible for the community members to create, share, modify the data and modelling resources that constitute the LHP
- bootstrap the process by sharing, within this new infrastructure, some valuable collections, which can be accessed only under a barter model

This involves the various institutions, each contributing different skills (Fig. 1).

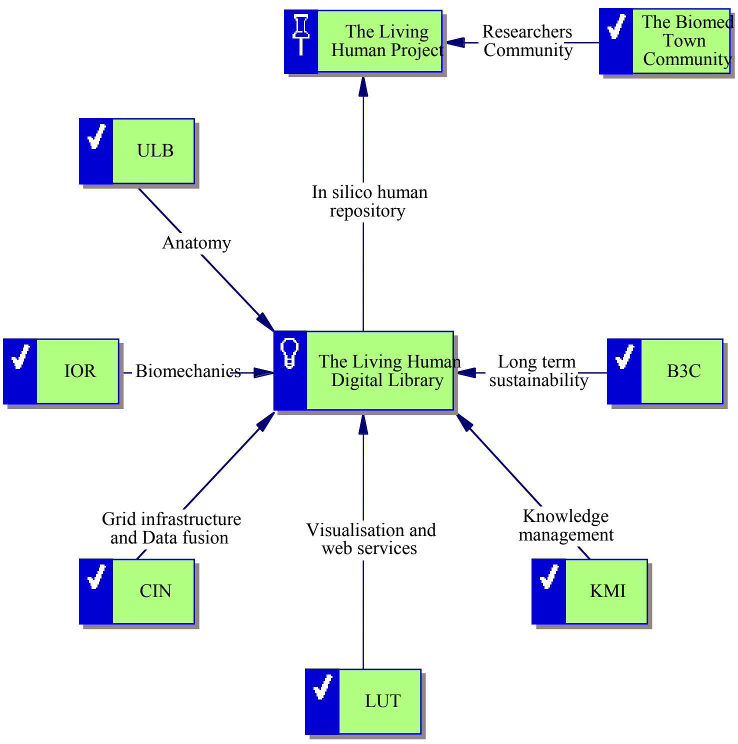

Fig. 1. The structure of the Living Human Project and the participant institutions

In the following pages we shall describe the current status and prospective plans for each of these activities.

3. COMMUNITY BUILDING

The LHP relies on the intensive community-building work that has been undertaken in recent years to make the biomechanics research community more sensitive to this idea, firstly with the BioNet[7] initiative and then with the BEL Repository[8]. All of this momentum is currently being re-organised into a new online community called Biomed Town (BT).

http://www.biomedtown.org/

BT is based on Plone[9], and open source Content Management Software, which makes it possible to deploy very quickly a complete community server, thanks also to a number of freely available add-ons that provide additional services such as WiKi collaborative editing, discussion forums, etc. To this base, the BioComputing Competence Centre[10], which operates BT, is developing custom-made extensions.

The first, called *Town*, provides the basic objects to implement the conceptual paradigm of the town: BT is a virtual town made of Buildings, Squares and Warehouses. Buildings host virtual organisations such as research consortia, companies, institutions, interest groups, etc.. At the Information Desk of the City Managers' Building, you will find all of the instructions on how to open a building representing your organisation, and the rules that regulate the construction of new buildings in our virtual town.

Once you have your building, you can create as many rooms as you like within it, and populate them with useful resources such as documents, web pages, folders, discussion forums, news, shared calendars, etc. This will allow you to create the best virtual collaborative environment for your organisation. Your building will be private, by default, and it will be up to you to decide – room by room – who can enter it.

Squares are where the people meet, discuss, and exchange experiences and pointers to resources; they represent the communities that populate our city, but that are not specifically represented by an organisation. At the Information Desk of the City Managers' Building, you will find all the instructions on how to recommend to the City Managers the creation of a new square representing a shared interest within the community, and the rules that regulate the construction of new squares in our virtual town. Squares belong to the City and are operated by the City Managers. Squares can contain Crowds, Billboards, and Directories.

Crowds are a special type of Forum folders, which contains public non-moderated forums. Billboards contain events, news, ads, and links relevant for that community. They are a special type of folder that can contain only certain Plone objects. Directories are selected lists of links to groups of people or to collections of other Biomed Town entities, such as buildings. Squares are the most anarchical objects; they do not have any local manager. Directories and Billboards are managed by the City Managers, as they define the public face of the town. Each user interested in the community located in that square can joint its crowds. The user can also submit objects for posting on the square billboards and Directories, which will be approved by the City Managers.

The second extension, called *Forum*, currently under development, will also provide complex workflows so that for each town, building, square, each activity follows a pre-

[7] http://www.biomedtown.org/biomed_town/LHDL/Reception/lhpdef/BioNet/
[8] http://www.tecno.ior.it/VRLAB/
[9] http://plone.org/
[10] http://www.b3c.it/

defined decisional process that imposes the necessary authorisations. This will provide the advanced collaboration features that this complex community requires.

The third and last product, called *Warehouse*, will be a fundamental component of the LHDL. Warehouses are special folders that contain the resources of Biomed Town. These resources can be data, programs, papers, instructions, etc. Initially warehouses will contain all data objects of Plone. Each warehouse will have local managers and reviewers of the content.

4. LIVING HUMAN DIGITAL LIBRARY

The logical architecture of the Living Human Digital Library (LHDL) is represented in Fig. 2. While its concrete implementation is still on progress, this description should provide an understanding of what capabilities this infrastructure will have when fully implemented.

The user can access the digital library using a standard web browser or using a dedicated application developed using the MAF framework.

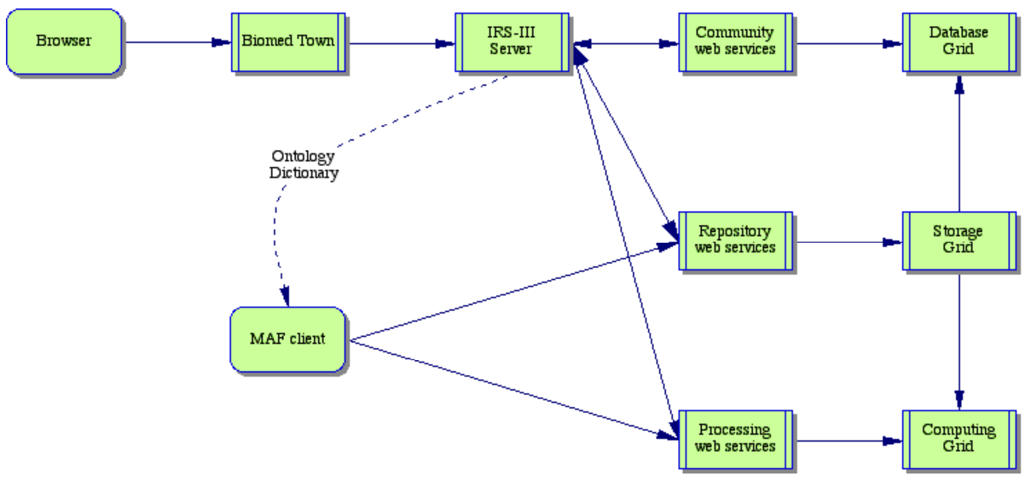

Fig. 2. Preliminary architecture of the LHDL

Through the browser, the user logs in on Biomed Town and then accesses the LHP WareHouse. Here, he will find list of services available; these services are being designed in term of user goals (search a dataset, download it, etc.). A semantic broker, the IRS-III server, will map each user goal into one or more backend web services, ensuring an extreme flexibility.

With this interface, the user starts searching certain resources among those available. LHDL will support two types of resources: data and services. Data are obtained from medical imaging, biomedical instrumentation or from simulation, while services expose algorithms for data processing, filtering, visualisation, analysis, etc.

Each data block is organised within a data object called a *Virtual Medical Entity*, VME. Each VME is enriched with a large set of meta-information relevant to the subject the data refers to, to the process used to generate the data, to the digital storage format, etc. Each of these can be used to search for the VME needed; thanks to the semantic engine, it will also be possible to make complex queries involving multiple meta-information.

From the list of VMEs that fulfil the search conditions, the user can selected one or more VMEs, which are then added to the basket. The user can also search all VMEs that belong to the same data trees of those found; so, for example, it will be possible, having found a surface obtained from segmentation of a CT dataset, to search for the CT dataset from which the surface was extracted. Once the basket contains all the necessary data, its content is downloaded to the client PC in a single file, which can be opened with the LhpBuilder application.

LhpBuilder is an application that is being developed using the Multimod Application Framework (MAF)[11]. The program would open by double clicking the file downloaded, and would expose an interface similar to that illustrated in Fig.3..

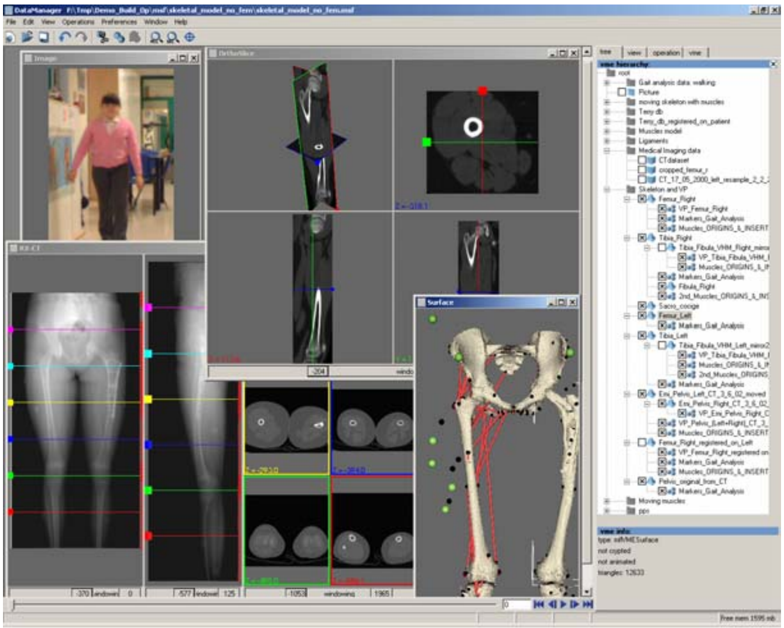

Fig. 3. User interface of Data Manager, a MAF application that will serve as a basis for the development of the LhpBuilder application

From within LhpBuilder, the user will interactively visualise the various downloaded VMEs re-organise them in any spatial hierarchy, rotate, translate, scale and synchronise in time (some of the data objects are time-varying). Special registration algorithms will make it possible to align the various data in space and time. Other tools will allow the location of anatomical landmarks on the anatomical regions, the measurement of relevant dimensions, and many other useful operations.

LhpBuilder is also the primary tool to add new VMEs to the digital library. A VME can be created directly inside the program, or by importing external data (e.g. DICOM images, segmentation surfaces generated by specialised programs, results set of simulation codes such as Ansys or Abacus, etc), or by digitally manipulating an existing VME with the operations available within LhpBuilder.

[11] http://www.openmaf.org/

Once the new data tree is ready, the user can upload it to the LHDL. The VME will be loaded in a private space called SandBox, accessible only by the user. From here the user can review his VMEs, enrich them with various forms of meta-information, have them reviewed by any quality procedure that might ensure the adequacy to certain standards, and finally publish them on the LHDL. When a VME is published, the user should be able to define an access policy, which formalises precisely what can be accessed by different types of user, and under what conditions.

Another way to create VME is to process published VMEs with available service resources. Using the same search interface, the user can find the type of processing service he needs; this may include simple reformatting, visual previews, but also complex registration or segmentation algorithms. They key point is that the services should be mostly faceless, e.g. that should be able to run in batch once the proper inputs are defined by the user. In this way, the user can apply a certain processing service to a group of VMEs, and obtain the results available on the LHDL as well. Once the LHP collection will be sufficiently large, this could make it possible to run studies on large populations, adding statistical power to many of our predictions.

5. CONCLUSIONS

From this brief description it is evident that the LHDL, in its final implementation, will be a powerful infrastructure that could seriously support the collaborative development of the VPH. Of course, the success of this endeavour will also involve human factors. In this sense, it will be fundamental to tackle two essential aspects: quality insurance and access policies.

The complexity of the resources we expect to share within the LHDL, make it impossible to imagine a centralised quality model, valid for all data and all services. The idea we are developing is for the Biomed Town community to develop QA procedures for various types of resources. For processing resources, this may involve the creation of a set of benchmark problems that each processing resource of a kind should successfully solve before it can be approved. For data resources, depending on the context, the QA criteria could be based on the nature of the data (resolution, noise to signal ratio, level of detail), the procedure used to generate them, or by peer review, the most obvious being that the data collection is described in a paper accepted for publication. The idea is that each of these QA criteria should be exposed as separate web services; at publication time, the data owner chooses from which QA service that VME should be ranked in terms of quality. Of cours,e some of these criteria can be totally automatic, such as those based on community voting, or on popularity.

The second aspect is that of the access policies. Here, it will be necessary to explore various options, as there is no outstanding solution, *a priori*. Probably the first implementation will be based on barter. Since Biomed Town is a closed community within which each participant is traceable, we could assign to each new user a small amount of credit. Each owner would set a price on his resources – when you download that resource that amount is transferred from your account to that of the resource owner. This should promote a balanced community in which everyone is both user and owner. In a second phase, it is clear that we shall have to move to more complex models, where some users can buy credits, instead of earning them through barter.