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Sharing and reusing cardiovascular anatomical models over the Web: a step towards the implementation of the virtual physiological human project

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Sharing and reusing anatomical models over the Web offers a significant opportunity to progress the investigation of cardiovascular diseases. However, the current sharing methodology suffers from the limitations of static model delivery (i.e. embedding static links to the models within Web pages) and of a disaggregated view of the model metadata produced by publications and cardiac simulations in isolation. In the context of euHeart—a research project targeting the description and representation of cardiovascular models for disease diagnosis and treatment purposes—we aim to overcome the above limitations with the introduction of euHeartDB, a Web-enabled database for anatomical models of the heart. The database implements a dynamic sharing methodology by managing data access and by tracing all applications. In addition to this, euHeartDB establishes a knowledge link with the physiome model repository by linking geometries to CellML models embedded in the simulation of cardiac behaviour. Furthermore, euHeartDB uses the exFormat—a preliminary version of the interoperable FieldML data format—to effectively promote reuse of anatomical models, and currently incorporates Continuum Mechanics, Image Analysis, Signal Processing and System Identification Graphical User Interface (CMGUI), a rendering engine, to provide three-dimensional graphical views of the models populating the database. Currently, euHeartDB stores 11 cardiac geometries developed within the euHeart project consortium.

Keywords: anatomical model; heart; database; model sharing; euHeartDB; CellML

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1. Introduction

The International Union of Physical Sciences (IUPS) physiome (Hunter *et al.* 2008) and European-based virtual physiological human (VPH) (Fenner *et al.* 2008) projects are international efforts to develop multi-scale models of eukaryotic and human physiology, respectively. Central to these initiatives is promoting the reuse and sharing of research products.

The physiome model repository (PMR) (http://www.cellml.org) designed to provide model upload, storage, curation and distribution capabilities has achieved the reuse and sharing of cellular models presented in a wide range of research papers through the development of an interoperable XML-based data format and a Web-enabled databasing system (Lloyd *et al.* 2004). Cellular models published in research papers are coded in CellML format and shared through PMR, thus making them instantaneously accessible to the entire research community. Moreover, CellML and PMR incorporate references to model metadata (e.g. publications or model applications), as these convey valuable information associated to the models. Specifically, CellML adopts the resource description framework (RDF) Dublin Core specification (http://dublincore.org/) to describe model author and curator data. Similarly, PMR includes graphical diagrams, representing the model structure, and links to publications describing and citing the models.

CellML and PMR have gained popularity in the biomedical community; however, to date the central focus has been on cellular models. This scope limitation has neglected cardiovascular anatomical models and atlases, which represent an entire research area (Young & Frangi 2009) and require considerable investments in terms of human resources and scientific equipments to be produced. Achieving an economy of scale in the production and use of anatomical models now requires that these research products also be efficiently shared among a wider audience in the cardiovascular community.

To date, anatomical models of the heart have been shared through a conventional Web approach, i.e. hosting them as static Web resources linked to HTML pages. For example, the Auckland canine heart model (Nielsen *et al.* 1991; LeGrice *et al.* 1997), one of the most reused computer models of the cardiac ventricles, has been available through the website of the Auckland Bioengineering Institute (ABI) for many years. As a consequence, considerable time is required to discover current and past applications of the Auckland model. Specific examples of this reuse are, however, plentiful. These include simulating electrical activation of the heart. Trayanova *et al.* (2001) investigated cardiac defibrillation on this canine geometry, using the bidomain equations as described by Henriquez (1993) to model the tissue behaviour. Similarly, to simulate cardiac mechanics, Smith *et al.* (2002*a*,*b*) embedded the cellular model of Hunter *et al.* (1998) and coronary vasculature (Smith & Kassab 2001; Smith *et al.* 2002*a*,*b*) within the Auckland geometry to obtain whole organ representations of the pump cycle. A further example is provided by Usyk *et al.* (2002), who investigated the role of electrical propagation on mechanical activation during the cardiac cycle, coupling the FitzHugh–Nagumo electrophysiology model (Rocsoreanu *et al.* 2000) and the Windkessel mechanical model (Kenner 1978).

In this paper, we aim to overcome the limitations discussed above with the introduction of euHeartDB (Gianni *et al.* 2009), a Web-enabled database for anatomical models of the heart. The database implements a dynamic delivery of the models by securing access to the data and by tracing the use of the models. Furthermore, euHeartDB is available online at http://euheartdb.physiomeproject.org/euHeartWebInt/ through the physiome project portal (http://www.physiomeproject.org), and integrates with the respective technologies. In particular, euHeartDB connects to PMR by linking geometries to embedded CellML models in cardiac simulation. By taking such an approach, euHeartDB establishes a knowledge link, and thus provides an integrative view of the anatomical models and of the related applications within simulation contexts. Moreover, euHeartDB adopts the exFormat, a preliminary version of FieldML (Christie *et al.* 2009), as an interoperable XML data format to effectively promote the reuse of models, and uses the Continuum Mechanics, Image Analysis, Signal Processing and System Identification Graphical User Interface (CMGUI; http://www.cmiss.org/cmgui), a VPH rendering engine, to provide graphical representations of the available geometries. Currently, the database is populated with 11 models from partners in the euHeart project consortium (http://www.euheart.eu) (Ecabert & Smith 2008). In particular, euHeartDB stores geometries from the ABI, the Institut National de Recherche en Informatique et Automatique (INRIA) ASCLEPIOS Team, Philips Research Europe (Aachen and Hamburg), the University of Sheffield–Academic Medical Unit and the Universitat Pompeu Fabra–Computational Imaging and Simulation Technologies in Biomedicine (UPF–CISTIB).

This paper is organized as follows. Section 2 details the demands of the cardiovascular community for a databasing system for anatomical models of the heart and shows how these needs translate into database requirements. Section 3 illustrates how these requirements are implemented, including a description of the main characteristics of the current database content and of the coupling with PMR. Finally, §4 presents a future vision for the use and implementation of euHeartDB.

2. Research needs and requirements

The limitations of static delivery of anatomic data and of the disaggregated view present in the current sharing methodology of anatomical models of the heart have motivated new needs in the cardiovascular community. These can be summarized as foundational need, control need, monitoring need, communication need and integrative need. The foundational need represents the essential demand of sharing and reusing anatomical models to progress research in cardiovascular diseases. The control need reflects the model owners' desire to maintain full control of their models. Similarly, the monitoring need meets the expectation of both model owners and users in providing an overview on the ongoing activities using the models. In addition to this, the communication need identifies the request for a virtual discussion forum covering the exchange of ideas and results. Finally, the integrative need highlights the importance of providing researchers with a comprehensive view of information related to the models, such as typical applications, publications describing and citing models, and related models in adjacent subdomains.

Table 1. Traceability matrix of the VPH community needs (rows) on euHeartDB requirements (columns). The matrix shows the euHeartDB requirements satisfying each community need. For example, the foundational need is satisfied with the implementation of functional requirements R1, R2, R4 and R5, and non-functional requirements R9, R10, R12, R13, R14 and R15.

	euHeartDB requirements															
	functional								non-functional							
VPH community needs	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13	R14	R15	R16
foundational	X	X		X	X				X	X		X	X	X	X	
control							X				X					
monitoring				X		X										
communication			X	X				X		X						
integrative								X								X

One strategy to address the foundational need in the context outlined is through the introduction of a community supported Web-enabled database of anatomical models. Within this framework, the control need requires that delivery of the models is implemented in a dynamic manner that leaves the ultimate control of actions to the model owners. The monitoring need can similarly be addressed with the adoption of logging capabilities on the actions taken. The communication need requires collaborative technologies that promote discussion and the exchange of ideas on a specific anatomical model. Finally, the integrative need, which partially overlaps with the guidelines of the VPH road map (Fenner *et al.* 2008), requires the establishment of a knowledge link among all the parties and on all the data involved in the development and use of the anatomical models.

After having identified the needs that motivated the introduction of euHeartDB, we derive the requirements that the databasing system must satisfy to meet the community's expectations fully (see traceability matrix in table 1). These requirements can be split into functional and non-functional requirements (Gianni *et al.* 2009).

The functional requirements are divided into those for model users and those for model owners. For model users, these include searching (R1), downloading (R2), commenting on (R3) and curating of models (R4). In addition, for model owners, the requirements are uploading (R5), activity monitoring (e.g. who downloads what) (R6) and accessibility settings of models (R7). In addition, the integration of bibliographic references (R8) (e.g. linking models to publications that describe, cite or use them) is required as it allows one to trace all the studies related to a given model. These functional requirements demand minimal description and, therefore, are not discussed further. Conversely, the non-functional requirements have to be addressed in conjunction with the functional requirements and deserve more attention. These non-functional characteristics include

— decentralized control of database content (R9),
— accessibility through the Internet (R10),
— secure control access (R11),

— semantic-based search of models (R12),
— graphical methods (R13),
— interoperable and standard XML data format for model importing and exporting (R14),
— support for popular model data formats (R15), and
— integration or coupling with established VPH tools and technologies (R16).

Decentralized control of the database content means that users can autonomously access the database to upload, search and download their models. While searching and downloading are generally decentralized by hosting these resources on a distributed environment, uploading is sometimes administered centrally by individuals charged with managing the database data-entry phase. To achieve automation, decentralized control of the database content is needed. This decentralized control, however, implicitly requires that users are able to connect to the databasing system independently from their computer platforms. In technical terms, this requires the use of Web technologies, which overcome platform heterogeneity and location issues. As a consequence, euHeartDB functionalities and content must be Web-accessible.

The universal accessibility offered by the Web also implies that non-authenticated and non-authorized Web users could access the interface services or could sample the database content when transmitted over the network. euHeartDB must avoid this type of use by implementing a secured control access. In particular, the interface access must be restricted solely to authenticated and authorized users, and all the database content must be transmitted over encrypted connections.

The fundamental database functionality for the sharing and reuse of models is the search. This should be supported by semantic-based criteria, such as a specified structural part of the heart for instance, in order to ensure more effective model retrieval. In addition, the search function should also be supported by graphical methods providing human users with a three-dimensional interactive visualization of the models before downloading the required model in an interoperable and standard XML data format (http://www.w3c.org/XML). Within the VPH, the FieldML markup language is currently being developed to meet this need of describing models that include spatial information (Christie *et al.* 2009). The goal is for FieldML files to contain all the parameters needed to mathematically specify spatial fields. The most common form of parameterization is a finite-element mesh, where the parameters are nodal parameters, element topology and the element-basis functions that interpolate the nodal parameters over the elements. However, FieldML is intended to handle more general parameterizations than just finite-element fields and also includes dense data formats (e.g. for images embedded inside models). While FieldML is currently still under development, other popular model data formats, such as the exFormat (http://www.cmiss.org/cmgui/wiki/TheCmguiEXFormatGuideExnodeAndExelemFiles), which is developing into FieldML, and Visualization ToolKit (VTK; http://www.vtk.org) format, must also be supported to effectively promote the use of euHeartDB within the entire cardiovascular community.

Finally, integration or coupling with established VPH tools and technologies, such as CellML and PMR, must be implemented in order to effectively contribute to the implementation of the VPH project. In particular, a bidirectional knowledge link (i.e. a link from cellular models to anatomical models and vice versa) is to be established on both euHeartDB and PMR sides. This will provide both researchers using and developing cellular models and researchers using and developing anatomical models with an integrative view of the applications of the respective models spanning the related research areas.

3. euHeartDB

In this section, we first illustrate how the database implements the above requirements. We then review the models currently stored within euHeartDB. We continue with an example euHeartDB use case through the navigation of the anatomical models and of the related cellular models in CellML format. Finally, we outline the coupling with PMR, the database of CellML models.

(a) *Characteristics*

The requirements identified in the above section have driven the implementation of the current euHeartDB. The database requires that the users are authenticated before being allowed to access the repository content. Interested users can apply for an account through the available Web form, and once enabled, they are allowed to log onto the system and to visualize the main menu and content pages over encrypted connections. The main page, which is displayed after a successful login, presents five submenus: authors, bibliographic references, anatomical models, myEuHeartDB and guide.

The authors menu redirects to a Web page offering the functions: insert a new author, search for an existing one and list all authors. The insert function creates a database record in which all the details of the author, such as name, email and affiliation, are contained. The search and the list all authors functions display the resulting sequence of names, each of which can be clicked to reach the author's page containing all the associated data. In addition to the user-typed data, this page displays links to the author's publications and anatomical models available within euHeartDB.

Similar to the authors menu, the bibliographic references menu offers three options: insert bibliographic reference, search for existing ones and list all publications. In addition, the publication home page is available within the scope of this menu. This page contains the details of a publication and the references to the anatomical models the publication describes or cites. A publication home page can be reached by browsing the search results, by navigating the list of all the bibliographic references or by accessing the pages of the anatomical models menu.

euHeartDB core functionalities are available in the anatomical models menu. In this menu, the possible operations are again insert, search or list all models.

The insertion of a new model is a two-step process. The first step consists of the insertion of all the model data and metadata. This step requires the selection of the data format—e.g. exFormat or VTK—and the insertion of the model description, keywords and file data. Once confirmed, the user proceeds with the second step. This step consists of browsing of the foundational model of anatomy (FMA) ontology (Rosse & Mejino 2003) to semantically classify the model being uploaded. The browsing starts with the heart as root concept, and continues with

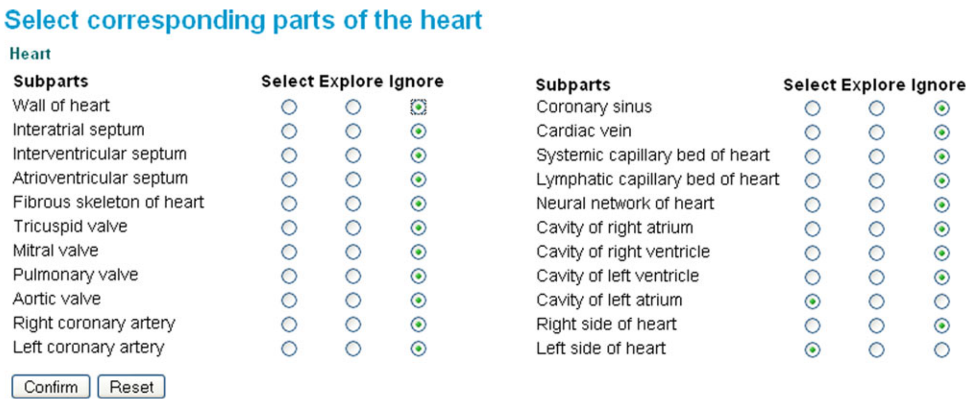

Figure 1. Selection of the FMA ontology concepts for the classification of the model.

(*a*) (*b*)

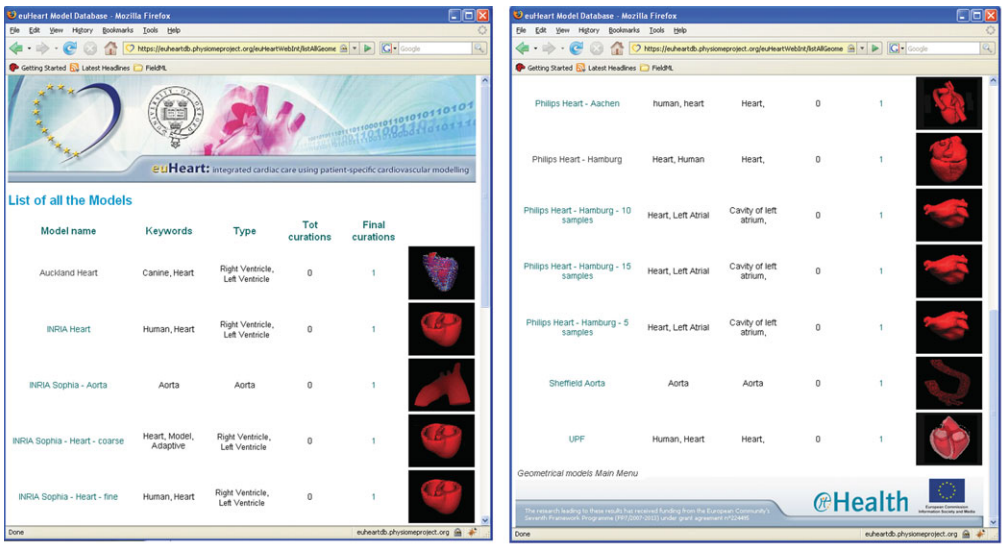

Figure 2. Current list of all the models: (*a*) top and (*b*) bottom.

the exploration of the heart subparts, depending on the user selections. In figure 1, we show an example selection of the FMA concepts. In this case, the left side of the heart and the cavity of left atrium concepts are associated with the model being loaded into euHeartDB.

The search function displays the list of models matching the typed keyword. Similarly, the list all models produces a Web page containing a list of all the available geometries in euHeartDB.

Selecting the list all models option currently displays the Web page shown in figure 2. Each item in the list in this page consists of: the model name, the associated keywords, the model type, the total number of curations, the final curations and a model preview. The model name identifies the model in a user-readable manner. The name also links to the model's home page, which contains a comprehensive model description. The keywords are model owners' defined descriptors. The model type represents the list of the FMA concepts classifying the model. The total number of curations indicates the number of model versions uploaded as corrections of the original model. If the number is not zero, a Web link to a page displaying the hierarchical curations tree is available. Similarly, the final number of curations indicates the number of final versions of the models—including the original one if no curation has been added. Finally, the model preview offers a static graphical view of the model. For models uploaded in exFormat or VTK format, the preview also links to the URL that allows a three-dimensional interactive visualization within a Firefox browser provided with the Zinc plugin (Stevens *et al.* 2005).

By clicking on the model name, the user is directed to the model home page in which all the information concerning the model is provided. Specifically, this page contains: the model name, the list of the authors, the FMA classification (i.e. model type), the keywords, the model owner's description of the model and a static model preview image. In addition to these, the following links are available: model visualization, list of cellular models (typically represented in CellML format) embedded within the geometry, link cellular model, model data download, list of bibliographic references describing the model, see comments, add comment and add curation.

The model home page is titled with the model name. The authors are listed below the title and their names can be clicked on to reach each author's home page. The classification of the model in terms of the FMA ontology identifies the structural part of the heart that the model represents. The keywords index the model for the euHeartDB search function. The description of the model is contained in an open text box area spanning several rows of the Web page. The description presents the main details of the model, as provided by the model owners. The model preview follows if a static image has been uploaded for the anatomical model. The model visualization link for the three-dimensional interactive visualization is available below, if the model has been uploaded in exFormat or VTK format. The visualization operates using the Firefox plugin Zinc (Stevens *et al.* 2005), which encapsulates the CMGUI rendering engine previously mentioned. The list of the cellular models in CellML format is included, if any of these models has been embedded within the geometry. In this way, users can navigate from an anatomical model in euHeartDB to the related CellML models in PMR. For instance, the INRIA Heart model is associated with the cellular models Aliev–Panfilov (Aliev & Panfilov 1996) and Mitchell–Schaeffer (Mitchell & Schaeffer 2003), as joint simulations of these models are documented in the literature (Sermesant *et al.* 2008). To report a new application embedding a CellML model, a user can click on link cellular model and insert both the CellML model name and the PMR exposure. The model data download link enables users to save the data on the local machine. The data format can be exFormat or VTK, or other types, depending on the type of data uploaded. The list of the bibliographic references link follows and produces the list of papers describing the model. For example, the Philips Whole-Heart currently associated with Ecabert *et al.* (2008) and Peters *et al.* (2008). Similarly, the model home page of the INRIA Heart refers to Sermesant *et al.* (2006, 2008) and Peyrat *et al.* (2007). These references, however, are not exhaustive and the uploading of more papers is in progress. The see comments link follows and provides access to the community feedback. Finally, the add comment and the add curation links allow users to post their experiences with the model and to upload a curated version of the given model, respectively. All the above functionalities, i.e. downloading, visualization, curation, commenting are subject to the accessibility settings that the model owner has configured for the model. For example, a model owner might want to restrict the downloading of the model data or the curation of a model to a specified set of users, or similarly deny them to a defined group of users. In this latter case, the respective URLs are not available and the links are not displayed in the model page.

The myEuHeartDB menu is included below the anatomical models menu on the main page and provides a personalized view of the database. Specifically, this menu includes the functionalities to monitor a user's own activities and other users' activities. In addition, the myEuHeartDB menu offers the services to edit and to update the data associated with the user's own models and to set the accessibility rights for these models.

The guide menu concludes the available options on the main Web page and presents a short set of instructions for users, including the software requirements to enable the three-dimensional visualization within a Web browser.

In the following section, we show a practical example of the use of euHeartDB to deliver and visualize the database content.

(*b*) *Model review*

The list of the models currently available in euHeartDB can be obtained by browsing the anatomical model menu and then by selecting the list all models option. The Web page shown in figure 2 will be displayed as a result of this selection. Currently, the list contains the following models: ABI model of the cardiac ventricles (Nielsen *et al.* 1991; LeGrice *et al.* 1997), INRIA model of the cardiac ventricles (Peyrat *et al.* 2007), which includes both coarse- and fine-grain versions (Lamecker *et al.* 2009), INRIA Aorta, Philips Whole-Heart (Lorenz & von Berg 2006), Philips Whole-Heart with Extended Vessels (Peters *et al.* 2008), Philips Hamburg Left Atrium with multiple anatomical variations (Lorenz & von Berg 2006), Sheffield Aorta (Barber *et al.* 2007) and finally the UPF-CISTIB Biventricular Heart Atlas (Ordas *et al.* 2007). The original authors have set the accessibility of the geometric data for each model. Some models can be accessed by the entire VPH community, whereas others are currently only available to specific subgroups of researchers (e.g. euHeart community). In cases where the data files are available, they can be visualized using CMGUI as a stand-alone application or parsed into alternative data formats through interpretation of the exFormat or VTK formats (see Web addresses provided in §2).

These models, which have been developed within the euHeart project consortium, are visualized in figure 3. These geometries can be classified by the species (e.g. canine or human), by the constituent parts of the heart (e.g. whole heart, aorta, cardiac atlas or left atrium) and by the production techniques (e.g. manual measurement or statistical analysis of magnetic resonance imagings (MRIs)). The first model on the list, the ABI model of the cardiac ventricles (figure 3*a*), was produced by manual measurements on a whole canine heart in diastole (Nielsen *et al.* 1991; LeGrice *et al.* 1997). Except for this model, all the

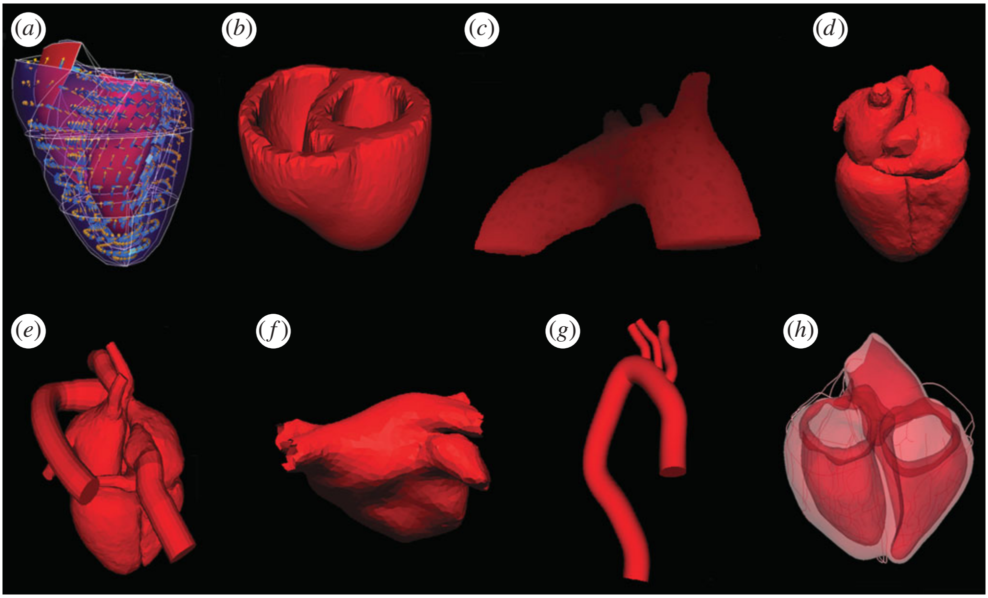

Figure 3. (*a*) Three-dimensional visualizations of Auckland Heart, (*b*) INRIA Heart, (*c*) INRIA Aorta, (*d*) Philips Whole-Heart, (*e*) Philips Whole-Heart with Extended Vessels, (*f*) Philips Left Atrium, (*g*) Sheffield Aorta and (*h*) UPF-CISTIB Biventricular.

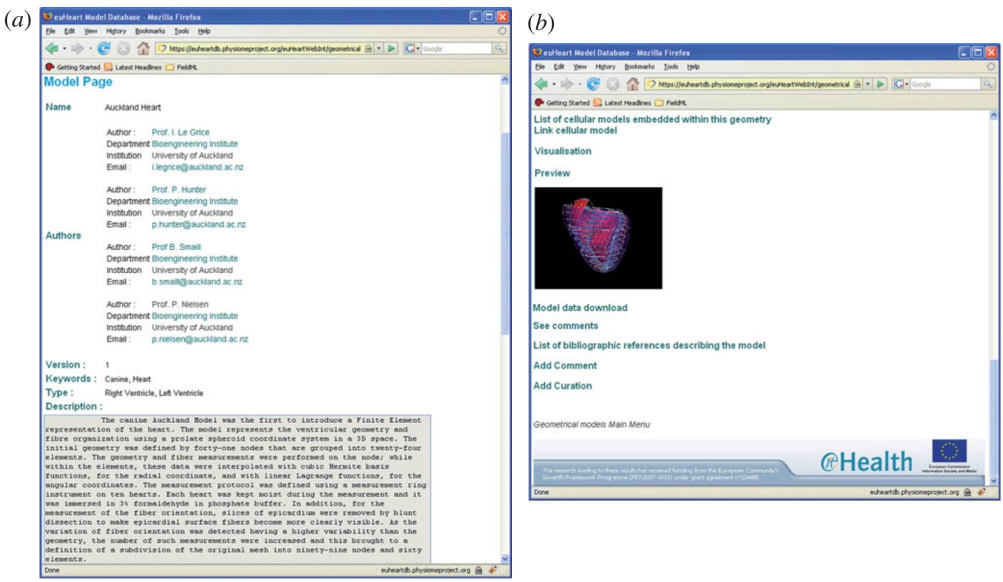

Figure 4. Auckland Heart model page: (*a*) top and (*b*) bottom.

remaining geometries represent human hearts or part thereof. For example, the INRIA model (figure 3*b*) represents the human cardiac ventricles as a result of innovative statistical techniques for model production from MRI data (Peyrat *et al.* 2007). This model was successively refined to produce coarse- and

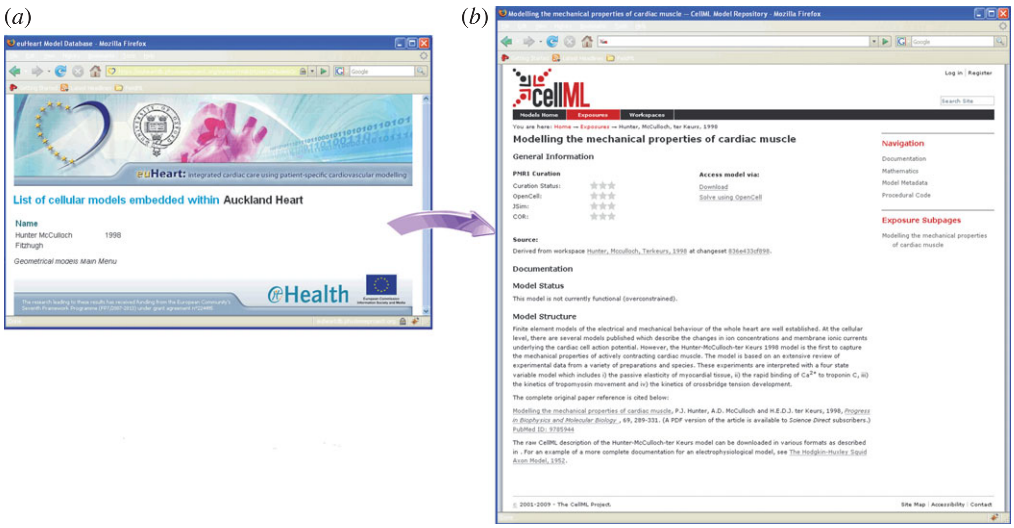

Figure 5. (*a*) List of cell models embedded within Auckland Heart and (*b*) link to PMR exposure.

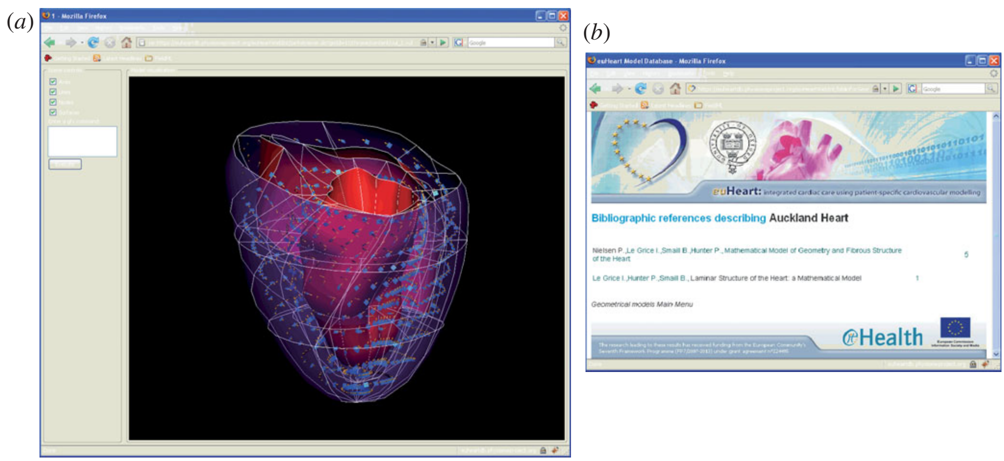

Figure 6. (*a*) Visualization of the Auckland Heart model and (*b*) list of bibliographic references for this model.

fine-grained versions, for mechanical and electrophysiological simulations, respectively (Lamecker *et al.* 2009). The INRIA Aorta model (figure 3*c*) describes the anatomy of the human aorta. The Philips Whole-Heart model is derived from multi-slice computer tomography (CT) techniques and represents the four heart chambers, the left ventricular myocardium and the trunk of the great vessels (Lorenz & von Berg 2006; figure 3*d*). This model can be automatically adapted to CT, magnetic resonance and three-dimensional rotational X-ray images to generate patient-specific geometric representations of the heart (Ecabert *et al.* 2008; Peters *et al.* 2010). The Philips Whole-Heart model with extended vessels is an extension of the previous model with the connected vasculature including aortic arch, pulmonary veins, coronary sinus, inferior and superior vena cava (figure 3*e*; Peters *et al.* 2008). Next is the Philips Left Atrium model (figure 3*f*), which consists of three versions. Each version presents a different number of veins draining into the right side of the atrium (2, 3 and 4), and considers a different number of samples from the human population (5, 10 and 15, respectively) (Lorenz & von Berg 2006). The Sheffield Aorta (figure 3*f*) was produced using scripting techniques that transform the input images of a series of vessels and related parameters, such as vessel radius, using tetrahedral meshes (Barber *et al.* 2007). Finally, the UPF-CISTIB Biventricular model (figure 3*g*) was obtained through a statistical analysis on a cardiac atlas sample of the human population (Ordas *et al.* 2007).

(*c*) *Use case*

To tangibly demonstrate euHeartDB functionality and to provide an overview of the database content, we consider a simplified use case navigation that includes three activities: listing all the models in the database, browsing a model page and finally reaching a CellML model in PMR. The list of all the models can be produced by selecting the list all models option within the anatomical model menu. The current list as shown on the Web page is illustrated in figure 2.

Clicking on the Auckland Heart model on the list page, the model page as shown in figure 4 is displayed. This page starts with the model name, Auckland Heart specifically, and continues with the list of authors. Each of the names can be clicked to display the details of the author, such as research group, affiliation and email address. The model version number within euHeartDB follows, and is defined as 1 for the Auckland Heart. The keywords field gives the indexing terms used by the internal searching engine and the type reports the FMA concepts classifying this model. For this heart model, the keywords currently associated are canine and heart, as shown in figure 4, and the FMA classification is right ventricle and left ventricle. The model description follows and is included in a scrollable text area. On the bottom part of the page, the link for the list of the cellular models embedded within this geometry is available. When clicking on this link, the page shown in figure 5*a* will be displayed. This page currently contains a list with two items: the Hunter–McCulloch–ter Keurs 1998 model (Hunter *et al.* 1998) and the FitzHugh–Nagumo model (Rocsoreanu *et al.* 2000). Each item can be clicked to reach the CellML exposure in PMR. For example, by clicking on the Hunter–McCulloch–ter Keurs 1998 model link, a user can reach the CellML model page shown in figure 5*b*. Below the link to the cellular models on the model page, an option for the linking of a new CellML model in PMR is available. In this way, users of the Auckland Heart model can share the types of applications using this model with the rest of the community. For example, investigations of stretch-induced changes in the heart rate (Kohl *et al.* 1999) or of cardiac activation within the bidomain framework (Buist *et al.* 2003) might be referenced. The model page continues with a link to the visualization window. When clicked with a Firefox browser enabled with the Zinc plugin, the interface of figure 6*a* is visualized. This interface consists of two vertically adjacent panels. The left panel allows basic setting control and the input of CMGUI commands to the rendering engine. The right panel visualizes the geometry and the associated fields. Below the visualization link, a static model preview is included to enable users of non-Firefox browsers to see a graphical representation of the geometry.

The other available links enable the user to download the model data, to list the community comments on this model and to list the bibliographic references describing this model. Currently, euHeartDB stores two bibliographic references for the Auckland model—as shown in figure 6*b*, but others are being inserted to provide a more comprehensive view of the applications of this model in cardiac simulations. Finally, the add comment and add curation links conclude the page.

The link from euHeartDB to PMR has been established to provide euHeartDB users with a view of the anatomical model applications within the context of PMR cellular models. In the following subsection, we outline the coupling requirements for the future implementation of the reverse link—i.e. from PMR to euHeartDB. This link will provide PMR users with a view of the cellular model within the context of euHeartDB anatomical models.

(*d*) *Coupling requirements for the physiome model repository*

Integrating model metadata into model-sharing technologies is essential for the efficient reuse of research products. CellML and PMR have embraced this concept and have included references to model metadata, such as authors, curators and publications. Within the cardiovascular domain, a more comprehensive view of the CellML models can be obtained by linking CellML files to data related to cardiac simulations, such as anatomical models. As euHeartDB is a repository of anatomical models of the heart, it can be used to enhance the scope of PMR within cardiac applications by associating CellML models with anatomical models. This has motivated the establishment of a knowledge link between PMR and euHeartDB. More technically, a URL to navigate from a CellML model to one or more anatomical models in euHeartDB will be available to provide additional information on the application of specific cellular models. Future development of this concept could include using the FMA to annotate cellular models based on the regions of the heart within which they are valid, and then apply these annotations to retrieve all models having exposure to those anatomical regions.

To exploit the full potential of CellML and PMR, the link between euHeartDB and PMR must also incorporate the new PMR versioning capabilities (Yu *et al.* 2008). These capabilities have been developed to primarily address the requirement of collaborative production of CellML models. However, the versioning capabilities are also needed in coupling anatomical and cellular models, for two reasons. First, the establishment of an accurate link between an anatomical model and a cellular model requires that the link refers to specific versions of these models. Anatomical and cellular models are both subjected to curation processes and therefore they cannot be uniquely identified by the respective model names. On the euHeartDB side, this has been solved by providing each anatomical model curation with a unique key within the system. On the PMR side, a unique identifier is already available for each CellML file within the versioning control system. For this reason, versioning capabilities are needed to correctly reference the CellML file in the knowledge link between the two databases. Second, the PMR versioning system manages all the changes to CellML files, and therefore can alert all the stakeholders of a CellML model when a curation occurs. euHeartDB is linked to PMR and therefore needs to be informed when a referenced CellML model is modified. This is especially needed for anatomical models representing simulation output data because the validity of these data depends on the CellML model embedded in the cardiac simulation. For this reason, the PMR versioning system will establish a notification channel that links CellML models in PMR to anatomical models in euHeartDB.

4. Future vision

The need to share anatomical models has motivated the introduction of euHeartDB. However, sharing represents only the most basic level of use for this repository. We foresee three types of future uses and research directions for our database. These are related to: (i) the use of euHeartDB to support the investigative process, (ii) the central availability of the models, and (iii) the handling of model data over the Web.

The first of these directions derives from the generalization of the role of anatomical models. From a more abstract point of view, cardiac geometries do not only represent valuable data to be shared among model developers and users. Anatomical models also constitute the simulation output data, i.e. the data resulting from simulation of cellular models embedded within an input cardiac geometry. For this characteristic, we foresee a potentially wider scope of the application and use of euHeartDB to support additional elements of the investigative process by making simulation output data available on the Web. This process involves four main types of actors (patient, clinician, imaging researcher and functional researcher), and its relevant steps are outlined in figure 7.

The investigative process starts with the clinician producing computer-readable images (e.g. MRIs) of the patient's heart—uniquely identified by the health record—and storing the images in a repository (step 1). The repository can be accessed by imaging researchers, who retrieve patient images and produce the respective anatomical models (step 2). The models are coded in a computer-readable format and can then be stored in euHeartDB (step 3). From this repository, the geometry can be downloaded by functional researchers (step 4) and used within cardiac simulation. For this purpose, functional researchers must select the most appropriate CellML model from PMR (step 5). The organ-level simulation output data can then be obtained by embedding the CellML model within the patient geometry in computer simulation software, such as OpenCMISS (http://www.opencmiss.org). Currently, the output data are privately stored on functional researchers' local hard drives, and therefore these data are not accessible to the remaining actors. Depositing and sharing the output data in euHeartDB (step 6), and linking them to the data used for their production, is a key aspect in building an integrative environment. The final goal is to encompass all of the various stages of the process by providing all the stakeholders with a unified view of the activities and of the data.

For this reason, we foresee that euHeartDB could expand its role beyond the sharing of heart geometries. In particular, euHeartDB will contribute to the ongoing effort of establishing a research infrastructure linking the images and patient repositories and stakeholders as in figure 7. More technically, euHeartDB will link simulation input geometries (descriptive data) and simulation output geometries (predictive data).

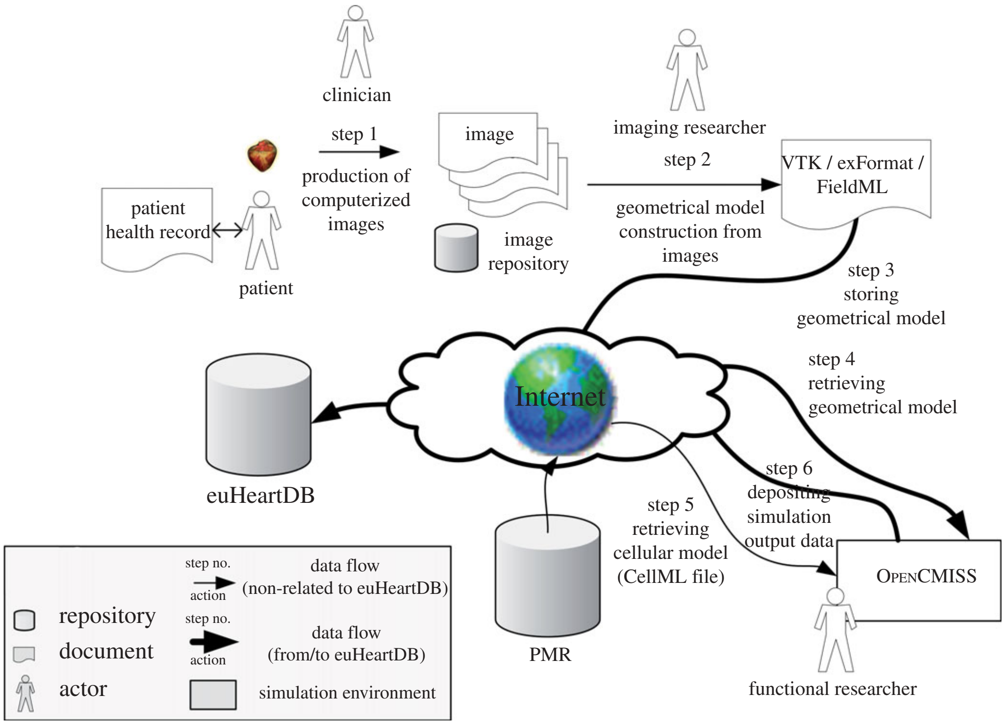

Figure 7. Diagram of the future investigative process with euHeartDB. The diagram shows a subset of the relevant steps composing the investigative process. Each step represents a data flow between either two data objects (i.e. heart or documents) or two software systems (i.e. repository or simulation environment). The process actors (i.e. patient, clinician, imaging researcher and functional researcher) are positioned in proximity of steps they are involved in (refer to text for description of the diagram).

The second direction includes all the possible applications that could be implemented once the models are centrally available within a universally accessible repository. In particular, euHeartDB has the potential to: (i) support coupling of anatomical models, which is needed to exploit model reuse by assembling available models, (ii) allow benchmarking of simulation results, which is needed to establish correlations between simulation output data and pathologies, (iii) support anatomical surveys on models of the heart, which is needed to improve statistical analysis of the clinical data upon which the models are based, and (iv) store documentation of different diseases on the heart geometry, which aims to ease statistical inferences of correlation between geometries and diseases.

Finally, the third direction represents the technical challenges that the fully operational implementation of the database requires be addressed. These challenges include integration with other tools which, for example, include the VPH and euHeart tool Graphical Interface for Medical Image Analysis and Simulation (GIMIAS; http://www.gimias.org/). In addition to many of the visualization functionalities of CMGUI, GIMIAS will also introduce additional functionality for handing medical images and models in a common environment.

From a general visualization perspective, we anticipate the introduction of a multi-scale technique for the visualization of anatomical models over the Web. In analogy with multi-scale simulation, which reduces the execution time while maintaining accuracy of the simulation results, multi-scale visualization will reduce the data download time while maintaining an accurate visualization of the anatomical models. The download time, which is approximately given by the ratio between data size and network bandwidth (i.e. the network transmission rate), can become quite high for large datasets. Since anatomical models often consist of large datasets, they therefore might require considerable download times. A Web visualization process must operate with a determined quality of service (i.e. of the order of seconds for response times) and therefore it requires a multi-scale technique that reduces the amount of data transferred from euHeartDB to the user's computer.

5. Conclusions

Sharing and reusing models promotes the advancement of knowledge in the biomedical field. CellML and PMR have embraced this concept and have addressed the sharing and reuse of cellular models. In the cardiovascular community, however, the limited scope of CellML and PMR has motivated the development of a database for anatomical models of the heart. The production of anatomical models requires considerable efforts in terms of human resources and scientific equipment. In addition, the current sharing methodology of these models does not satisfy the community needs of enabling dynamic model delivery and of enabling an integrative view. In this paper, we have sought to address these needs with the introduction of euHeartDB, a Web-enabled database for anatomical models of the heart. euHeartDB satisfies the need of enabling dynamic model delivery by providing decentralized and secured access to the models and by tracing the models' applications (e.g. cardiac simulations). euHeartDB also introduces an integrative view of cardiac geometries by linking an anatomical model to both its related publications and its CellML models in PMR. Besides addressing the community needs, euHeartDB presents three other features that facilitate sharing and reuse of models. Firstly, euHeartDB exports the data in the interoperable exFormat format, which is currently being developed into FieldML. Secondly, the database encapsulates the three-dimensional CMGUI rendering engine to visualize the model within the Web browser, thus making the models more accessible to human users. Thirdly, euHeartDB is available online and currently stores 11 cardiac geometries from partners of the euHeart project consortium.

We envision the development of euHeartDB moving in three distinct directions: (i) more extensive integration with other VPH repositories to support the investigative process, (ii) introduction of a more comprehensive set of functions on the management and use of cardiac geometries, and (iii) design of multi-scale techniques for the visualization of anatomical models over the Web.

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