Combination of Visual and Symbolic Knowledge: A Survey in Anatomy

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Abstract

In medicine, anatomy is considered as the most discussed field and results in a huge amount of knowledge, which is heterogeneous and covers aspects that are mostly independent in nature. Visual and symbolic modalities are mainly adopted for exemplifying knowledge about human anatomy and are crucial for the evolution of computational anatomy. In particular, a tight integration of visual and symbolic modalities is beneficial to support knowledge-driven methods for biomedical investigation. In this paper, we review previous work on the presentation and sharing of anatomical knowledge, and the development of advanced methods for computational anatomy, also focusing on the key research challenges for harmonizing symbolic knowledge and spatial 3D data.

Keywords: Computer-aided medical decision support systems, knowledge in medicine, information systems, medical informatics, IT applications in health care.

1. Introduction

Anatomical knowledge covers diverse perspectives and the correlation among them is at the basis of a true understanding of the functioning of the human body and related pathologies. On the one side, huge amounts of spatial data about the human body are available in digital form; on the other side, symbolic anatomical knowledge could also support automated reasoning. Coupling these two aspects is likely to open new frontiers to support experts in complex correlation tasks and to express medical knowledge in such a way that it can be effectively used by domain experts *via* a unified access.

Studying anatomy by looking physically inside the human body has evolved over the centuries: nowadays, medical imaging allows us to understand the human organ structure and its functionalities without dissection. In the current scenario, *"anatomy"* is regarded as a science that addresses the investigation of the human body structure with the final aim of understanding the functioning of the body parts. Accordingly, we will discuss anatomy as the hinge around which clinical studies, formalized biomedical knowledge, and digital data of the human body can be integrated in a complex knowledge management and visualization system.

The foreseen integration requires the harmonization of several aspects (e.g., terminology, communication praxis, approaches) of medicine and computer science, which are quite distinct. Hence, there are still large gaps to fill between clinical concepts and quantitative data/information extracted from the digital data. Addressing these gaps is crucial to develop the next generation of *Computer Aided Diagnosis* (CAD) systems, which will allow doctors to use computer output as a *"second opinion"* to derive the final diagnosis. A fundamental requirement of such systems is to support a smooth transition from the reasoning on conceptual/knowledge-related issues to the reasoning on quantitative information/data.

Motivation. Starting from the beginning of medical history, two conceptually different modalities have been adopted in parallel for representing the human anatomy: *spatial data* depicting the appearance of anatomical parts (e.g., 2D/3D images, 3D models) and *symbolic information* producing a descriptive documentation of anatomy (e.g., taxonomies, ontologies, reports, clinical notes, electronic patient-records). In the age of digitalization, the massive explosion of spatial data along with symbolic information outstrips the manual ability to correlate and comprehend the entire source of anatomical knowledge. As a result, a large portion of accessible medical data and information is under-exploited (IBM report April 2013 [1]) and medical diagnosis in practice follows a *"trial-and-error"* policy [2], by analyzing and correlating recently acquired spatial data with patient's symptoms.

An important trend for the future of healthcare technology is the increasing use of *intelligent software agents*, which can access the available information about patient history and symptoms, interpret the content of spatial data, and simultaneously parse the relevant knowledge about diseases, diagnostics, drugs, and treatments. The final goal is to support the medical doctors in clinical decision by finding and supplying the relevant clues. Following the human cognition, the next-generation clinical software agents should be guided by a formal symbolic knowledge to automate the analysis of spatial data (e.g., image segmentation), to structure medical data bases (e.g., platforms for collaborative sharing and manipulation), to search and visualize medical data and information (e.g., knowledge-driven profiling of search). However, a primary hurdle for the development of knowledge-driven healthcare solutions is that the knowledge underlying the input spatial data is rarely linked or embedded within them, and the correlation between spatial data and symbolic information is not yet completely comprehended. These aspects become even more challenging when visual 3D data are included in the analysis of a given pathology (Sect. 6).

Scope. Starting from 1970s, several surveys have addressed separately the developments in clinical data visualization and symbolic knowledge representation. The same trend is also present in the recently published reviews on visualization [3],[4] and symbolic representations [5],[6]. In contrast to previous work, our report takes a different perspective and focuses mainly on the integration between spatial data and symbolic information to identify the feasible path in which their combination can be best applied to support the development of knowledge-driven clinical methods. Despite the significant amount of research contributions in the integration aspect, there is no comprehensive review that analyses the existing tools/systems for understanding the remaining "gaps". Given the growing interests and changing trends, we believe many researchers with background in computer science and in medicine would benefit from this survey, and it can stimulate new research directions.

We start with a discussion of the state-of-the-art on spatial data visualization and symbolic representations independently; then, we focus on the integration aspect from various perspectives. Due to the large number of publications on visual and symbolic modalities, the review of existing methods/tools will be focused on the main achievements in each field, thus supporting the reader in the understanding of the trend of next-generation medicine. Indeed, our objective is not to dig into detail of each approach, but rather give the reader a feeling of the two complementary anatomical knowledge representation schemes (i.e., visual and symbolic) and highlight how the latest methods in each scheme are going in the direction of integration. In particular, we discuss the literature in both domains to answer the following questions: what are popular tools/methods to depict canonical and patient-specific anatomy? To what extent the existing methods can sustain the next-generation knowledge-guided clinical services, and which are the restraints? What are the ways to exploit the full potentiality of patients' data and information in the next-generation clinical framework?

Organization. The survey begins by exploring the evolution that computer science and digitization technologies brought in the field of anatomical knowledge illustration (Sect. 2). In the following (Sects. 3, 4), we highlight the changing trends in anatomical knowledge representation concentrating on the modality, clarity in conveying knowledge, practical and prospective usages. The second part of the survey is centered around integration aspects *via* annotation and discuss the existing tools in medicine (2005 - 2015) that combines the symbolic knowledge with spatial data, thus supporting an enhanced understanding of anatomy (Sect. 5). A discussion is given as a bottom-line clarifying the limitations of existing techniques. Finally (Sect. 6), we underline the key challenges towards the realization of a comprehensive integration between 3D patient-specific model of anatomy and formalized domain knowledge for conceiving the "*Digital patient*" - a computational framework for understanding patient-specific anatomy.

2. Historical background

In this section, we give an overview on the representation of anatomical knowledge before the beginning of medical data digitalization age. In Fig 1, we present the time-line of its evolution: starting from the beginning of medical history, anatomical knowledge has been illustrated either in a symbolic manner (e.g., names and synonyms of anatomical structures, functionalities, classification, definitions, spatial relationships) or in a visual (e.g., sketches, drawing, physical samples, images) way. The first historical evidence of the systematic study of human anatomy is *"Egyptian EbersPapyras"* (1600BC), which described the human anatomy in a symbolic way with the help of formulas (almost 700) and remedies. Herophilos (335-280 BC) and Erasistratus (304 -250 BC) were the first who studied anatomy *via* visual means

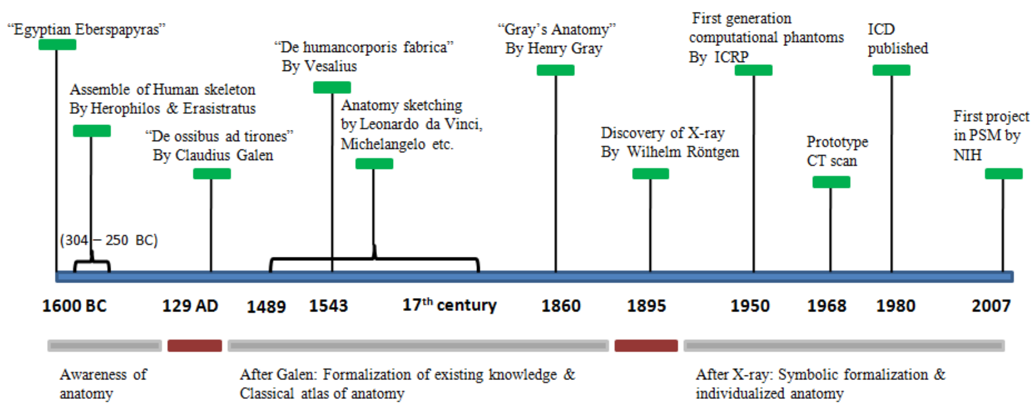

Figure 1: Evolution of anatomy (science) [1600BC - 2007]

by assembling a first human skeleton for osteology. With Claudius Galen, a new age in anatomy began, where he attempted to structure conceptual knowledge of anatomy in his book *"De ossibus ad tirones"*, by combining and compiling all existing sources of information. The next milestone of anatomical study was Vesalius's work: *"De humani corporis fabrica"*(1543), where emphasis was given to the *"anatomical view of body"*, by representing internal organs and their functioning in a three-dimensional space by realistic sketches.

Afterwards, many famous artists studied anatomy and published their works on anatomy sketching, e.g., Leonardo da Vinci, Michelangelo, Rembrandt. The use of sketching became one of the preferred ways of transferring anatomical knowledge, but symbolic representations were equally indispensable. Anatomical illustration *via* classic atlases was a successful attempt that provides a complementary way of expressing anatomy: pure visualization through sketches emphasizes immediacy and direct access to information, whereas annotation in natural language targets the expressibility and communicability of anatomical knowledge. In 1895, the discovery of X-ray provided the first means to capture a snapshot of the interior of an in vivo body without dissection, and the modern phase of anatomical knowledge representation initiated. However, a proper interpretation of these radiographic snapshots needs particular expertise in anatomy.

The history points out that anatomy is indeed highly visual in nature; at the same time, it requires a highly descriptive documentation for optimal understanding. Over the ages, classical atlases have been the popular medium for conveying canonical knowledge; starting from the beginning of the digital age, patient-specific anatomy has been represented *via* two complementary approaches, relying either on formalized knowledge (reports, clinical notes, electronic patient-records), or on multi-modal medical imaging (visual content, X-ray, CT, MRI). Less endeavors have been noticed in terms of achieving a comprehensive integration between these two modalities for creating a *patient-specific atlas*.

3. Symbolic representation

Tools and methods. Starting from the beginning of digital age, textual documents are a prominent medium to convey knowledge at the symbolic level. Beside classical textbooks, there is a huge amount of information that comes naturally in textual form: generic information - names, synonyms, and physiological functions of the anatomical entities, or patient specific information - clinical diagnosis report, physician notes, treatment plans. Natural language is the most certain choice to represent these descriptive information, as the communication is primarily among humans. However, expressions in natural language are often affected by a certain degree of subjectivity due to several factors: (i) variety of expertise and backgrounds - radiologists define *"femoral cartilage"* as a constitutional part of the knee joint in the biological scale *"organ"*, while biologists classify *"femoral cartilage"* as connective tissue; (ii) multi-lingual context - *"knee"* [English] anatomical joint is represented as *"ginocchio"* [Italian] and *"rodilla"* [Spanish].

Standard formalization in anatomy dates back to the mid 19-th century, but the major initiatives appear concurrently with the widespread use of computerized systems in the 1970s and 1980s, with major developments in the last decade. The advent of *knowledge formalization technologies*, indeed, made it clear that the communication could be directed not only to humans but also to computers, combining the expressive power of the language with the computational power of machine. Standardization, interoperability and machine readability were the strict requirements for the integration.

Medical terminologies and vocabularies provide a list of terms, and their semantics or definition, related to various medical concepts and knowledge, e.g., diseases, diagnoses, findings, operations, treatments, drugs, administrative items. The examples are the Standardized Nomenclature of Disease (SND), Systematized Nomenclature of Medicine (SNOP), Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT). With these vocabularies, a standard definition and organization of medical terminology have been achieved; the next issue is to manage the resources to enable the interoperability among various formalizations.

The Unified Medical Language System (UMLS) [7] is a large repository designed to bring together biomedical vocabularies and standards, to integrate and distribute key terminology, classification, and coding standards in biomedicine, to manage resources for the creation of effective and interoperable biomedical information systems. The goal is to support the exchange of information across communities, based on reliable and formalized descriptions of the domain that can establish a shared understanding of concepts among domain-experts. However, in an inter-disciplinary context, agreeing on the semantics of anatomical terms is definitely a time consuming and resource intensive task.

Going beyond elemental knowledge, a standard formalization of *patient-specific* information (e.g., Electronic Patient Records (EPR)) supports the access and sharing of data and information about a specific patient across different healthcare platforms. Health Level 7 (HL7) [8] is a well known and accepted standard for sharing and integrating electronic health information among various healthcare providers. Modeling patient-specific information in the form of textual EPRs is certainly one of core functionality of this framework. Particularly, HL7 specifies the structure and semantics of a wide range of clinical documents about the patients, such as admission records, discharge summaries, progress notes, and subsequently it allows to transfer the data/info among various software applications adopted by the distinct providers. On the imaging content side, the Digital Imaging and Communications in Medicine (DICOM) standard [9] achieved nearly universal level of acceptance in medicine for handling and transmitting medical images (e.g., MRI, CT) together with information related to the patient (e.g., age, gender) and the acquisition session (e.g., intensity of the magnetic field, acquisition parameters). The formalizations provided by HL7 and DICOM support efficient communication of patient-specific information among various healthcare professionals, and allow the integration between clinical hardware and software systems.

At the conceptual level, anatomical taxonomies and clinical vocabularies formalize only parent/child relationships (IS-A) between anatomical terms. A substantial step forward is the development of *biomedical ontologies* [10], which can be seen as a constructed model of the biomedical domain [11] that defines a rich set of inter-relationship among the concepts. Most importantly, this formalism represents information in a form that supports reasoning, inference, and assertion of new knowledge, and can act as a basis for *future clinical systems.*

Given the variety of perspectives and specializations in medicine, referring to one single conceptualization is difficult. The OBO Foundry [12] was formed to certify a set of inter-operable human validated reference ontologies, named OBO member ontologies, which cover a wide range of life science phenomena in a modular way. The most popular OBO member ontology for anatomy is the Foundation Model of Anatomy (FMA) [13], which defines the classes and relationships necessary for the symbolic description of the human body structure. FMA satisfies a comprehensive suite of requirements deemed to be fundamental for considering it as the reference domain ontology for anatomy. It also provides templates for evolving biomedical domain ontologies (e.g., Physiology Reference Ontology (PRO), Pathology Reference Ontology (PathRO)). FMA's richness lies in a detailed anatomical terminology, but it does not define rich relationships among the involved classes. With the emerging popularity of biomedical ontologies, the National Center for Biomedical Ontology (NCBO) was developed to support the use of biomedical ontologies in the management and analysis of data derived from complex biomedical experiments. Starting from 2006, OBO ontologies also became a part of the resources of the NCBO and emerged as a central component of the NCBO's BioPortal [14].

Practical usages of formalized symbolic representation. With the progress in intelligent programming ontologies have been employed in several clinical applications and not only for describing complex anatomical concepts. For instance, Radlex [15] was created to support the formalization of knowledge in radiology, with links to anatomy by importing the FMA conceptualization. At the beginning, Radlex only aimed to provide a standard lexicon and unified language to organize, index, and retrieve a variety of radiological data and information for learning, research, and clinical reporting procedures. Recently, Radlex has become a *de facto* standard for imaging terminology in the Society of Radiology, and has been adopted in several clinical and research applications; e.g., decision support software - iVirtuosoYottaLook, Goldminer; clinical reporting - Commissure RadWhere, StructuRadReport-Now; research projects - NCIA, Ontology of Biomedical Investigations.

Furthermore, ontologies have been extended to represent the structural, functional, and topological connections that exist among the various facets of anatomical knowledge. A notable example is the MyCorporisFabrica ontology (MyCF) [16], which focuses on the formalization of anatomy along with its behavioral function. An important contribution of MyCF knowledge base is the introduction of links between symbolic descriptions of anatomical entities and digital models of anatomy, by declaring the 3D models directly as the instance of anatomical concepts and by characterizing the instances with physical and functional meta-data. These links can be exploited to support automatic reasoning for complex queries, which shows an added-value for CAD system and interactive visualization [17].

Moreover, the MyCF knowledge base has been extended with bio-mechanical parameters (canonical and patient-specific), which allow the user to intuitively create a patient-specific 3D representation from a formal description of anatomy, and automatically export this description to test a physical simulation. In absence of patient-specific data/parameters, the system also supports the adoption of canonical instances of anatomical concepts. Going one step further, the Virtual Soldier project by the U.S. Defense Advanced Research creates a computational model of the thorax by utilizing FMA and the Visible Human data set. The objective is to model injury impacts and it serves as a template for individual physiognomic databases.

Finally, we report the use of ontology in managing textual resources. For instance, Clement Jonquet *et. al.* [18] described an ontology-based resource management system that allows users to locate publicly available biomedical data related to particular ontology concepts in the NCBO Bioportal. It also supports the semantic expansion of annotation through hierarchical relations in the ontology, and establishes direct links between metadata, radiological descriptions, clinical reports, PubMed abstracts, and ontological concepts. For instance, if a resource element (e.g., a GEO protein expression), is annotated with *"pheochromocytoma"* concept from the ontology National Cancer Institute Thesaurus (NCIT), then a query can be executed in Bioportal for *"retroperitoneal neoplasms"* and retrieves data sets related to *"pheochromocytoma"*. In fact, *"pheochromocytoma"* is formalized as direct child of *"retroperitoneal neoplasms"* in NCIT. Additionally, the recent development on the top of modern ontologies has targeted computational frameworks for clinical decision support systems. For instance, OntoQuest system [19] is built over a large hospital database and supports ontological queries for computing the semantic similarity among different patients, according to their diagnosis sets defined by using International Classification of Diseases (ICD-9). This kind of computational framework can reduce the medication prescription errors by facilitating the interaction with computerized order entry.

Prospective usages. Ontologies are quite popular in bio-medicine, however, their concrete value should be assessed against their actual usage in the clinical practice. Since they were introduced as a means to achieve the sharing and interoperability at system level: *what is the extent to which they succeeded?* For this assessment, re-usability is a key aspect and should involve a through investigation of the knowledge source, perspective and scope, semantic and syntactic interoperability, and its maintenance aspect. Note that for the re-usability of biomedical ontologies, *"granularity"* (i.e., at which level of detail anatomical concepts have been formalized) is another important issue because of the multi-scale nature of anatomy. Up to now, the FMA can be considered a reasonably complete resource for representing canonical human anatomy, and several applications were built on top of it to support the knowledge exploration. In radiological applications, Radlex supports data and information management and supplies the knowledge background for building decision support tools for the radiologist.

Nowadays, an efficient adoption of biomedical ontologies in patient-specific data management, clinical decision support system, and patient healthcare planning is one of the leading research topics. Structural knowledge of anatomy alone is not enough for comprehensive reasoning: knowledge formalization should take into account temporal changes in anatomical structure, functional behavior and pathologies of the organ system, clinical research models [20]. More importantly, the formalization should be brought beyond the scope of establishing a common knowledge, by developing tools and methods to support a dynamic evolution of ontologies by inferring new knowledge [21], exploiting the richness and variety of digital patient data. The utilization of ontology in managing inter-patient variability and capturing temporal changes in anatomy still remains an unsolved problem.

4. Visual representation

Tools and methods. "Use a picture. It's worth a thousand words." - the phrase illustrates the importance of visualization to represent complex knowledge. There is no doubt that visual representations are vital and commonplace in anatomy; not only medical data often come in visual form, but visual representations play a crucial role for their capability to convey immediate knowledge. In a large number of situations, indeed, the pathological conditions of anatomical parts are highly correlated with visual aspects of their shapes (e.g., normal versus abnormal shapes, erosions, spikes). Spatial data, and the information they carry, are mainly utilized by the clinicians in medical diagnosis and treatment planning. However, the portrayal of anatomy through spatial data is often not explicit and computationally unaccessible. For instance, medical images are unstructured raw data, which capture a snap-shot of structural (e.g., organ shape, size, texture, positioning) and/or functional (e.g., tissue composition, metabolic or functional behavior) aspects of an individual's body interior.

Knowledge carried by images can be detected by visual inspection: while visualization is the direct modality of interaction with images, the complexity and volume of the shapes digitized may hinder understanding. Relying on efficient and user interpretable rendering of the visual content is crucial, and it encourages the quest *"for better viewing for better understanding, and better understanding for better medicine"* [22]. For medical applications, the challenge is not only visualization but the practical use of rendering techniques beyond just looking at the data. As main examples, we mention the commercial DICOM viewer OsiriX [23], open source viewers - 3DSlicer [24], Yadiv [25]. Most of these packages support visual inspection thanks to advanced rendering techniques, including classical iso-surface rendering, or 2D/3D texture mapping.

"Wealth of information is buried inside the acquired data" [26]. Acquired images capture the snapshot about individual anatomy, which needs to be processed and analyzed for extracting knowledge about, volume-of-organs, shape-of-organs, positioning, abnormalities, progression of pathology. In the image interpretation workflow, *segmentation* plays a crucial role as it provides manual or semi-automatic ways to identify regions of interest (ROI) with clinical relevance. Manual ROI recognition is time-consuming task and the results may suffer from intra- or inter-observer variability. In the past few decades, the incorporations of modern mathematical and physical techniques have greatly enhanced the accuracy of the computer-aided segmentation, but still a huge number of published scientific articles in the same area points to an evident insufficiency [27]. One of the most popular techniques for 3D segmentation is the deformable model, where an elastic template model (e.g., 2D curve or 3D surface) is transformed according to image parameters and prior information on the targeted object shape. To reduce the bias introduced by the selection of the model parameters, various deformable models have

been designed and we refer the reader [28] for further detail.

After the segmentation of images, 3D reconstruction allows to go one step forward, by generating a digital model which mirrors the accurate appearance of the patient-specific anatomy in 3D space. Moreover, 3D models can be used to perform computer measures on the acquired human body parts, and most importantly, to support simulations of their behavior. Their potentiality can be exploited to support virtual surgery, bio-mechanical simulation, prediction of pathology growth, and many other medical areas.

Practical usages of visual representation. It is well acknowledged that spatial data about anatomy, either in the form of images or processed 3D models, had and will have a strong impact on judging the patient condition in clinical scenario. Besides, the trend of visual 3D data usages evolved over the time in terms of multifaceted nature of knowledge illustration. Segmentation and reconstruction procedures are useful only if they can provide reliable results. Therefore, it is important to compare results obtained with different techniques to assess their quality. A large number of data sets have been created and shared in the scientific community with the primary motivation of benchmarking and testing specific medical visualization softwares with multimodal data. *Generic scan data sets* are a few anonymous DICOM data sets freely available in web for scientific research OsiriX data set, S. Barre Samples, Phantom Images. All these data sets contain a limited number of multi-modal anatomical images (mostly MRI, CT, XRay) which may emphasize some structural or anatomic peculiarities upon visualization. For instance, OsiriX group primarily released their anonymized MRI, CT, PET, XA angiogram, hybrid scan (MRI-PET and MRI-CT) data set to assess their DICOM viewer performance, and declare the exclusive availability of the data set for scientific research and teaching.

Alternative data sets produced for scientific purposes are the complete human body: *"Visible Human male"* (1994) and *"Visible Human female"* (1995) [29]. These were released by the U.S. National Library of Medicine (NLM) within the framework of *"Visible human project"*. The main goal was to facilitate experimentation of analysis and processing of digital representations of anatomy. These data sets contain high-resolution images acquired by MRI, CT scan and anatomical images (RGB cross sectional image) of male and female human cadavers. Afterwards, various projects (e.g., VisibleHuman browser, Voxelman, AnatLine, W3D-VBS, etc.) used this raw data set to describe knowledge about human anatomy in a computer-simulated framework by integrating either the 2D images with lexical knowledge or 3D virtual model with symbolic label.

However, these data sets suffers from data loss of the three junctions caused by physical segmentation of cadaver bodies, and it is only typical of the Caucasian population for both male and female. To overcome the data loss and ethnicity limitation of visible human data set, the Visible Korean Human (VKH) [30] and Chinese VisibleHuman (CVH), [31] data sets were released. These data sets contain the MR and CT images, as well as comprehensive anatomical images of Chinese (male and female) and Korean (male) cadavers. Recently, interesting data sets and benchmarks were released (VISCERAL datasets) to support the evaluation of automated identification in anatomy and pathology from 3D (MRI, CT) and 4D (MRI with a time component) radiology images [32]

The second relevant usage of 3D data that we want to discuss is the creation of *canonical* or *3D atlases* of anatomical parts. *3D canonical model* are *"synthetic"* digital models [33], [34] created with prior knowledge and/or simulated data to represent the canonical appearance of the anatomy. Turbo Squid, SawBones are commercial companies which produce 3D anatomic models to overcome the scarcity of legitimate data set. However, the synthetic models are often over-simplified, and the accuracy entirely depends on the designing methodology. This kind of canonical models can be seen as the 3D counterpart of 2D sketches done for illustration purposes.

"Data-driven" anatomical models provide a mathematically-defined 3D representation of canonical human body parts. Their potentiality lies in the realistic representation of anatomy, based on processing of acquired data. Several whole body [35], [36] and partial body [37], [38] anatomical models are constructed from acquired images (X-Ray, MRI, CT) of healthy volunteers, patients or cadavers. Some full body modeling attempts [39], [40] used high resolution RGB cross sectional image of cadavers, to realize the representation of anatomy. Most of the approaches follow either volumetric or surface modeling. Volumetric methods are a quite popular choice in anatomical modeling, although traditional fixed resolution volumetric method is not competent to represent precisely small anatomical details [41].

The conveyed anatomical knowledge *via* the data-driven models is often incomplete, since one single static model may not be able to describe the variability in anatomical structures that is inherent across the human population. Virtual family [42] is an interesting initiative that generated four whole body models of two adults and two children to represent the anatomical features variability based on age and gender. However, the Virtual Family models are unable to capture the large anatomical differences among individuals within the same age and gender group.

Prospective usages. A conceivable future research direction is *patient-specific modeling* (PSM) that aims to implement the powerful modeling tools and techniques for three-dimensional computational reconstruction of the anatomy or a mathematical model of the organ for individual patient, based on imaging scans or other individualized parameters. The target is to exploit the models for calculations/simulations that can provide a diagnosis, prognosis or prediction of treatment outcomes. Segmentation and reconstruction are the crucial components at the basis of any PSM; interesting work have been done in the area of bony joints [43], heart [44], and brain [45]. In the scope of PSM, previous work has tried to maximize the level of information and accuracy in the generated model [46] and to minimize the manual effort in terms of time and selection of parameters. In this context, a recent work [47] creates patient-specific models based on a minimal prior knowledge about the target and deformation of anatomy templates. The current barriers for modern PSM technologies to become a clinically acceptable standard are: scarcity of required information, complexity in data interpretation, successful validation of the predicted outcome measures, and inadequate inter-disciplinary endeavor between medical and computer professionals.

An alternative way of building approximated lost-cost patient-specific model is to increase the statistical relevance in the data-driven modeling by using a large number of input data set, i.e., sample population to model the randomness of biological variability. The sample population generally consists of healthy patients for characterizing the anatomical variability and patients with a particular disease for understanding developmental and anatomical aspects of the disorder.

Statistical models are mainly composed of two components: the *mean model* - the average shape or appearance of the organ within the population, and *statistical variance* with respect to the mean model. In theory, a good statistical model should represent most of the variability that existed within the sample population using less number of variance. For several years, statistical model creation of bony anatomy [48], and cardiac structures [49] got an increasing attention of the scientific community. However, highly varying soft-tissue structures (e.g., liver, vessel-systems, muscles) are much harder to model, and random shapes (e.g., lesions, tumors) are unsuitable for statistical shape analysis with most of existing methods.

5. Integration between visual and symbolic representation

Both visual and symbolic representations have equal importance for depicting anatomy, and the optimal solution goes in the direction of a tighter integration of the two, which can be realized through the *annotation of spatial data with symbolic information* [50] (Fig. 2). The classical atlases, up to the digital atlas annotation of spatial data, provides an optimal understanding of anatomical knowledge. Moreover, the integration between spatial data and symbolic knowledge supports an effortless dynamic navigation in the knowledge space, thus creating advanced pathways in the modern clinical society and stimulating new medical reasoning and correlations finding [51].

The process of tagging single/multiple texts (metadata) with the spatial data, which may represent semantics, comments, links, and any other textual information, is known as *linguistic annotation* and can be classified as *free-text-based* and *knowledge-driven annotation.* In free-text based annotation, the users are free to tag an object with any keyword he/she has in his/her mind, e.g., notes, observation. On the contrary, in *knowledge-driven* annotation, the terms are fixed and defined by an underlying formalized knowledge, e.g. taxonomy, ontology.

Most of the existing medical image visualization software (OsiriX, Yadiv, 3DSlicer) allow the user to manually or automatically mark the ROI inside the images and to tag it with user-defined observations (free-text). However, mostly, manually added keywords are unable to capture the objective meaning of the targeted data. In fact, the textual abbreviation reflects the perspective and interest of the user only, without placing the annotation in a diagnostic work flow that could be shared with other clinicians. Additionally, annotation expressed in natural language, is influenced by several factors, such as language or context, and can be limited or ambiguous. Indeed, it is convenient to use the free text annotation in an isolated interpretation environment, but it may not provide meaningful results in a network-based collaborative scenario.

On the contrary, the formalized semantics of the annotation ensures a common and shared understanding, restricts the use of an exhaustive set of terms, and allows the annotation only with the *'controlled vocabulary'*. Indeed, the main difference among existing methods is the trade-off between flexibility and meaningful. Previous work [52], [53] associates virtual body

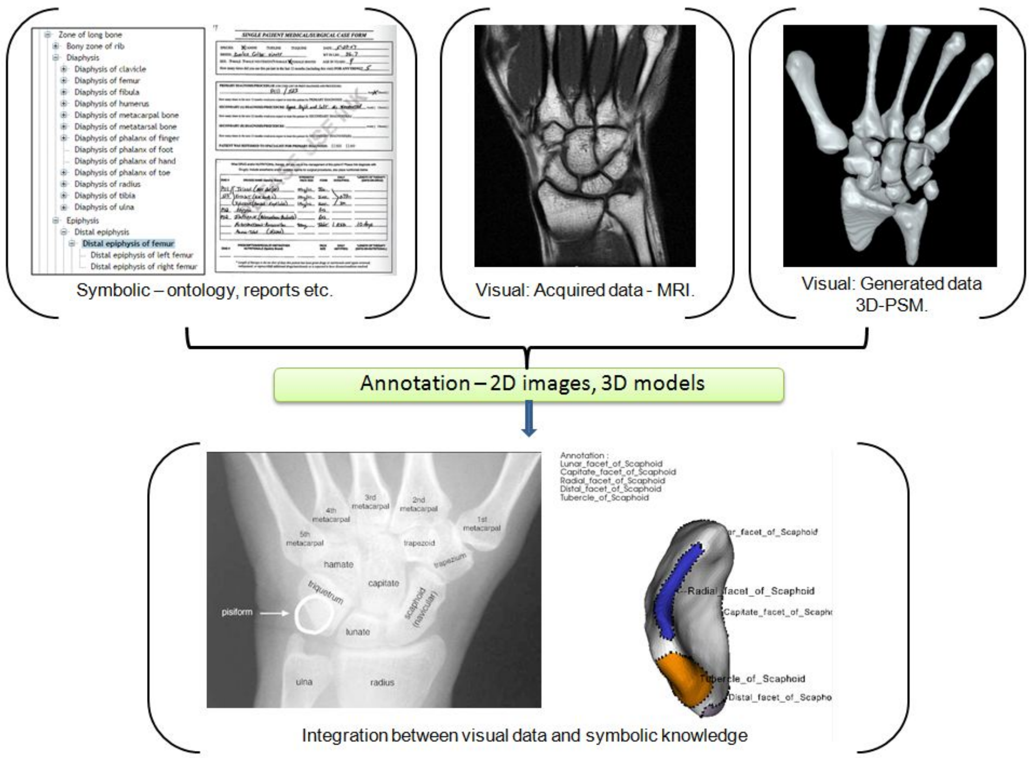

Figure 2: Present: Anatomical knowledge representation facets.

models, generated from the Visible Human dataset, with a knowledge base of descriptive information (symbolic), which permits an intuitive method for anatomy training in a distributed environment. However, semantic annotations has potentiality to go beyond simply portraying the anatomy for training and can bridge the ambiguity of the natural language by expressing notions and their computational representation in a formal language. Moreover, encoding how data items are related and how these relations can be evaluated automatically, supports the definition of complex filters and search operations. For example, a MRI data set annotated with conceptual tags *'FMA:Knee joint'* can be interpreted as - it captures the spatial representation of *'FMA:Knee joint'* that has constitutional parts, such as *'FMA:Lateral meniscus'*, *'FMA: Patellar Ligament'* etc.. These facts imply that the visual content of MRI data set also represents *'FMA:Lateral meniscus'* and *'FMA: Patellar Ligament'*. Indeed, the annotation refers not only to the textual tag but also to the concept *'FMA:Knee joint'*, which has formal definition in FMA [54]. The combination of controlled annotation of patient data with a richer vocabulary and a sophisticated reasoning policy can dramatically increase the performance of data management, information navigation, and data retrieval system.

Performing a comprehensive semantic annotation for all medical datasets is beyond the human capacity due to its massive volume. However, the efficient combination of man and machine can improve the speed and efficiency of annotation, and can offer ultimate understanding and utilization of anatomical data. In other words, semantic annotation softwares which extract the implicit content of the input data, parse all available symbolic information about patient history, and take into account the formalized medical knowledge, are becoming more and more relevant in this context. However, such automatic methods heavily count on the availability of solutions to deal with the "gap" between computational and semantic features, inter-subject variability, and the enormous amount of accessible information.

Existing tools. To the best of our knowledge, we have selected some suitable approaches that were published between 2005-2015 and presented an investigation summary in Table 1. Each of the solutions shows a specific way to link visual 3D data with symbolic knowledge on anatomy. We mainly analyze each approach according to: which type of spatial data (synthetic, acquired or generated) is being described? Which kind of symbolic knowledge is associated: anatomy, pathology or just the personal observation? How it has been exploited in clinical applications? However, the features focused here are only the tip of the iceberg of possible medical interests on the way to a comprehensive representation of the generic and patient-specific anatomy.

To give the reader a more comprehensive overview, we decided to position the prime solutions in a *Spatial-Symbolic* space (Fig 3) based on what type of spatial data have been integrated with which sort of symbolic knowledge. Afterwards, depending on the analysis (Table 1) we clustered them to recognize the remaining "gaps". First of all, at the beginning of spatial axis we plotted a few platforms that has been developed for exploring 3D anatomical atlas (canonical) mainly for training purposes. Some of them used static database to manage pre-defined anatomical labels; for instance, the Medical Information Service [55] and the Zygote body (previously known as Google body browser) [33]. In contrast, Bio-digital Human [34] stores the pointers of the web-resources (wiki, books) to support the association of external source of information along with the static labels. However, we cluster them under the

Table 1: Systems that integrate spatial data with symbolic knowledge.

	Google body [33]	Bio-digital human [34]	Medical info service [55]	Voxel Man [56]	W3C- VBS [57]	Bodyparts 3D [58]	Medico [59]	epad [60]
	Symbolic knowledge							
Type	Canonical	Canonical	Canonical	Canonical	Canonical	Canonical	Subject-specific	Subject-specific
Span	Anatomy labels	Anatomy & pathology	Anatomy & pathology	Anatomy	Anatomy & pathology	Anatomy labels	Anatomy, pathology & clinical notes	Anatomy, pathology & clinical notes
Rep.	Vertex labels	Tagged with 3D models	Static relational database	Knowledge-base	Gray's anatomy (Digital)	FMA	FMA, ICD10, RadLex	Radlex
Link	N/A	Pointer to web-resources	Internal link	Semantic network	Database relations	Semantic relations	Semantic relations	Semantic relations
	Spatial data							
Type	Synthetic	Synthetic	Synthetic	Data-driven	Data-driven	Data-driven	Patient-specific	Patient-specific
Rep.	3D model	3D model	3D model	Visible human data	Visible human data	Segmented data	CT images (dicom)	Acquired image
	Features and applications							
Framework	Web-based	Web-based	Web-based	Standalone	Web-based	Web-based	Web-based & MITK client	Web-based
Annotation	No	link pointer	No	Free text	Free text	No	Formalized & Free-text	Formalized & Free-text
Search	Keyword-based	Keyword-based	Keyword-based	Keyword-based	Keyword-based	Semantic	Semantic	Semantic
Usage	Education	Education, virtual dissection	Education	Virtual surgery	Learning	Learning & simulation	Sharing, retrieval	Analysis, retrieval

same top class *Atlas with synthetic data* since these 3D atlases are fabricated by using synthetic data tagged with static labels of generic information, such as anatomy labels, its synonyms, function of the organ, etc. On the symbolic axis, they reside in the middle because they incorporated the textual labels from a pre-define vocabulary rather than free-texts.

In the next cluster - *Atlas with real data*, VoxelMan - Intelligent volume [56], W3D-VBS [57] and other web-based three-dimensional anatomy training systems have been grouped that use images (using axial, coronal, sagittal views) and/or 3D virtual structures generated from acquired data, and annotated them with pre-defined labels to provide a more realistic picture of visual-spatial relationships of anatomy. BodyParts3D [58] and Biolucida platform [61] can also be clustered as *Atlas with real data* that creates the

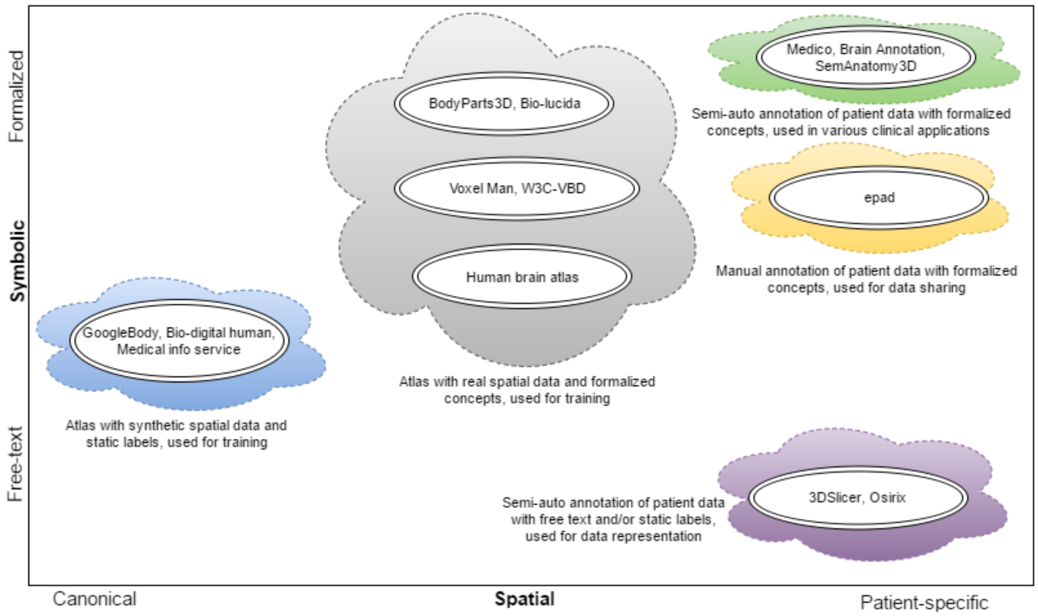

Figure 3: Existing solutions in Spatial-symbolic space.

link between canonical models and structured knowledge by populating the FMA [13] with 3D models of body parts of distinct individuals, and allows a hierarchical navigation through the FMA ontology. However, the subgroup of BodyParts3D stays higher in the symbolic axis, since they adopted ontology-driven annotation of the canonical dataset.

Beside realistic atlas creation for anatomy training, a main challenge is to devise methods that can integrate patient-specific spatial data and symbolic information to support knowledge-driven clinical trials. Moving towards the "patient-specific" direction of the spatial axis, we first cluster the medical data visualization software (e.g. 3DSlicer [24], OsiriX) that allow the human operator to annotate the patient's data with free-texts (e.g. anatomy, disease status, clinical notes) for optimizing the representation. ePad (earlier known as iPad [60]) is a web-based medical data visualization and sharing platform, and allows the user to add semantic tags from the RadLex ontology [15] to 2D acquired images. However, the process is mostly manual and can only support the annotation of DICOM images.

In the next cluster, we grouped the semi-automatic annotation platforms that integrate patient-specific 2D/3D data with formalized symbolic knowledge. For instance, the Medico system [59] applies a semi-automatic detection and localization of anatomical structures within CT scans of the human torso and maps them to the concepts that are derived from FMA [13]/ICD10 [62]/RadLex [15]. However, this approach is applicable only to CT data sets of human torso, and verified only within a small set of sample images. Another similar system [63] uses numerical atlas and symbolic knowledge (ontology and description logic rules) in an integrated way to achieve semi-automatic annotation of brain MRI images.

Following the semi-automatic ontology-driven annotation trend, the next challenge is to build an efficient knowledge-driven segmentation-annotation platform to handle different types of medical images, 3D models, and to incorporate automatic characterization of the object geometry within the scope of formalized knowledge-base. In this context, SemAnatomy3D [64] demonstrates the idea of automatic ontology-driven annotation of patient-specific 3D models (segmented from MRI and CT images) and its relevant subparts by coupling 3D geometric characterization and knowledge formalization techniques. However, it is restricted to a specific input data representation, i.e., triangulated mesh.

6. Key challenges towards a comprehensive integration

In modern anatomy, an imaginable future advancement is the *"Digital patient"* that should represent, model and abstract the real patient in all of his/her medically relevant aspects to support computer assisted clinical diagnosis. The European project DISCIPULUS [65] published a research agenda in May, 2013 for the realization of digital patients. In the DISCIPULUS roadmap, the integration of descriptive symbolic data/information with digital images and models is listed as one of the key research issue because the amount of medical data acquired and stored has increased enormously due to successful developments in data generation/medical scan techniques. However, an efficient use of such data for computational modeling and simulation has not yet been achieved. To dig into the issues, we narrowed down our discourse only to the patient-specific 3D models, and present the challenges which are the key to enforce the role of 3D models into computer assisted clinical applications, e.g., diagnosis, virtual surgery, bio-mechanical simulation.

Extraction of knowledge out of 3D data. In the perspective of extracting the knowledge content of the patient-specific 3D data with minimal human intervention, automatic tools/methods are needed to be developed for identifying anatomical features (e.g., muscle insertion, contact area) and recognizing anomalies (e.g., degradation, lesion) from the geometric appearance of the patient's organ, and then, based on the extracted features classify the models into the corresponding categories (e.g., according to disease progression, healthy vs abnormalities).

So far, most of the methods/tools developed in the Computer Graphics field aimed at the generic 3D shape understanding and analysis (e.g., Eigen decomposition, curvature analysis, geodesic). Put it differently, they can only support the characterization of the geometric and structural properties of the 3D models, but most of the shape descriptors are not suitable for extracting the clinically relevant information from the anatomical shapes. This is mainly due to the fact that: (i) often the anatomical landmarks and pathological markers belong to the geometric featureless regions; (ii) the medical definition of the features is intrinsically vague, and thus, the features cannot be coded or identified by mathematical formulation; (iii) the shapes often are highly variable between individuals.

There is a need for focused 3D characterization techniques that can address the feature recognition problem in the specific medical context. Specialized techniques can be developed by capitalizing the existing shape analysis and segmentation methods, proposed in the computer graphics field, and then couple the relevant ones to devise a tailored characterization algorithm for the specific clinical context. Another crucial aspect for medical data characterization is to capture the normality, and differentiate abnormalities from the healthy shape variations. The statistical models which capture the healthy shape variabilities, can act as a vital component for the characterization of abnormalities.

Integration of symbolic knowledge with patient-specific 3D models. The integration is more valuable when the symbolic definitions are associated not only to the whole 3D model but to the parts of interest, which can represent anatomical or pathological features. This integration can be considered as a step towards part-based indexing of the 3D model to support efficient retrieval relying on linguistic queries. Such framework can be a great support to the clinical studies by retrieving "similar" cases and allowing the inter-patient comparative analysis at the required level of granularity. In order to fulfill the objective, there is a demand of a significant amount of work not only in the area of developing annotation techniques, but also agreeing on a *"common standard"* or stable 3D markup to link the annotations to the 3D geometry and make the metadata and knowledge-base consistent.

The Annotation and Image Markup (AIM) standard [66] is developed for storing descriptive and quantitative clinical image markup data in DICOM-SR, HL7 CDA, or XML formats to facilitate the communication of image annotations and markup data in a standard manner. However, at this stage, such standard is mainly limited to 2D/3D images, and no state-of-the-art solution applies to patient-specific 3D model. Besides the AIM, a number of semantic annotation data models have been proposed for generic annotation of digital resources, such as the Annotea model [67] and the Open Annotation (OA) [68]. Unfortunately, none of these common models provides sufficient specifications for annotating free form parts of a 3D model. The OA data model [69] developed by W3C Open Annotation Community Group specifies a extensible data model to support inter-operable annotations without using a particular set of protocols. Thus, a straightforward way is to extend the OA model (or similar model) or design a new data model from scratch to manage 3D part-based annotations.

Only an information model is not enough to manage efficiently the annotation of 3D-PSMs, a link need to be established between annotation and the 3D geometry. A popular way of addressing a part of digital resource in web is *via fragment-identifier*. However, fragment identifiers for 3D objects are not popular because the 3D data streams are often too large to be directly encoded into an URI string. Another approach is to store the 3D data streams within an independent file linked to the annotation *via* an URI using the Linked-Data approach. There exist some XML-based standard formats to record the annotated geometry of a 3D object, such as X3D [70] or Collada [71]. However, XML-based formats are mainly designed to support the description of compound scenes as assemblies of simpler objects, and they are not very efficient to store multiple annotations of a large mesh. This is mainly due to the fact that the whole geometry has been replicated and indexed while storing a single annotation. Therefore, exclusive formats are needed for delivering a high performance 3D annotation service. Moreover, to date, no previous effort has focused on methods to compress these 3D annotation file formats.

Management of heterogeneous 3D data sets and information in an interconnected manner. Integrative anatomical modeling requires the fusion of knowledge coming from various sources, distinct medical disciplines, and numerous clinical issues. In fact, 3D data and information about anatomy are available in a range of different formats, and high level computational expertise is required for performing analysis and integrating data coming from various backgrounds. We argue that *biomedical ontology based data management* is a promising choice that allows to interpret the data through the explicit definition of terms and relationships in an ontology, and able to resolve any semantic heterogeneity that is present within the data. Single ontology approach uses one global ontology where pre-defined correspondences have been established between the ontology and data sources. To avoid the static correspondences, instead of using a common ontology multiple ontologies could be adopted where each data source is described by its own ontology separately and mappings are used to express the relationships between the ontologies. For this purpose, an additional representation formalism is necessary for defining the *inter-ontology mappings* which allows a quasi-dynamic modification of the data sources.

Given these technical challenges, sophisticated digital healthcare platforms could be envisaged in the light of digital patient where the true potentiality of patient-specific 3D models will be fully exploited in the complex medical data analysis scenario. Bridging the semantic gap between patient-specific 3D data and formal knowledge is a challenging and demanding area of research. Indeed, an interdisciplinary effort between medical professionals and informatics scholars is needed to build a new generation healthcare system such that a human specialist can access effectively the machine interpreted knowledge about the patient.

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