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Computational methods for the morphological analysis and annotation of segmented 3D medical data

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Computational methods for the morphological analysis and annotation of segmented 3D medical data

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Abstract

The document reports some of the main issues related to the semantic annotation of medical data acquired from MRI scans and describes possible solutions.

Keywords: Semantic annotation, shape processing.

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1. Introduction

Computational methods play a prominent role in supporting collaborative investigation of the human body, as foreseen by the Virtual Physiological Human framework, especially for supporting descriptive and predictive actions. This is particularly relevant for computational methods involving the processing of anatomical structures and the simulation of complex physiological systems, such as the musculo-skeletal one. In this context, the semantic characterisation of elements can offer advantages, thus here we provide an overview of the existing most pertinent ontologies and annotation tools. Then, we describe the main acquisition methodologies, processing and segmentation methods of medical data, with a specific attention to the case of bones and tissues of musculo-skeletal atlases. The segmentation methods of 2D or 3D images are reviewed according to different factors, such as the degree of user interaction; computational cost; underlying methodologies, which include image or volume processing; use of prior information; and support to semantic annotation. Then, we introduce the stages of the rheumatoid arthritis, the main characteristics of the analysis of baseline and follow-up data; in particular, we focus on the Omeract-Ramris scoring system. Finally, we describe quantitative methods for the evaluation of the rheumatoid arthritis and detail the proposed morphological analysis of follow-up data. Then, the extracted information can be associated with the input data through the semantic annotation and can be used by experts to compare follow-up data or to compare the same pathology for different patients. Results with a main focus on the wrist sectors are presented.

The report is organized as follows: we introduce the semantic annotation of biomedical data (Section 2), the morphological analysis of MRI images for semantic annotation (Section 3) and the workflow for the morphological analysis and annotation of biomedical data (Section 4).

2. Semantic annotation of biomedical data

We now introduce the ontologies (Section 2.1) used for the semantic annotation of biomedical data (Section 2.2).

2.1. Ontologies for semantic annotation of biomedical data

Knowledge formalization techniques provide a possible way to build a formal framework to organize data at the various biological scales which contribute information related to the digital patient (*shared conceptualization*). Based on this integrated view, various modalities to access and visualize data, concepts and information relevant to characterize diseases can be devised. Knowledge specification can be also used to bridge properly the morphological, structural and functional aspects of medically-relevant parts of the human body and used to navigate interactively the data and its properties (e.g. anatomical information and image orientation).

For the aforementioned purposes, ontologies are efficient tools for structuring and storing different types of information and their dependencies. Ontologies are not new in the medical domain: they have been introduced and used since years in order to systematize medical knowledge. Also, the

importance of semantics-driven annotation of medical data has been subject of many scientific and technological efforts and supported the development of systems to support clinicians in their activities.

Existing biological and medical ontologies offer complementary information (e.g., geometric/topological information, disease evolution) on the human body and its functioning or diaseses. Some of them also make available navigation, browsing, and search modalities, which suggest new ways to exploit the multi-scale and multi-modal nature of the knowledge captured.

Ontology usage in the medical context. One of the most prominent advantages of ontology is that it can provide a common vocabulary. According to this role, the uses of ontologies in medicine started with focus on the representation and (re-)organization of medical terminologies e.g. FMA (Foundation model of anatomy), International classification diseases, Systematized Nomenclature of Medicine (SNOMED).

Given the advancement of semantic web technologies, the scenario of bio-medical ontology design and usage is evolving: beside common terminology, ontologies can also be used to manage structural, functional, and morphological information extracted from the medical data. The development of ontologies has therefore been considered also to support computational frameworks for clinical decision (e.g., OntoQuest) or to study the human anatomy and the functional behavior of the organ in a more interactive way (e.g., MyCorporisFabrica).

Making one step further, linking the clinical knowledge with the geometry extracted from the patient record is likely to open a new pathway for clinical analysis. In medicine, this knowledge could be useful to drive automated analysis to support diagnosis, therapy planning, surgery, radiotherapy, and legal medicine. In the following, a brief description of the most considered and used ontology is provided:

- Medical Subject Headings (MeSH)¹, is a controlled vocabulary thesaurus defined and maintained by the National Library of Medicine's. It is aimed at indexing and retrieving medical literature. It consists of sets of naming descriptors hierarchically structured to allow searching at various levels (up to thirteen) of specificity. Among the considered top-level categories, we can find Anatomy which includes the various bone organization, and Diseases listing the various pathologies. The thesaurus includes terms' synonymies and is available in different languages, thus providing certificate terminology (no Italian version available).
- International Classification of Diseases (ICD)² serves as a detailed index of known diseases and injuries. It provides codes to classify diseases and a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances and external causes of injury or disease. It is conceived as the standard diagnostic tool for epidemiology, health management and clinical purposes. This includes the analysis of the general health situation of population groups. It is used to monitor the incidence and prevalence of diseases and other health

¹https://www.nlm.nih.gov/mesh/meshhome.html

²http://apps.who.int/classifications/icd10/browse/2010/en

problems. It has been translated into 43 languages and its main usage is for supporting the compilation of national statistics.

- Foundational Model of Anatomy (FMA)³ represents anatomical entities ranging from biological macromolecules to cells, tissues, organs, organ systems, and major body parts, including the entire body. It is strictly constrained to "pure" anatomy, i.e., the structural organization of the body. The FMA is concerned with the representation of classes and relationships necessary for the symbolic modeling of the structure of the human body in a form that is both understandable to humans without wrong interpretation and navigable by machine-based systems. The FMA is one of the largest computer-based knowledge sources in the biomedical sciences. It contains approximately 75,000 classes and over 120,000 terms; over 2.1 million relationship instances from over 168 relationship types link the FMA's classes into a coherent symbolic model. It has four interrelated components: Anatomy taxonomy, Anatomical Structural Abstraction, Anatomical Transformation Abstraction, and Metaknowledge. The first one classifies anatomical entities according to the characteristics they share (genus) and by which they can be distinguished from one another. The second component specifies the part-whole and spatial relationships that exist between the entities. The third component specifies the morphological transformation of the entities represented in At during prenatal development and the postnatal life cycle. The last one indicates the principles, rules and definitions according to which classes and relationships in the other three components of FMA are represented. In summary, this model serves as the reference domain ontology for the discipline of anatomy and provides a template for evolving biomedical domain ontologies (e.g., PRO, the Physiology Reference Ontology).
- Systematized Nomenclature of Medicine (SNOMED) [30] aims to provide comprehensive coverage of the health care domain such as diseases, findings, procedures, microorganisms, pharmaceuticals. It is one of the most comprehensive clinical terminology available. It allows a consistent way to index, store, retrieve and aggregate clinical data across specialties and sites of care and also helps to structure and computerize the medical record. One of the interesting features of SNOMED is that in addition of giving a detailed and linked structural description of anatomical entities as well as micro-level entities, it allows to link instances of such structures to clinical procedures to reduce the encoding variability for clinical care. Certified translations in various languages have been provided (no Italian version available).
- **RADLex**⁴ is a controlled terminology project from the Radiological Society of North America (RSNA). Its aim is to provide a uniform or standard lexicon for indexing and retrieval of a variety of radiology data to be used for teaching, research and reporting procedures. It unifies and supplements other lexicons and standards, such as SNOMED-CT and DICOM. In particular, the Playbook ontology module provides a standard system for naming radiology procedures, based on the elements that define an imaging exam such as modality and body part. By adopting the best features of existing terminology systems and producing

³http://bioportal.bioontology.org/ontologies/1053

⁴http://www.radlex.org/

new terms to fill critical gaps, it provides the basis to obtain operational and quality improvements, such as workflow optimization, radiation dose tracking, enterprise integration and image exchange.

- My Corporis Fabrica(MyCF)⁵ focuses on the formalization of anatomical knowledge and suggests its computational representation for anatomy modellng. The main objective is to increase the development of new 3D technologies and knowledge systems, based on semantics, ontologies and statistics. It also provides a framework to manage the links between abstract anatomy and real patient to produce relevant physical anatomical models through virtual representations of human body.
- MultiScaleHuman Ontology⁶ has been developed by CNR-IMATI and includes a formalization of the following aspects: MSH Glossary, which describes the main terms of the MSH Ontology with a short explanation of each; MSH Data Ontology, which provides all the metadata necessary to describe the data used by the MSH Partners, in particular MRI, micro-CT, 3D shapes, and simulation data: MSH Knee District Ontology, which contains the anatomy description for the knee district and the lower limb (e.g., organ identities, adjacency relations useful for anatomic reasoning); MSH Simulation Ontology, which describes the information relevant to the characterization of motion simulation and evaluation, including references to landmarks used for simulation and motion capture; MSH Cell Ontology, which contains terms and relations for the representation of the knowledge related to cells of tissues and bones, according to the needs of tissues' analysis and characterization. The MSH Disease Ontology contains a formal description of MSH-relevant musculoskeletal diseases and it is mainly based on the usage of the ICD Ontology - International Classification of Disease. The MSH Ontology is intended to support the development of a knowledgebased system which offers functionalities for the storage, access to and visualization of patient-specific data, such as raw data (e.g., MRI, PET-MRI, Micro-CT data), motion capture data, processed, segmented, and simulation data, as instances of the classes of the MSH Ontology. The knowledge-based system gives the possibility to document and characterize software tools for data processing, visualization, and segmentation, and it offers services for browsing and searching, data and information visualization, and semantic annotation of data (Sect. 2.2).

2.2. Semantic annotation

Most of the existing medical image visualization software (OsiriX, Yadiv, 3DSlicer) allow the user to mark the ROI inside the images (manually or automatically) and tag it with user-defined observations (free-text). However, manually added keywords are unable to capture 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 workflow that could be shared by other

⁵http://www.mycorporisfabrica.org/

⁶http://www.ge.imati.cnr.it/index.php/activities/projects?layout=edit&id= 129

clinicians. Additionally, annotation expressed in natural language, is also influenced by several factors, such as language or context, and they can be limited or ambiguous. Indeed, it could be 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.

In knowledge-driven annotation, anatomical and pathological terms are fixed and defined by an underlying formalized knowledge. While, the formalized semantics of the annotation ensures a common and shared understanding, at the same time, it restricts the use of an exhaustive set of terms and allows the annotation only with the 'controlled vocabulary'. Semantic annotation can go beyond familiar textual annotation, and makes the annotations computationally accessible. 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 Ligaments' etc., which implies that the visual content of MRI data set also represent 'FMA:Lateral meniscus' and 'FMA:Knee joint', which has formal definition in FMA [41]. Controlled annotations can dramatically increase the performance of an data retrieval system by representing annotation in a computer-accessible way.

We identified a few platforms that has been developed for exploring 3D anatomical atlas (canonical). Some of them used static database to manage pre-defined anatomical labels: for instance, the Medical Information Service [27] and the Zygote body (previously known as Google body browser) [10]. In contrast, Bio-digital Human [39] stores the pointers of the web-resources (wiki, books) to support the association of external source of information along with the static labels. To illustrate canonical representation of human anatomy, these 3D atlases are fabricated by using synthetic data tagged with generic information, such as anatomy labels, its synonyms, function of the organ, etc. To disseminate a more realistic picture of visuo-spatial relationships of anatomy, VoxelMan - Intelligent volume [46], W3D-VBS [52] and other web-based three-dimensional anatomy training systems use realistic images (using axial, coronal, sagittal views) and 3D virtual structures generated from Visible Human data set [2] annotated with pre-defined labels. BodyParts3D [34] platform creates the link between canonical models and structured knowledge by populating the FMA [42] with 3D models of body parts of distinct individuals, and allows a hierarchical navigation through the FMA ontology. Finally, we mention (Section 2.1)

- the *MSH semantic annotation platform* (standalone), which supports the semantic annotation of multi-modal medical data through the integration of 3D surface characterization algorithms and the MSH domain knowledge. It also provides a user-friendly interface for the (semi-)automatic part-based annotation of patient-specific data (mostly 3D) with the concepts formalized in the MSH domain ontology, calculated/measured clinical parameters, shape characterization, user insight etc.;
- the *MSH data sharing and retrieval platform* (web-based), which supports user-guided interaction for data uploading, searching, and navigation, information filtering/refinement, knowledge visualization, and user management.

	$ \begin{array}{c} \mathcal{X} \\ \mathcal{Y} \\ \mathcal$								k K X	y y
Bone One-side Hausdorff distance										
	Capitate	-	10.2	58.3	-	44.2	-	13.6	57.4	
	Hamate	12.2	-	48.2	-	-	-	-	7.5	
	Lunate	58.2	48.2	-	-	17.3	-	-	60.3	
	Pisiform	-	-	-	-	-	-	-	44.7	
	Scaphoid	44.1	-	17.3	-	-	-	19.5	-	
	Trapezium	-	-	-	-	34.9	-	60.1	-	
	Trapezoid	12.7	-	-	-	19.6	60.1	-	-	
	Triquetal	57.2	7.5	60.4	44.1	-	-	-	-	
				(0	c)					

Figure 1: (*a*) One-side Hausdorff distance and (*b*) carpal bones. Arrows are a pictorial representations of distances. (*c*) Adjacency matrix for the wrist and intra-bones distance variation between the follow-up and the baseline.

3. Morphological analysis of MRI images for semantic annotation

We discuss the data segmentation and morphological analysis of anatomical districts (Section 3.1) and their semantic annotation (Section 3.2).

3.1. Background on data segmentation and morphological analysis of anatomical districts

We briefly review the segmentation of medical data (Section 3.1.1) and their morphological analysis (Section 3.1.2) for the characterization of rheumatoid arthritis (Section 3.1.3), which have been applied to the proposed approach for the morphological characterization and annotation of segmented 3D medical data.

3.1.1. Data segmentation

Nowadays, medical data are acquired through different modalities, such as radiography, computerized tomography, ultrasound, positron emission tomography, and magnetic resonance imaging. Multimodal modalities (e.g., PET-MRI, MRI-CT) have been introduced to fuse different information and to give a broader characterization of anatomical structures. Their main open issues are the alignment and fusion of different data types, sources, and resolutions. Segmentation of medical images is challenging due to several factors, such as data anisotropy, noise, non-uniform intensity, partial volume effects, data complexity and variability among individuals.

Medical data are segmented into target structures through thresholding, clustering, deformable models, and atlases. Thresholding [36, 45] segments images according to the pixel intensity. Region-growing methods [25] group pixels according to a homogeneity criterion through an expansion process that starts at predefined seed locations. Their main issue is the sensitiveness to noise and over-segmentation, which are generally solved by imposing the homotopic consistency between the initial and segmented region. Both thresholding and region growing generally use a low prior information (e.g., specific thresholds, seeds) on the input data, with no reference to the underlying geometric structure. *Clustering techniques* [6], such as the k-nearest and fuzzy c-means algorithms [17, 55], segment the input data through an iterative partitioning of each class and the evaluation of its properties, such as planarity, Euclidean distance, etc. Their main issues are the sensitiveness to local noise and inhomogeneous intensity, and the inclusion of geometric and/or topological information. Graph-cut techniques [12], such as the fuzzy connectedness [53], the watershed algorithm [54], and the image transform [21], are typically applied to a graph whose nodes are the image pixels and whose edges encode relations among them. Deformable models [33, 49] effectively segment medical data through the expansion of contours or surfaces driven by imagebased forces that evolve to equilibrium. The underlying continuous approximation is stable to data noise and resolution. Atlas-based segmentation maximizes the prior information to overcome the data variability, noise, low gradients, and resolution. Generic anatomy atlases are designed using modeling software and include the anatomical structures and their relationships. Patient-specific anatomy models are the output of a scanning device and include a statistical shape for each structure. Atlas-based segmentation [38] adapts a reference scheme to patient-specific data through an iterative application of linear or non-linear transformations. Image and shape primitives, whose identification is based on the intensity values and topological/geometric properties, are interpreted through anatomical knowledge and user expertise.

For the segmentation of bones and tissues of musculo-skeletal districts, statistical methods, such as intensity thresholding and maximum likelihood, do not give reliable results, due to bone overlapping and smooth intensity changes. Region growing is sensitive to the seed points and can merge bones if they are separated by weak boundaries. Watershed segmentation can result in oversegmentation if the image is noisy or if a structure has zones with different intensities. Deformable models [47] (e.g., snakes, bubbles, and geodesic active contours) require the user interaction for a proper initialization and generally perform well on the wrist sector. For the segmentation of soft tissue, Baudin *et al.* [4] report an automated random walk algorithm with prior knowledge applied to 3D (voxel) muscle segmentation from MRI images. Malattia *et al.* [32] applied an automatic method based on statistical segmentation (e.g., maximum likelihood) to detect synovia volume (i.e., swelling detection) in 3D MRI images. Langs *et al.* [29] developed an automated method that has been applied to X-ray projection to compute joint space value.

3.1.2. Morphological analysis of segmented images

Literature on 3D semi-automatic erosion detection is mainly focused on algorithms' validation against a reference value, obtained by the Omeract-Ramris scoring system [7]. Semi-automatic procedures aim to improve the reproducibility and sensitivity of the semi-quantitative scoring systems [40], and different methods [8, 14, 31] have been validated on images and on surface meshes. High or low field MRIs can be used with negligible differences on erosion detection [19]. Leung *et al.* [31] proposed a global measures (e.g., volume) for monitoring the erosion progression. Comparing a sequence of bones acquired at different times with a reference atlas, they found an unexpected volume fluctuation in time, which does not identify a clear erosion as a matter of an inaccurate identification of the boundaries of segmented bones.

In [18], a semi-automated analysis of the carpal bones district from CT images is based on a segmentation that starts with a manually seeded edge detection and progresses with an automated active contour method. Multiple iterations of the active contour method on each slice produce the final segmentation. Indeed, the expert judgment has a crucial role in the discrimination of anatomical structures, especially if they are separated by weak boundaries. Local assessment is performed by monitoring only specific regions, which are identified as lesions. Cartilage damage assessment, which is useful for the early stage detection and monitoring of the disease, can be performed through the analysis of its thickness.

To train users of Omeract-Ramris, Ejbjerg *et al.* [19] developed an atlas with example images for the semi-quantitative scoring of synovitis, bone oedema, and erosion. Moving towards computeraided assessments, Bird *et al.* [7] investigated the inter-reader reliability of computer-assisted (manual) erosion volume measurement in patients with rheumatoid arthritis and compared the results with the existing Omeract-Ramris scoring system. They found a strong positive correlation between the total erosion volumes and scores for all acquisitions, and a positive agreement between the manual evaluation of volumetric erosion by OsiriX [1] and the Omeract-Ramris classification. However, the inter-reader reliability was not sufficient to perform consistent multi-center studies, at least without a prior and homogeneous training of the users.

3.1.3. Rheumatoid arthritis: stages and features

We briefly report [50] the evolution of rheumatoid arthritis (RA), identifying those aspects that have a clinical interest and can be detected by image analysis. RA is a chronic systemic disease that involves soft tissues (e.g., synovial tissue), cartilages, and bones of the peripheral joints. The temporal evolution of the disease is non linear and the disease stages evolve from reversible to permanent, depending on the involved structures. The early stage of RA involves synovial tissue, with a change in its properties that cause a subsequent contamination of cartilages and bones. The bones inside the synovial capsule are partially covered by cartilage and present bare zones in direct contact with the synovial layer, which are sites of the first stages of erosion.

The capability of the acquisition methodology to accurately discriminate among bones and surrounding tissues is crucial for the quantitative assessment of bone erosion in RA. MRI images show a good contrast both for bones and for soft tissues in their immediate neighborhood, thus



Figure 2: (a) Segmented wrist district, (b) baseline (orange) and follow-up (grey) data, (c) co-registration. (d,e) Identification of local erosions of single bones and (f) eroded volume. The colormap varies from blue (lowest distance) to red (highest distance).

allowing an accurate detection of erosion even with respect to CT [23], [22], once an accurate definition of "erosion" has been provided [24]. Indeed, MRI can be assumed as a reference acquisition technology for RA diagnosis and monitoring, due to its ability to detect early stages [23] and local erosion with respect to CT [16].

RA stages can be divided into two groups, with or without effects on the geometry of hard structures, such as bones and cartilages. In the first group, we include early stage inflammation, synovitis, and effusion; in the latter group, we consider the joint space narrowing and erosion. *Early stage inflammation*, visible as an hyperemia, and *synovitis*, characterized by swelling and effusion, are detected by contrast-enhanced MRI [11]. These stages can regress completely and can be correlated to subsequent erosion [26]. *Effusion* is generally detected with contrast-enhanced combined MRI sequences and with ultrasound. *Joint space narrowing* is a symptom of disease progression caused by cartilage destruction, which consists in a reduction of the distances between adjacent bones in a joint [37], and is considered at the boundary between the two groups. *Erosion* of cartilage and bones is detected with MRI, CT, and US, and consists of a local loss of material in a bone. *Massive erosion* leads to relevant volume changes, bones destruction and creation of intra-articular loose bodies by cartilages and bones fragments.

The Rheumatoid Arthritis Magnetic Resonance Image Scoring (*Ramris*) for the evaluation of RA has been defined by the Outcome Measures in Rheumatology Clinical Trials (*Omeract*) [7]. This semi-quantitative system standardizes the acquisition technique for RA images and the scoring criteria. Synovitis, bone edema and erosion are evaluated separately. Synovitis is assessed on a scale from 0 to 3 (none, mild, moderate, and severe), edema on a scale from 0 to 3 (none, one



Figure 3: Local erosions of two wrist districts.

third, two thirds, and full), and erosions on a scale from 0 to 10 (none, 10%, 20%, 30%, ...) and on radiological appearance. Low field MRI scanners are used for this purpose, as their diagnostic adequacy was demonstrated in [20].

In a semi-quantitative method based on discrete scoring systems, a small change in the image appearance can result in a change of score (if the original score is near a threshold), thus reducing the ability of the system to detect small changes (e.g., between two different populations in an epidemiological approach), and requiring large populations to observe significant results. Results obtained by user-based methods suffer from the influence of intra- and inter-observer agreements. Ramris scoring system suffers from both these aspects.

A main open issue is the inclusion of patient-specific anatomical data and information to support clinical trials. iPad [44] extends the functionality of the popular image viewing platform OsiriX [43] for adding semantic tags from the RadLex ontology [28] to 2D acquired images through a simple user interface. However, the process is mostly manual and can only support the annotation of DICOM images. The Medico system [48] applies an 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[42]/ICD10[51]/RadLex[28]. However, this approach is applicable only for CT data sets of human torso, and verified only within a small set of sample images. 3DSlicer, a medical image visualization tool [35], attempts to annotate the organs segmented from images by a hierarchical structure of pre-defined anatomical labels to provide a flavor of semantic annotation of patient-specific data.

3.2. Morphological analysis for semantic annotation

The input to our process is a set of low-resolution and up-sampled MRI images of complete joints, which are segmented with a geodesic active contour method [13] and are associated with a semantic label. For the carpal bones of the wrist district, the labels are: capitate, hamate, lunate, pisiform, scaphoid, trapezium, trapezoid, and triquetral.

For the analysis of a single exam (e.g., bone or complete joint), intra-bones distances are computed on the basis of anatomical atlases, where couples of neighbor bones are identified in the joint by the corresponding entries of an adjacency matrix (Figure 1c). The *intra-bones distance* between two adjacent bones X, \mathcal{Y} is computed as $d(X, \mathcal{Y}) := \max\{d_X(\mathcal{Y}), d_\mathcal{Y}(X)\}$, where $d_X(\mathcal{Y}) := \max_{\mathbf{x} \in \mathcal{X}} \{\min_{\mathbf{y} \in \mathcal{Y}} \{||\mathbf{x} - \mathbf{y}||_2\}$ is the one-side Hausdorff distance. Each distance is then stored and compared with the following acquisitions to evaluate the joint space narrowing.

For the analysis of series of exams, we perform a shape registration and a local distance evaluation to identify shape changes and eroded regions. To avoid errors related to the joint mobility, the shape registration (Figure 2(b,c)) is achieved by minimizing the ℓ_1 norm of each couple of corresponding bones, through an iterative closest point algorithm [5, 15]. For the detection and quantification of local morphological variations (e.g., erosion) on a bone with respect to its baseline, we apply the two-side Hausdorff distance computed between the co-registered shapes. For each vertex of the baseline surface (Figure 2(d,e)), the distance of the closest vertex of the followup surface is rendered according to a color map, where blue and red identify small and large distance values, respectively. Exploiting this correspondence, a set of "eroded parts" is built on the baseline shape by coupling the vertices of each triangle of the baseline surface with the corresponding closest vertices of the follow-up surface. Then, the volume of each eroded part is computed and gives a quantitative local information that is less affected by the global variability of the pipeline (Figure 2f). This information on the position of the eroded regions (Figure 3), their area and volume variation is annotated in the segmentation. In Figure 4, we show the annotation of the bones of different patients and identification of morphological features (red regions) associated with a different level of variation with respect to the corresponding baseline. Each level is annotated together with its region. The color coding and the 3D model facilitate the inspection of the annotated areas by the medical doctor.

Pipeline repeatability assessment on the hand-wrist district. To evaluate the variability associated with the user-guided segmentation process, we consider a set of low-resolution MRI images (0.20 Tesla, $256 \times 256 \times 104$; x, y, z spacing 0.55 mm, 0.55 mm, 0.60 mm). Considering the voxels' dimension, the relative errors for intra-bones distance and global volume evaluation are about $\pm 15\%$ and $\pm 25\%$, respectively. Inter-observer and intra-observer agreements of global bone volume computation were evaluated with a data set of 117 and 32 bones, respectively. Three expert users segmented all the bones, and results were compared and analyzed by Bland-Altman statistics [9]. Inter-observer agreement analysis for each couple (user_i vs. user_j), i, j = 1, 2, 3, gives biases and confidence bounds ($\pm 1.96 \cdot \sigma$) of $-0.5 \pm 20.0\%$, $-18.1 \pm 27.2\%$, $-11.1 \pm 29.6\%$. Intra-observer agreement analysis gives limits of agreement ($\pm 1.96 \cdot \sigma$) of $-3.2 \pm 19.5\%$ for user₁, $0.7 \pm 16.5\%$ for user₂, and $-4.2 \pm 13.3\%$ for user₃, user₂. Given the geometric complexity and scale of the wrist sector, we conclude that this variability is due to the image quality; in fact, these results are in agreement with the evaluation of the relative errors based on image.

Follow-up volume variation and joint space narrowing. A set of 120 bones (15 wrists), segmented by an expert in rheumatoid arthritis and acquired from 5 different patients, was analyzed to check if the global bone volume and the intra-bones distance (related to joint space narrowing) can be correlated to the disease evolution, in terms of erosion progression, assuming that erosion produce a global volume reduction. For each bone, volume variations are computed with respect to the



Figure 4: (b,c) Annotation of the bones of different patients and identification of morphological features (red regions) (c-e) associated with a different level of variation (a) with respect to the corresponding baseline. Each level is annotated together with its region. The color coding and the 3D model facilitate the inspection of the annotated areas by the medical doctor. To avoid the over-smoothing of the surfaces, due to light conditions, the light is not used for the rendering of these results. 14



Figure 5: (a) Bones volume variations and (b) joint space narrowing for each follow-up exam for carpal bones. V_i and D_i are the volume and distance at the *i*-th temporal acquisition, respectively.

baseline acquisition (earliest exam); a negative value indicates a reduction in the bone volume. Results are dispersed (Figure 5a) and the mean value for the volume variation is $(+1.76 \pm 10.71\%)$. Checking for statistical significance of results, we found a p = 0.89, a value which reflects the difficulties of operating on complex and low-resolution data already noted in the data variability analysis.

Intra-bones distance variations were evaluated on the same data set, to check if this measure is able to track the joint space narrowing evolution (connected to bone erosion, also in the early stages of the disease), assuming that the intra joint distance decreases in time, as typical of the rheumatoid arthritis. On the basis of an anatomical atlas, the adjacency matrix for the wrist sector (Figure 1) was used to couple neighbor bones. Figure 5b shows the mean distance variation for each wrist sector with reference to its corresponding baseline exam. Each point on the graph represents the mean of the distance variations of a complete joint acquired at a time following the baseline, and the corresponding confidence bound. The global mean value $(\pm \sigma)$ is $-5.3 \pm 8.1\%$. Also in this case the check of statistical significance is critical, as we obtained a p = 0.64.

Morphological analysis of up-sampled MRI images. Image up-sampling allows us to achieve a more accurate segmentation and quantitative analysis of morphological parameters of segmented 3D anatomical districts from low field MRI images, reduce the effect of volume variability, and improve the consistency of the results for follow-up data. To this end (Figure 6), a MRI image $128 \times 128 \times 51$ has been up-sampled to a finer $256 \times 256 \times 102$ resolution and the comparison is conducted setting the same segmentation parameters for the low- and high-resolution images. The segmentation algorithm works better on higher resolution images because it penetrates higher frequency features more easily and can reach the segmented object boundaries more closely. Main improvements (Figs. 3, 7) after up-sampling include a higher precision along contours (from left image) and less smoothed bones (right image). Due to a higher precision in the identification of the seed voxel used by the segmentation with geodesic active contours, we avoid segmentation errors, such as the spurious connected components (first upper bone on the right), induced by a



Avid Mew P Zoom: 6.92 Side: 287

(b) $256 \times 256 \times 102$

Figure 6: Single bone segmentation. Two views (a) of a slice are compared with the two corresponding views (b) of the up-sampled image. The image up-sampling facilitates the selection of the seed points of small bones and tiny cartilage for a more detailed and reliable segmentation based with the geodesics-active contour.

wrong selection of the pixel seed used for the segmentation of the low-resolution image.

The morphological characterization of segmented data is general enough to be applied to different anatomical districts for the identification of artifacts in the acquired data, the analysis of the effects of degenerative pathologies of soft and bony tissues, and the localization of shape variations due to posture. Initial tests have been performed on knee sectors from low field MRI images (0.25 Tesla; x, y, z spacing: 0.70 mm, 0.70 mm, 0.90 mm), acquired at two different postures, with a joint angle of 0° and 80°, and segmented by an expert. The evaluated variation of the intrabones distances on two scans of the knee district of four patients shows a homogeneous reduction ($-24.0 \pm 22\%$) for the 80° posture with respect to the 0° posture. The distances between adjacent structures is mapped on the bones and the quantification of their variation is useful to characterize different diseases, such as cartilage destruction or other pathologies involving a geometrical modification of the joint structures.



 $128 \times 128 \times 51$



 $256 \times 256 \times 102$

Figure 7: Segmentation of an MRI 3D image: coronal view to the left side and 3D rendering to the right. The upper image corresponds to a volume with resolution $128 \times 128 \times 51$, whereas the lower image is its RBF up-sampled version, with resolution $256 \times 256 \times 102$.

4. Workflow for the morphological analysis and annotation of biomedical data

The previously described analysis for the identification and annotation of morphological variations of bones and tissues that might have clinical interest on a single exam and for the analysis of patient follow-ups can be performed according to specific processing pipelines. Generally speaking, the detection of anomalies can be achieved considering the following main steps:

- 1. Acquisition of MRI images
- 2. Image segmentation
- 3. Creation of a 3D model of the district
- 4. Semantic annotation of the bones
- 5. Post-processing

- (a) Morphological analysis
- (b) Feature annotation
- (c) Parameter extraction
- (d) Semantic annotation of the bones with the extracted parameters

In case of follow up evaluation the main steps to be performed are partially the same:

- 1. Acquisition of MRI images
- 2. Image segmentation
- 3. Creation of a 3D model of the district
- 4. Semantic annotation of the bones
- 5. 3D model comparison
 - (a) Shape registration
 - (b) Local distance evaluation
 - (c) Semantic annotation of the bones with the extracted parameters

A clear and formalized definition of such pipelines, which indicates the tools to be applied, can offer a valid support to clinicians to better achieve useful results for the diagnosis. In this work, researchers can also benefit of such a formalization by understanding at which steps they can improve the process or reusing already developed tools. To this aim, we exploited the organization and capabilities provided by the Virtual Visualization Service (DSW.v5, [3]) of the VISIONAIR Infrastructure⁷. It is a well recognized infrastructure in the international computer graphics community; it consists of web available repositories of shape models and catalogue of resources for their processing organized and documented using ad hoc ontologies. For the formalization, we adopted the Workflow Ontology (WO), in which two subclasses have been created, WorkflowStatic and WorkflowExecutable, for the instantiation of documental (that are static) for best practices, and executable workflows, which directly allow the execution of sequences of software procedures on shapes. Static workflows are meant as sequences of at least two activities that are elements of the Activity class. Simple activities, i.e. corresponding to a single functionality, can be grouped in macro-activities when they contribute to a unique logical action, which is normally performed by using the same software system. They are elements of the SimpleActivity and MacroActivity classes, respectively, both subclasses of the Activity class. Indeed, steps 1 to 5 should be encoded as MacroActivity, while steps 5(a), 5(b), and 5(c) are SimpleActivity. In addition to provide useful information, each activity can be described in more details by specifying additional information: hints and constraints on the correct performing of the activity can be provided as instances of the Tip and Restriction classes of the ontology. Tips and Restrictions can be referred to the general criteria or to the use of specific tools for performing the specific activity. In our case, tools of interest are those provided by the I-REUMA Partners. Indeed, in the DSW.v5 tool repository, we inserted the information related to

• *RheumaSCORE* from Softeco/Esaote for the image segmentation and 3D model reconstruction;

⁷http://visionair-v1.ge.imati.cnr.it/workflows/



Figure 8: One of the created static workflows, showing the important processing steps for the bone annotation.

- *Morph-Annotator* from IMATI for the computation and annotation of the (i) inter-bone distance, (ii) erosion variation, (iii) rugosity (i.e., measure of small-scale variations of amplitude in the bone surface); and
- SemAnatomy3D from IMATI for the semantic annotation of bones and anomalies.

Moreover, new instances of functionality have been added in the DSW.v5 tool ontology to include those necessary for the MRI processing for rheumatoid arthritis detection and monitoring. Figure 8 depicts one of the workflow created, showing some of the metatada associated to the Part-based semantic annotation. In addition to the formalized workflows for the detection and annotation of bones and their significant morphological characteristics, two recurrent pipelines for the geometric model enhancement, which is required when 3D digital models are created from acquired data (e.g. from laser scanner or from 3D imaging), have also been formalized and defined as executable workflows. The first includes the following steps: 1) cleaning of data; 2) mesh smoothing and reconstruction; 3) simplification; while the second considers: 1) sampling of data; 2) meshing; 3) simplification; which for further usage flexibility, we also made available as single web services. The services included in the repository are described by a set of specific metadata, which are used to properly combine the selected services in a workflow. Figure 9 shows the web page for the access to the single processes.

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Figure 9: List of the single web services made available for 3D geometric model enhancement.

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