Technical Report

Front- end functionalities of Decision Support and Diagnostic Data Analysis Services in Heart Failure Management

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Foreword

This technical report details the activity carried out within the European Project HEARTFAID, a knowledge based platform of services for supporting medical-clinical management of the heart failure within the elderly population.

The main focus of the document is on the needs of end-users of the HEARTFAID platform, as well as the functional specifications of the platform of services.
HEARTFAID platform offers a number of services aimed at supporting different categories of end-users: clinical decision support system; inferences on knowledge base and patient data; explanation system that describes the reasoning performed by the inference engine; knowledge base consultation; pattern matching on patients' historical data, extraction of useful information from diagnostic data consisting in signals and images.
In this document, the set of high level services necessary to both interact with the decision support and diagnostic data analysis tools are discussed, including the management of the image archive.

After introducing the main aspects of end-user functionalities definition, the different categories of users are discussed by describing a practical situation, the so-called echocardiography workflow scenario which covers the clinical course leading from visit scheduling to therapeutic choices, highlighting the intervention and the value added by the decision support service.

Then, a summary of the peculiarities of data processing and decision support services is reported, emphasizing how they respond to HEARTFAID users needs.

Finally, the functionalities supplied to the front-end are introduced by discussing data analysis, decision support tools and the interactions with the image archive.

1 Introduction

HEARTFAID aims at defining a platform of services based on efficient and effective health care delivery organization and management models for the “optimal” management of heart failure (HF) patients.
The core of HEARTFAID platform (HFP) is constituted by a Clinical Decision Support System (CDSS) based on knowledge representation and discovery analysis, guidelines formalization, and inferences on patients’ clinical data.
CDSS main goal is to support, at decisional level, the HF health care operators, by making more effective and efficient all the processes related to diagnosis, prognosis, therapy and health care personalization of the HF patients.
Since diagnostic imaging and biomedical signals have a prominent role in diagnosis and prognosis processes, services for signal processing and image analysis are integrated with the aim of extracting objective representation features, both classical and innovative, to be exploited by the CDSS.

All HFP services should be opportunely integrated to provide a unified HEARTFAID access point for all users. The front-end of the platform, represented by the end-user graphical interface (GUI) is in charge of all the interactions and communications with the users. The actual value of the system as perceived by the users heavily relies on the usability of the GUI.
Given this level of responsibility, the interface must deal with factors related to human interaction, accessibility, erase of use, user skill level, error capture and reporting, and issues related to documentation.
This is true in general, but when dealing with clinical practice the front-end functionalities become even more important. In this sense, the consistency to the practical needs of medical professionals is a fundamental requirement for the acceptance of the CDSS in practice. The user interface should then presents all the HFP functionalities in a proper and integrated fashion that will require the users neither too much learning nor relevant changes to their routine activities, while meeting their needs as much as possible.
For responding to these requisites, the peculiarities of CDSS and data analysis services ought to be detailed and discussed along with the front-end functionalities of the same services.
A reference scenario turns out useful for better illustrating such functionalities in practice: an echocardiography workflow is then introduced in the following section.

2 End-users needs analysis

Many groups of people will be affected by the services that HEARTFAID offers. These groups have been individually identified and classified into user profiles, to assist in user rights and accessibility management. The requirements of each user profile are studied separately and the facilities to be offered are based on the conclusions drawn from this analysis. The distinct stakeholders and the examination of user needs are presented below. Such information has been extensively reported in the previous technical reports.

In this section, a real scenario is described for illustrating the different users and the HFP services with a practical situation.

2.1 Echocardiography Workflow: the life of Pietro Guarneri in the HEARTFAID age

We consider Mr. Pietro Guarneri, a 65 years old patient, former smoker, suffering from hypertension from several years. Five years before he had an Acute Myocardial Infarction and he underwent to aorto-coronary bypass. The patient had a post ischaemic dilated cardiomyopathy, with a systolic dysfunction. The patient was enrolled in the platform six months ago and during this period he has been telemonitored. He referred slight limitation of physical activity, comfortable at rest but ordinary activity resulted in fatigue and dyspnoea and he belongs to NYHA class II.

The TTE (*transthoracic echocardiography*) examination showed an LV EF (*left ventricle* ejection fraction) of 40%, ESV (end-systolic volume) of 114 ml, EDV (end-diastolic volume) of 190 ml, and SV (Stroke Volume) of 76 ml, the LV end-diastolic diameter 6.0 cm.

The patient was treated with ACE-inhibitor, beta-blockers, spironolactone, aspirin and statin. Neither pulmonary nor systemic congestion signs were present. Blood examinations of renal function and electrolytes were normal. As mentioned previously, during these six months, the patient has been telemonitored. In particular, the pharmacological therapy has been followed with care and no relevant changes have been identified by the platform.

Present situation

Suddenly, the patient observes a worsening of its symptoms, with a marked limitation of physical activity. After he completes a periodic questionnaire suggested by the platform (based, for example, on Minnesota questionnaire) the change in the symptoms is automatically detected and found relevant. Minnesota Questionnaire score is 52. A medical visit is proposed and performed immediately.

At the visit the NYHA class changed from II to III. No changes in the signs is observed by the physician, apart from a slight worsening of blood pressure (150/90 mmHg) and a heart rate increased of 10 beats. After an ECG is performed that confirms the increase of 10 beats in the heart rate. The physician, supported by the CDSS, decides however to evaluate other parameters by echocardiography. TTE is performed during the visit and a list of parameters is evaluated and images are analyzed by the sonographer.

After the examination is performed, the images and the parameters manually computed by the sonographer are uploaded in the platform.

Left ventricle volume and ejection fractions are computed again by automatic methods, exploiting the available image sequences. They are compared with the historical data of the patient.

EDV increases to 210 ml, ESV increases to 145ml, SV is 65 ml, EF decreased from 40% to 30%. Mild tricuspidal insufficiency is Doppler-detected by its regurgitation. By tricuspidal regurgitation entity, the pressure gradient (mmHg) between right ventricle and right atrium is measured. Pulmonary pressure was then estimated. With this aim the subcostal view is taken into account; so as to determine Inferior Vena Cava (IVC) diameter and its collapsibility index. Collapsibility index refers to the inspiratory response of the IVC diameter and is defined as the decrease in percentage of the diameter.

The pulmonary pressure is estimated to be 40 mmHg by using a lookup table with entries consisting in the tricuspidal gradient, IVC diameter and collapsibility index. Since this value indicates a sligth pulmonary congestion, the CDSS suggests to the physician to integrate the pharmacological therapy with diuretics, for example loop diuretics or thiazides.

Since in the last month there are no up-to-date information about the renal function and electrolytes, the CDSS suggests a safe low dosage and to perform blood examinations, which are scheduled for few days later. The therapy consists in loop diuretics, for quicker beneficial effects.

The patient returned to his home and continues to be monitored in the subsequent days. In particular control of weight, urine output, blood pressure, symptoms are scheduled daily and after the first week of treatment, blood examinations are requested to the patient.

The blood examinations, after the first week, are uploaded to the platform. An up-titration program for the diuretics is compiled by the CDSS, considering in particular symptoms and electrolytes balance, creatinine clearance, blood pressure, weight slope and urine output. Control of weight and urine output is daily scheduled and blood examinations every week.

After review and approval by a physician, the up-titration program is sent to the patient. A visit is scheduled in one month, to appreciate the response to the therapy.

During the first week of this month the patient is monitored, he has persistence of symptoms, thus he follows the up-tritation program of diuretics and for the other part of the month symptoms get better until the visit. During that visit, the patient feels better and the symptoms are relieved, so NYHA class is moved back to II. However, the CDSS suggests to the physician to explore the possible origins of the change in the symptoms reported in the previous visit (the probable cause of heart failure decompensation). In particular with the aim of controlling the ischaemic disease, a stress test is scheduled.

3 The HEARTFAID services

In this section, a summary of the peculiarities of HEARTFAID services for decision support and diagnostic data analysis is provided, highlighting the consistency with the users needs.

3.1 Data processing and feature extraction

The HF platform will enable collection of large amount of different patient data. Besides data describing patients at the first visit (patient enrolment), the platform will collect also patient data during follow up visits, including the findings of several diagnostic tests (e.g. echocardiography, ECG, Holter…) and, whenever possible, the associated raw data (e.g., respectively, ultrasound images, chunks of ECG recordings, RR intervals…).

Especially relevant is the fact that HFP will enable collection of relevant continuous monitoring data like heart rate, weight, body temperature, respiratory rate, and water content.

In respect to such data set the platform will be a unique source of valuable information about HF patients. The results of the analysis of the collected data will be used for the constant improvement of the platform's knowledge base that is used by the decision support system. But the results could be relevant also in the broader sense for better understanding of the disease in general and as a starting point related to different research activities.

In this setting, signal and image processing represents a fundamental tool for the automatic or semiautomatic data analysis and for the extraction of features relevant to knowledge discovery purposes.

Further, of course, signal and image processing may provide methods for the computation of parameters which are often manually computed and whose interpretation can then be readily performed by a physician. Thus, signals and image processing is useful to speed up diagnostic procedures, while, at the same time, reducing intra- and inter-observer variability through the use of automatic or semi-automatic methods.

In summary, data processing and feature extraction services in HEARTFAID have a twofold goal: from one side they focus on data extraction and analysis for knowledge discovery purposes (as described in Section 3.1.1 below), while for the other side, they should provide tools for feature extraction from raw data by signal and image processing methods, as described in Section 3.1.2.

3.1.1 Data extraction and analysis services

The most relevant task of the data extraction and analysis service is to enable user directed access to the collected data and to data in the form appropriate for the subsequent analysis. Data extraction is based both on the subset of attributes (i.e. laboratory assessment, medication, changes in CHF status) that have to be analysed and on the subset of examples (i.e. patients older than 75 years that are in NYHA class 3 and have ejection fraction less than 40) that are set of examples for which the analysis if performed. Optional conditions for data extraction may be the location and time of data collection.

In the data extraction service the special attention must be devoted to the preparation and transformation of temporary related data. It can be noted that not only continuous monitoring data are temporary related. Actually the majority of the data collected by the platform are time related sequences of the data because most of the patient information is recollected at each visit (therapy, physical examination, laboratory assessment, chest X-ray and so on). The data analysis process must enable analysis of the changes in the data sequences (significant increases and/or decreases of constantly monitored data, patient worsening status, changes in therapy) but also this properties must be allowed to determine selection of the patient subpopulation that is analysed (patients that during follow up changed from NYHA 2 to NYHA 3, patients that stopped taking some medication).

In general there are significant differences between sequences of continuously monitored data and sequences collected at visits to specialized institutions. The former are long numerical sequences with more or less constant time difference among samples. There is small or no significance of a single measurement. In contrast to that the later are short (with 1-8 samples), with variable distances among samples and high importance of each sample. Analysis of long sequences must be based on statistical properties where the major problem is the selection of the time interval in which analysis will be performed. Short sequences should be analysed primary on the bases of the differences in detected or measured values in subsequent visits.

Special, but very important subtype of data extraction is when we want to analyse causes or consequences of some important events. For example, events can be decompensation, changes in NYHA class value, or changes in therapy. In this case we are interested especially in the time interval before the event (i.e. in case of worsening) or after the event (i.e. in case of medication). Such analysis requires very complicated data transformation process and complicated user interface. It is a relevant research task to determine if there is a possibility to include also such data extraction options into HF platform web-based interface.

It is assumed that in principle the data analysis process itself will be performed outside the platform with tools most appropriate for the goals that the user has to achieve. But there is a possibility that the platform itself enables some data analysis. At the basic level it is statistical analysis of patient characteristics for the selected subpopulation. Significantly more complicated is implementation of data mining tools for the knowledge extraction purposes. The HF platform will have the possibility that the data prepared and extracted by this service directly enter the knowledge discovery process under the web-based control. Moreover, the presentation of the results obtained by such analysis will be also web-based.

3.1.2 Signal and Image processing services

Signal and Image Processing (SIP) services aim at extracting in an automatic or semi-automatic fashion parameters useful in other components of HEARTFAID platform, e.g.:

- Parameters to be inserted directly into the platform as a finding of some examination (for example left ventricle ejection fraction from US images or heart rate variability from RR intervals in a Holter recording)
- Parameters needed to activate some type of reasoning/inference in the CDSS (for example, if inference on the knowledge base shows that the computation of parameter *X* may break ties during a diagnostic task, then SIP services are invoked to compute parameter *X*)
- Optionally, parameters to be computed off-line for knowledge discovery purposes

Since SIP services have many connections with other HFP components, their integration requires special care. In particular, since some image processing algorithms will be only semi-automated, easy-to-use interfaces should be implemented to allow for user interaction and feedback.
The situation is best explained through the following example, taken form echocardiography workflow and regarding the computation of left ventricle ejection fraction.

An over-reading sonographer would like to compute the left ventricle ejection fraction. The first point to be addressed is access and selection of the data on which some kind of processing should be performed. In this case, the sonographer will have very likely to choose an image sequence taken from an apical two or four chambers view.
Therefore, among the bunch of images and images sequences (about 20/30 instances in our validation sites) contained in an echo examination, he needs to choose quickly the right one for his purposes. Since image quality is not important for this preliminary selection, low resolution images are enough so as to prevent tedious long data transfers (the full examination may require 100Mb).
Supposing that the examination is already stored in an archive in a structured format, the selection task could be accomplished through a web interface (see Section 4.3.4 for topics concerning interaction with the image archive through the web).
Then, the sonographer will need to run a segmentation algorithm on the selected image sequence and appreciate its results. For this purposes, he needs higher resolution images that should be transferred to his client station. Further, very likely, such algorithm wouldn't be able to run within the browser sandbox. Thus, an external application is required. Somehow, the unique identification number of the image sequence selected in the web-browser is passed to the external application.
Only at this point, real image processing starts. Before starting image analysis, anyway, the sonographer may want to perform for example pan and zoom and

contrast enhancement by tools provided in the GUI. A set of algorithms is provided in the GUI among which there is, for example, computation of left ventricle ejection fraction. Clicking on this algorithm, the user is prompted to click on a point in the image belonging to the left ventricle cavity. After that, a segmentation algorithm is triggered. Default parameters and the coordinates of the point selected by the user are passed to the algorithm. When the algorithm stops, the result of segmentation are shown to the sonographer. The sonographer is prompted to state if the result is satisfactory. If the answer is positive, ejection fraction is computed according to Simpson's rule. Otherwise, the user may choose to run the algorithm with manually tuned parameters or, even, decide to manually trace the contour, a last chance to be used in presence of extremely poor acoustic windows or implanted artificial valves. When a satisfactory result is eventually reached, the sonographer should be able to store the segmented image sequence in the image archive for further reference and to insert the computed value of ejection fraction in the eCRF.

This short example sheds light on several features of SIP services: the need of quick data selection tools within a web interface perhaps, the exchange of information between the web interface and an external application in which algorithms eventually run and the interaction with HEARTFAID repositories, namely the eCRF and an image archive.

3.2 The decision support system

Within HFP, an informative and decision support set of services, the HEARTFAID Clinical Decision Support System (CDSS), will be devised for intelligently aiding clinical operators in the daily management of HF patients. Actually, HF routine practice presents several aspects in which an automatic, computer-based support could have a favourable impact. Precisely, four problems have been identified that would highly benefit of HEARTFAID CDSS point-of-care intervention; they can be referred as *macro domain problems* and listed up as: (i) HF diagnosis, (ii) prognosis, (iii) therapy planning, and (iv) follow-up.
Further detailed decision problems have been identified for specifying these macro domains, focusing as much as possible on the medical users' needs; explicative examples are:

- Diagnosis, assessment and severity evaluation of heart failure
- Identification of suitable pathways
- Planning of adequate, patient's specific therapy
- Analysis of diagnostic exams
- Suggestion of changes in management and treatment
- Early detection of patient's decompensation

In order to design and develop an effective and reliable CDSS able of facing such decisional problems, innovative results on computational modelling, knowledge discovery methodologies, visualization and imaging techniques, and the medical knowledge of the relevant domain have to be opportunely integrated. In deed, the core components of HEARTFAID CDSS are

- formalized clinical knowledge, consisting of pre-existing guidelines, experts' know-how procedures, and new elicited knowledge discovered by KDD processes;
- robust and reliable reasoning approaches, based on computational models of *Machine Learning* (ML) and *inference* methodologies on declarative and procedural domain knowledge;
- innovative methods for biomedical signal and image processing.

The decision support services mainly rely on *inferential reasoning* on the available domain knowledge, which has been formalized according to a *symbolic* representation formalism based on *ontologies* and *inferential rules*. However, computational approaches appear also beneficial in most of the problems to be addressed and are currently under development. Actually, mathematical models and ML methods allow for facing those decisional problems whose solution cannot be formalized in *symbolic* representations, owing either to the lack of assessed knowledge or to the characteristics of the problem (i.e. high levels of complexity and variability). In some cases, making a decision requires an investigation on the hidden, complex, often non-linear correlations among data, together with high-level analytical processing functions. In such cases, the knowledge needed for the solution should be acquired directly from data (*inductive knowledge*) and stored in the developed model (e.g. *Artificial Neural Networks* – ANN, *Support Vectors Machines* – SVM), which induce sub-symbolic knowledge from a data-driven processing.
Moreover, the analysis of biomedical signals and images relevant to HF (e.g. ECG, Echocardiography,…) is a peculiar functionality due to the need for providing well-established and defined parameters extracted from the data as part of the inputs to the CDSS. In addition, within a long-term research environment, signals and images processing may provide *novel representation features*, i.e. non-standard parameters that can add more insight in heart failure domain, for example giving new methods for early diagnosis and prognostic stratification.

A better insight into the decision support services can be obtained by analyzing the decision-making problems addressed and the main functionalities of the HEARTFAID CDSS, as summarized in the following sections.

5.5.1 Decision-making problems

Improving the effectiveness and efficiency of HF clinical practice requires the HEARTFAID CDSS to face the main decisional problems as detailed below.

<u>*Diagnosis*</u>
The CDSS will aid physicians in improving their diagnostic performance: even though diagnostic procedures are very well codified in HF Guidelines, diagnostic errors are still present in clinical practice. The CDSS will be able to process patient's status and assess the accordance of patient's symptoms and signs with

the diagnostic criteria. More in general, the response of the CDSS diagnostic functionality will regard:

- diagnosis of HF;
- assessment of HF severity;
- evaluation of patient's current clinical conditions.

The knowledge required consists in the evaluation criteria, specified in the guidelines and in procedural rules elicited from the clinicians. Confidence values will be evaluated and associated to the different passages of the diagnosis, so that more possibilities can be presented to the clinicians, supporting differential diagnosis. Moreover, the CDSS can suggest further diagnostic examinations to be performed, if necessary for reaching a more reliable diagnosis.

Prognosis

Prognostic evaluation is among the hardest decisional tasks in HF management due to the absence of generally agreed operative information. In addition, for each of the possible conditions (i.e. *stable, improving, rapidly worsening,* or *slowly worsening*) both the predictive value and the prognostic evaluation objectives may change. Prognostic stratification during an acute unstable phase, for instance, should guide immediate decisions, while, in a stable phase, it could have a long term aim and should predict destabilization and death in mid and long term.

In this context, HEARTFAID CDSS will formulate patient's prognosis, taking into account the implications of different patient's status. Additionally, it should also help in verifying if the clinical classification of acutely decompensated HF adds prognostic value to the NYHA classification.

Computational decision models for predictive analysis can be required to accomplish this task. Innovative techniques for survival analysis using ML and statistical methodologies should be then provided. Moreover, if new cut-offs and/or reference values for individual, or combinations of parameters will be discovered by KDD processes, they should be suitably encoded into the HEARTFAID CDSS knowledge bases, thus allowing to a further increase of the efficacy.

Therapy planning

HEARTFAID CDSS will suggest, based on guidelines recommendations, the pharmacological and non pharmacological measures that best apply to each individual patient. The number of possible actions and the complexity of the whole context suggest the usefulness of an automatic tool able to remind the available therapeutics options.

In particular, HEARTFAID CDSS should provide assistance in planning the therapy by carefully considering HF aetiology, gravity, physiopathological conditions, and by evaluating interactions with other coexistent diseases and/or drugs taken by the patient. Altogether, the response of the CDSS will regard:

- pharmacological treatment suggestions
- life style modification alerts
- uptritation support
- compliance to guidelines recommendations.

Follow-up

The CDSS is responsible of assuring the adequate follow-up of HF patients by interpreting telemonitored data so as to prevent adverse events and early detect patients' worsening. Telemonitoring will play a key role in such situations by assuring the collection of relevant information inherent symptoms and biomedical parameters (e.g., blood pressure, heart rate, respiratory frequency).

The available domain knowledge will be formalized to allow the CDSS interpreting the acquired data and early detecting patients' decompensation, suggesting changes to the therapy, advising new diagnostic examinations. Among these tasks, the automatic recognition of decompensation events is an absolutely innovative functionality, which will likely benefit from the definition of reliable computational decision models able to process a set of telemonitored symptoms and signs.

The follow-up can be conceived as the overall functioning of the HFP and, hence, represents the most complex problem, which can entail facing all the other problems, i.e. making a diagnosis for assessing the patient's status, planning a new therapy, formulating a prognosis and scheduling new examinations/next visits.

5.5.2 Decision support functionalities

The CDSS supports HF management, i.e. diagnosis, prognosis, therapy and follow-up, by using patients' heterogeneous information (i.e. actual status, anamnesis, clinical history, diagnostic parameters, clinicians' evaluation) and applying two type of reasoning: *inferential* and *computational*.

Inferential reasoning consists in *inductive* and *deductive* reasoning on the available domain knowledge, and it is strictly correlated to the knowledge representation formalism. The fundamental aim is developing a formal description of the domain (i.e. relevant concepts, their properties and interrelations) and carefully formalizing the declarative and procedural knowledge, derived from the guidelines and the experts' know-how. Ontologies combined with rules have been chosen since the more suitable and up-to-date methodology for solving both tasks. Actually, rules-based approach appears the more appropriate, since easily understandable by a non-specialised audience, e.g. clinicians. In this way, they can be more tempted in contributing to the knowledge elicitation and representation processes. An inference engine can then be devised for the corresponding reasoning processes.

Computational reasoning is involved in those difficult HF decision problems whose solution is still debated in the medical community, due to the lack of validated and assessed evidences. It consists of *inductive reasoning* and relies on applying computational decision models, which can be developed according to different methodologies (e.g. ML including *Soft Computing* and *Statistical Pattern Recognition*, or *Linear* or *Constraint Programming*).

Defining ML decision models requires the identification of a set of input parameters for modelling the problem to be faced; a set of *exemplars* of the

problem, and a *training* process for data-driven knowledge extraction. This process relies, in practice, in tuning the *model free parameters,* iteratively until the desired decision accuracy is reached.
Processes involved in the CDSS functioning can be, then, grouped into the following categories:

- *Signal and images processing*, developed for assessing patients' status and acquiring diagnostic parameters. Processes belonging to this category consist of calls to algorithmic procedures, are activated on demand, and might require the user's interaction, e.g. procedure for estimating the ejection fraction in echocardiographic images;
- *Inference,* involved in inferential reasoning, for assessing patients' status, formulating diagnosis and prognosis, assisting therapy planning, and patients' monitoring. Generally speaking, they consist in querying the knowledge base for inferring new facts or new actions to perform, are activated on demand and can involve the users' in interactive dialogues;
- *Computational decision,* concerned with computational reasoning for patients' HF severity and prognosis assessment, and for patients' monitoring. They mainly correspond to on-demand applications of the decision models developed.

The HEARTFAID CDSS architecture has been designed according to a multilevel conceptualization for distinguishing among

- the *knowledge level*, corresponding to all the information needed by the system for performing tasks, e.g. data, domain knowledge, computational decision models;
- the *processing level*, consisting of the system components that are responsible of tasks accomplishment by using the knowledge level;
- the *end-user application level*, including the system components whose functionalities are specifically defined for interacting with the user.

More in detail, the CDSS architecture consists of the following components (Fig. 1):

- *Domain Knowledge Base*, consisting of the domain knowledge, formalized from the guidelines and of the clinicians' know-how;
- *Model Base*, containing the computational decision models, signals and images processing methods and pattern searching procedures;
- *Meta Knowledge Base,* composed by the strategy knowledge, i.e. about the organization of the CDSS tasks.
- *Brain*, the system component endowed with the reasoning capability, which is divided into the meta and object level;
- *Explanation Facility*, providing a means to explain conclusions taken.

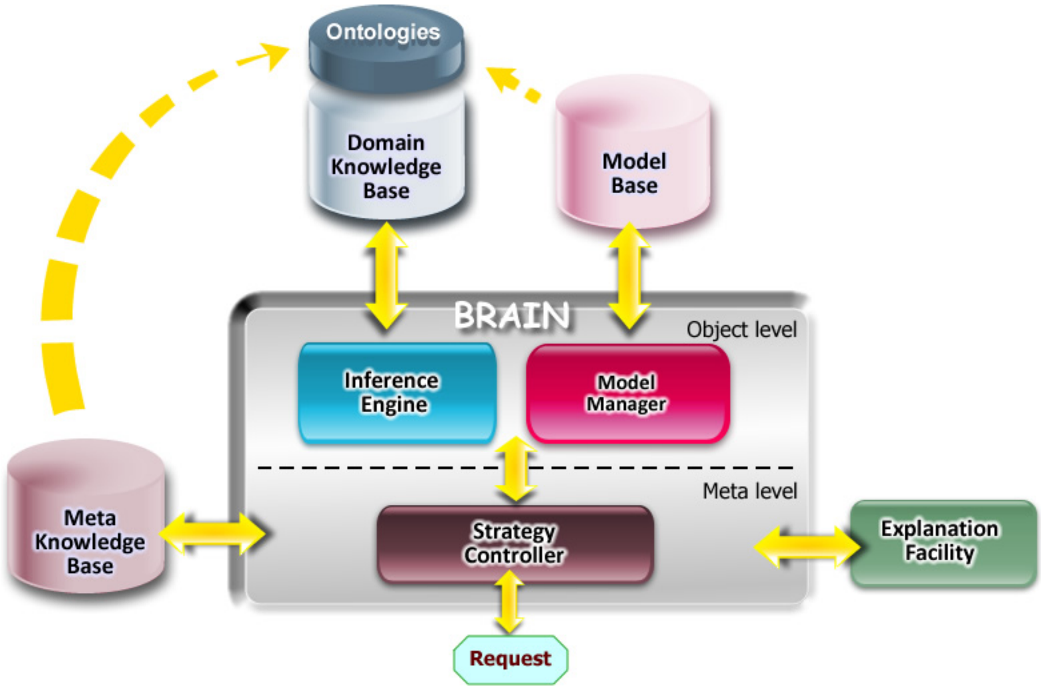

Figure.1. *The general view of the HEARTFAID CDSS architecture – dashed arrows correspond to reference to the ontologies, while the others denote a direct communication*

4 Functional specifications of the HEARTFAID platform of services

The HEARTFAID platform of services encompasses all utilities that have been developed for the users of HEARTFAID. This entails both decision support and data analysis as the core services of the platform. The functional specifications give an accurate picture of the final product that will be developed to address each of these areas. Any decisions that are made in the basis of functional or technical considerations are explained and any alternative courses of action are outlined.
In the following sections, the main functionalities available at the front-end are presented, discussed and exemplified.

4.1 Functional specification for data processing and feature extraction

4.1.1 Signal and Image Processing services

The signal and image processing services will cover the following topics:

1) Complete web-based diagnostic viewing

Physicians may need to have quick access to raw data (US images, ECG recordings…) stored in HFP repositories for reviewing and for selection of particular instances that should be treated in post-processing workflows.

Therefore services for browsing data like image sequences, ECG recordings, RR intervals acquired for one patient or a user-defined group of patients should be provided. The quality of the retrieved data is not a primary concern here and, thus, for example, compressed versions of the images stored in the archive would suffice.

For what regards images, some of these characteristics are implemented in standard DICOM servers, although with some limitations (see Section 4.3.2.2), whereas in electrocardiography the lack of an accepted standard could lead to some complications.

2) Additional integrated application for signal and image processing in post-processing workflows

A part from the previous web based data browsing, it is likely that signal and, especially, image processing will need an additional external application. This application, installed to a workstation, should be able to cover all the issues in post-processing workflow, ranging from data retrieval to actual processing and secure storing of the results. More in detail, the following items should be taken into account:

A) Query/Retrieve of images and signals

It should be possible to query and download images and signals from HFP repositories, with the aim of processing them. In particular, methods for secure data transfer and suitable interfaces should be developed. In the realm of medical images, some standard methods to achieve these results are included in DICOM network services (see Section 4.3.2.1), while for signals (e.g. chunks of ECG recordings) this will be depend tightly on the actual implementation of the repository.

Further, it would be nice to allow for data exchange with the web based interface described in 1). More in detail, particular instances of signals and images selected browsing the data in the web interface should be easy to download in the external application, e.g. without retyping their unique identifiers. This issue may be solved, for example, by including a worklist in the web interface where the user can put the data he wants to review or process. Then, the external application may retrieve this personal worklist for the authenticated user and proceed with data retrieving from the repository.

B) Consistent display of images and signals

The retrieved signals and images should be consistently displayed to be meaningful for diagnostic purposes. In particular, the size of an image, its aspect ratio, orientation and color-map should be exactly the same as seen on the imaging device screen and, thus, these features must be maintained across different monitors.

C) Tools for performing common measurements

Apart from standard visualization tools (e.g. pan & zoom, contrast correction, selection of rectangular sub-region), the external application should provide methods to perform common measurements, such as linear, angular or area measurements on the image domain or on the area of display of a signal, involving some mouse interaction. Whenever possible, the results of these measurements should be converted into physical units; for example, the value of a linear measurement on an image should be converted from pixels to *mm.*

Further, it should be possible to label somehow the computed values, perhaps choosing from a predefined list of tags (for example choosing EDD from a list of tags for LV measurements to denote End Diastolic Diameter of the Left Ventricle).

D) Invocation of signal and image analysis algorithms implemented in the platform

The signals and image processing algorithms implemented in the platform (for example QRS detection from ECG recordings and left ventricle ejection fraction from US sequences as described in HEARTFAID Deliverable 15) should be integrated into the external application. Running this kind of algorithms may require some other user interaction, such as 1) clicking on a particular point in the image domain, 2) stating clearly which data type is being processed (e.g. an apical 4 chambers view *or* an apical 2 chambers view), 3) defining the range of

elaboration (e.g. the starting and end frame in an image sequence) and, finally, 4) setting some internal parameters of the algorithm.
Of course a basic interface should also be provided in which an algorithm runs with the default parameters associated to the data type.

E) Data visualization facilities

Some visualization facilities should be provided both for signal and image processing. For example the result of a segmentation algorithm should be displayed as a superimposed layer to the original image to evaluate (visually) the performance of the algorithm. This also applies to QRS detection and classification algorithms.
Besides it would be interesting to produce also some synoptic tables with the evolution of the patient's data. This could be useful for example in continuous monitoring of RR intervals and the computation of Heart Rate Variability (HRV). The trend of HRV, indeed, is of strong prognostic value. Such synoptic tables are currently implemented in many telemonitoring systems, e.g. in Medtronic CardioSight.

F) Numeric signal & image report

After having completed the processing task (for example after having performed some area measurement), it is important to provide a tool for unambiguous semantic documentation of the diagnosis. Besides information about the scheduled procedure, the observer ID, and links to previous reports, the report should include 1) links text with images, signal waveforms that are used as *evidence* in the report and 2) numeric measurements. The tags of numeric measurements should be intelligible by other components of the platform, such as the eCRF and the CDSS. To achieve this, some kind of universal identifiers, for example those provided by UMLS could be employed.

G) Secure storing of annotated reports

Finally, such annotated report should be securely stored in a repository. Only at this point, the data, contained in a structured and clinically meaningful report, will become available to the other platform components.

H) Secure storing of the results of processing in the form of annotated images and signals

At the same time, the images and signals waveform, linked to the report as evidence document, should be uploaded to a repository. This, apart from enhancing the clinical validity of the report, will allow for data reviewing and follow-up. For example a segmented image sequence should be saved as a DICOM object (carrying thus information about the patient, date of creation, modality, pixel physical units among others) with its own UID and sent to a DICOM server for secure storing.

4.2 Functional specification for the Decision Support Tools

The HEARTFAID CDSS supplies a set of functionalities specifically designed for aiding the clinicians in managing HF patients. Summarizing, such functionalities will allow the users to:

- formulate a diagnosis and exploit the CDSS to confirm it;
- query the system for obtaining diagnostic or prognostic evaluation;
- exploit the system for the prescription of the most appropriate therapy (in deed, the system is able to process all the clinical information about patients, available pharmacological treatments and their contraindication and inadvisability);
- obtain suggestions on patients status and actions to be done for their management.

The user interface is responsible for all the interactions and communications with the users and makes an important contribution to the CDSS value in terms of user productivity and effectiveness. Given this level of responsibility, the interface must deal with factors related to human interaction, accessibility, erase of use, user skill level, error capture and reporting, and issues related to documentation.

In particular, fitting the *routine workflow* of medical professionals is, among others, an important requirement for the acceptance of the CDSS in practice. The user interface should then presents all the HFP functionalities, including the CDSS ones, in a proper and integrated fashion that will require the users neither too much learning nor relevant changes to their routine activities, while meeting their needs as much as possible. This means, for instance, that users should be able to access the CDSS functionalities in an easy and natural way while managing the clinical information of a patient. A strong cooperation with the medical operators may be profitable for understanding their expectations on how the CDSS will support their activities.

From another point of view, the CDSS can be exploited by the clinicians for testing and research purposes, e.g., for exploring the consequences of therapy changes or for analyzing diagnostic examinations to assess new parameters. This implies an explicit intent of the clinicians to query the CDSS that goes beyond the routine practice. We can then foresee two different usages of the CDSS: *routine* and *research workflows*.

From the platform design point of view, the HEARTFAID CDSS component is a resource able to offer a number of functionalities and to interact with the other resources for performing its tasks.

Each decision-making problem, as introduced in the previous chapter, can be translated into a *request* or a *class of requests* committed to the CDSS, which is then activated *on-demand*. The system handles every request according to a specific encoded policy, interacting, when necessary, with the other platform components.

The interactions with the user interface can consist of exchanging messages, which can be made of strings, files, XML encoded files and so forth. After launching a specific command from the user interface, a specifically correspondent request message is sent to the CDSS which starts its processing for supplying a response. In particular, the response can consist of a composite answer that contains:

- a *conclusion*, which pertains diagnosis, prognosis, patient's state assessment and so forth;
- a *list of possible actions* to be undertaken by clinicians which can involve another functionality of the platform, e.g., scheduling of a new visit or new examinations, changes of therapy, repository update and so forth.

In this perspective, the user interface should assure an adequate visualization of the list of possible actions, suggested by the CDSS, and the management of the one selected by the user. To avoid burdening the interface and to increase the ease of requests handling, a specific component of the platform, more precisely of the middleware, should be in charge of activating the CDSS and opportunely handling its responses by transferring the request that corresponds to the action selected by the user to the pertinent platform component, e.g. the *agenda*, the repository management system and so forth.
Three scenarios of possible interactions can be identified:

- *Single request-response*: a request is issued by the interface and the CDSS directly supplies a single final response;
- *Interactive request-response series*: for responding a request, the CDSS requires to establish a dialogue with the user;
- *Execution of interactive algorithms* (*models*): during the elaboration of a request, the CDSS requires the execution of an algorithm, contained in the model base, which involves an interaction with the user.

In the first case, the CDSS does not need any further information to be supplied via the user interface; hence, the communication between the two components is a single step procedure, which ends with the opportune display of the response.
It can alternatively happen that the CDSS requires the user to supply additional information. In such situation, the interface should include a "section" for visualizing the requests form the CDSS and the answers from the user, e.g., a form of possible entries.
In the third situation, the *locus of action* should be passed to an application, contained in the Model Base, which implements a signal or image processing method. Such an application should be equipped with a dedicated, tiny user interface which allows the user to interact by setting some parameters or by graphically working on images (e.g., tracing a line or a rectangle).

For better illustrating the description above, we can consider the management of Pietro Guarneri as described in the scenario in Section 2.1, and point out the various operations involved. The situation falls within the clinicians' routine workflow, so CDSS interventions have to be managed by the platform.

The patient answers a questionnaire through his browser and sends the information to the interface handler that checks eventual missing values. Then the component in charge of managing the platform events (which can be referred to as

event controller – EC) stores this information into the repository, gets historical data and opportunely invokes the specific CDSS service in charge of handling the correspondent request.
The CDSS analyzes data and answers supplying the current patient's status, i.e. worsening of symptoms, and a set of suggested actions the clinician should undertake, i.e. schedule a new visit, change the NYHA class, and change the therapy and so forth. Then EC stores CDSS results into the repository.
When the physician-in-charge logs on into the HEARTFAID platform, the list of patients is displayed ordered by their severity status and the timestamp of the last related event. Then he chooses to analyze the situation of Pietro Guarneri and the change in patient's status is shown along with the list of suggested actions, for instance as a list of operations that can be selected. He then approves the schedule of the visit and the EC forwards the request to the *agenda* component that opportunely records it and informs the patient.
During the visit, the physician inserts his observations into the patient's record and decides to approve the change of the NYHA class: he selects the corresponding action within the list and the EC takes care of registering the change in the patient's record. He performs an ECG for further investigations. Once he submits the information obtained by the ECG, a request for its interpretation is sent by the EC to the CDSS, which suggests performing an echocardiography as displayed in the suggested actions list.

Within the research workflow, a specific area of the user interface can be dedicated to the interactions, it can be a separated window that the user can explore when needed. A list of possible query is displayed along with a set of parameters that the user can select to submit together with the query. The CDSS response can be displayed in the same area/window as conclusion and list of suggested actions.

4.3 Interactions with HEARTFAID Image Archive

4.3.1 Image archive for echocardiography workflows

Nowadays echocardiography is a digital modality, offering the opportunity to coordinate its workflow in an IT framework. When considering echo workflow, we are mainly interested in transthoracic echo (TTE), for its versatility and portability and for its fundamental importance in the management of heart failure patients.

An echo study generally consists of digital images (single- and multi-frame), measurements and an interpretive report.

Images are obtained by a sonographer who may make preliminary measurements and preliminary observations. According to IHE [1], the over-reading echocardiographer must have access to all of this data in discrete, structured format to synthesize a final report.

In an echo lab reached by HEARTFAID, it would be optimal to upload the original images, the annotated ones and the final report to the integrated HFP of services. However, the treatment of digital images, both original and annotated, poses several problems, due to the discrepancy between the ideal hospital (just from an IT point of view, of course) and the situation usually encountered in a real one.

4.3.1.1 Ideal echocardiography workflow

In the ideal situation, the hospital is equipped with a HIS and a PACS dedicated to cardiology and, finally, echocardiography devices are persistently connected to the hospital network. For a patient, pre-admitted and registered in the Hospital Information System before undergoing an echocardiographic examination, a visit is scheduled and demographics and procedure information (for example why the visit is required, which parameters should be estimated during examinations,...) are transmitted accurately to the echo device. After the examination, images are securely stored to the PACS and can be displayed at any imaging workstation. Echo measurements, performed anywhere, are correctly associated and securely stored with the study as discrete, structured data which can be interpreted by another workstation and finally incorporated into a report.

In particular, interoperability is guaranteed among HIS, PACS, Echo devices and various radiology workstations.

4.3.1.2 The actual workflow

In a real-world example, instead, echo devices are not connected to any network. Sometimes, a workstation provided by the echo device vendor and running proprietary software, is associated. This workstation has one (or several) storage units to setup a local picture archive for the echo lab. Although potentially connectable to the hospital or global network, the local archive often can export images only to physical devices (e.g. by CD-rom burning). In most cases, luckily, images are exported according to DICOM standard and, thus, there exists no format problem.

For what regards echo measurements and findings (usually printed to paper and inserted into a patient's folder) cardiologists typically have to retype the information into a separate reporting system, since cross document sharing (XDS) seems not to be feasible (via HL7 export, for instance). Further, review of already annotated images is not possible, since annotation is made through the proprietary software of the echo device.

4.3.1.3 Discussion

Given such a discrepancy between ideal and real world, the HEARTFAID image archive should try to cope with the nowadays IT structures of its validation sites, with a view towards the future that -as far as we can see- will resemble more and more the ideal situation described above. In particular, it is essential for the success and diffusion of the platform to offer:

- State of the art interoperability. In this way, HFP could easily be connected to an ideal hospital IT infrastructure, allowing for the exchange of images, measures, reports, demographics and procedural information directly from the HIS/PACS to HFP and *vice versa*. Notice indeed that whereas original images have of course as source only the echo lab, procedural information and reports will be mediated by the CDSS. For example, CDSS may suggest which kind of parameters is more useful to be evaluated for a given patient during a TTE session. This list could be directly sent to the echo device. In such a way the sonographer has directly on his screen, besides patient demographics (reducing the risk of misspelling in his name), the purpose of the examination. Further some of the measures and annotated images will be produced through image analysis tools provided by the platform; this data may be of interest also for the HIS/PACS.

In such a situation only (though by no means trivial) security/privacy/non-repudiation concerns are left.

- Customizable modules to solve IT infrastructure lacks. In particular, for what regards the image archive, this means to develop methods and interfaces for uploading echo images to HFP and query/retrieve images from the archive.

The rather obvious answer to these two items, at least for echocardiography workflow, is to adhere to standards (namely DICOM) and integration profiles (provided by IHE). The methods offered by the standards, suitably inserted in an interface, allow for image uploading, query/retrieve and review of reports from any workstation also in case of IT infrastructure lacks.

4.3.2 DICOM Servers

Since the 1970s, the emerging idea of a digital image archive (PACS) and electronic image distribution in a hospital created the need to exchange digital images between medical devices of different manufacturers. The American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA) formed a working group in order to develop an image exchange standard. After some first failure, DICOM [2] was released in 1993 to offer an open vendor independent platform for the communication of medical images and related data, supporting PACS networks and guaranteeing interoperability. DICOM standard, which is composed of several parts, is continuously being extended and updated. The last part “WADO” was released in 2003.

It is important to point out that DICOM is not just an exchange format for medical image data. Actually DICOM goes far beyond, defining among several others:

- Data structures (formats) for medical images and related data
- Network oriented services, e.g.:
    - Image transmission
    - Query of an image archive (PACS)
    - Web-access to images
    - Print (hardcopy)
    - RIS - PACS - modality integration

  Formats for storage media exchange Requirements for conforming devices and programs.

For these reasons, any implementation of a DICOM server can't be merely a database of images in DICOM format, since storing, querying, retrieving, web-access are prescribed by the standard.

4.3.2.1 Network Services

DICOM network services are based on the client/server concept. In case two DICOM applications want to exchange information, they must establish a connection and agree on the following parameters:

- Who is client and who is server
- Which DICOM services are to be used
- In which format data is transmitted (e.g. JPEG compressed or uncompressed)

Only if both applications agree on a common set of parameters, the connection can and will be established. In addition to the most basic DICOM service image transmission (the so-called *Storage Service Class* such as C-STORE), several advanced services are available. The following two, for example, may reveal useful in HFP:

- The DICOM image archive service ("Query/ Retrieve Service Class") allows to search images in a PACS archive according to user-defined certain criteria (patient, time of creation of the images, modality etc.) and to selectively download images from this archive
- The DICOM modality worklist service allows to automatically downloading up-to-date worklists including a patient's demographic data from an information system (HIS/RIS) to the modality.

4.3.2.2 Web Services

Users of medical information systems may benefit from rapid and reliable access to reports and images. For example it would be important during an examination to retrieve on the fly reports or even images of the previous examination. Within HFP it is likely that such access will be based on web technologies also for image retrieval and visualization. The access to relevant DICOM *persistent objects* (i.e. images and reports, not logs of workflows) should be either in native DICOM format for advanced use or rendered into a generic format (e.g. JPEG, PDF) that can be presented with off-the-shelf applications. DICOM standard offers the so-called "WADO" (Web Access to DICOM persistent Objects) to answer these needs. It is a web-based service for accessing and presenting DICOM persistent objects, consisting in a simple mechanism for accessing a DICOM persistent object from HTML pages or XML documents, through HTTP/HTTPs protocol, using the DICOM UIDs (study, series, and instances). We refer to [3] for a discussion of WADO and the presentation of several scenarios.

Security Concerns and Current limitations of WADO

Clearly the information contained within DICOM objects may be considered as Protected Healthcare Information (PHI). Thus the protocol used, that is HTTP, can be replaced by HTTPs for that purpose. Further, DICOM standard defines two optional parameters, *anonymize* and *annotation*, which control respectively the absence of patient identification in a retrieved DICOM object and the presence of patient identification burned into the pixel data of images. It is likely, however, that for patient enrolled into HFP personal information will be erased and replaced with an ID (the same used in eCRF) before storing images in the HEARTFAID image archive.

When dealing with echocardiography, one usually deals with multiframe images (i.e. image sequences). It would be interesting to be able to retrieve and visualize multiframe images via a web-based service. However, considering the size of such kind of images, some sort of *streaming* is necessary. Currently, up to the best of our knowledge, no kind of streaming is suggested or prescribed by DICOM standard. In particular, WADO consents the access only to the first frame of a multiframe image.

4.3.3 Beyond DICOM

As we saw, DICOM defines a complex standard to guarantee interoperability among different DICOM compliant devices ranging from DICOM server to radiology workstation, from imaging devices (US, CT, X-ray...) to HIS. Any DICOM compliant device comes with a DICOM conformance statement in which the portion of implemented DICOM features is described. In practice, however, conformance statements are only comprehensible by experts and they are frequently inadequate since often only a minimum set of features is documented. In some cases interoperability problems tend to occur because some inconspicuous details do not go together.

Further, DICOM standard alone is not able to cope with the complex echocardiography workflows described in Section 4.3.1.

To answer these needs, IHE (an initiative by healthcare professionals and industry) [4] tries to improve the sharing of healthcare information by promoting the coordinated use of established standards such as DICOM and HL7 to address specific clinical needs in support of optimal patient care.

IHE Technical Framework defines specific implementations of the afore-mentioned established standards to achieve seamless transmission of information among physicians, medical specialists, nurses, administrators and other stakeholders.

In particular IHE provided a Cardiology Technical Framework [5, 6] (written by the American College of Cardiology (ACC), the Radiology Society of North America (RSNA) and Healthcare Information and Management Systems Society (HIMSS)). Echocardiography workflow is included [1] with the aim of:

- Providing echo measurements interoperability
- Ensuring images and measurements are securely stored
- Uploading echo reports to a repository
- Reconciling patient demographics

In IHE terminology, this is obtained implementing several *actors* (ADT/HIS, Scheduler, Acquisition modality, Image Manager, Evidence Creator). Since there is an obvious relationship between IHE actors and various modules in the HFP related to the image archive, it is at least reasonable to explore IHE Cardiology Technical Framework in the close future. For the moment, it is timely to use a DICOM server implementation which integrates IHE actors, that is, according to IHE terminology, *Image Manager/Archive* and optionally *Report Manager* and *Report Repository*.

4.3.4 Interfacing the Image Archive

4.3.4.1 Current Implementation

From the previous discussion, the good features expected from HEARTFAID Image Archive may be summarized as follows:

- DICOM network services
- Web access to DICOM objects
- Easy development of web interfaces for Image Archive Management
- Easy development of web interfaces for image uploading
- Implementation of IHE actors
- Extendibility to meet HFP needs (interaction with CDSS and Image Analysis Tools)
- Multi-platform or platform independent

Among different open-source implementation (CONQUEST [7], DCMTK [8], DCM4CHE [9]), DCM4CHE, a Java implementation of DICOM, has been chosen according to the previous requirements list. For sake of completeness, an overview of DCM4CHE components is presented in **Errore. L'origine riferimento non è stata trovata.**.

Besides being an image archive, DCM4CHE provides a toolkit of standalone applications and methods to make network communication and interface development easier. Unfortunately, the documentation of DCM4CHE is not completed yet, so it is somewhat difficult to grasp its architecture.

In the current installation, DCM4CHE has an underlying MySQL DB, though other choices (e.g. PostgreSQL) are conceivable. Both the Dicom and MySQL servers accept network connection. Thus it is possible to query directly the DB for low level platform management purposes (e.g. user name, group, password harmonization).

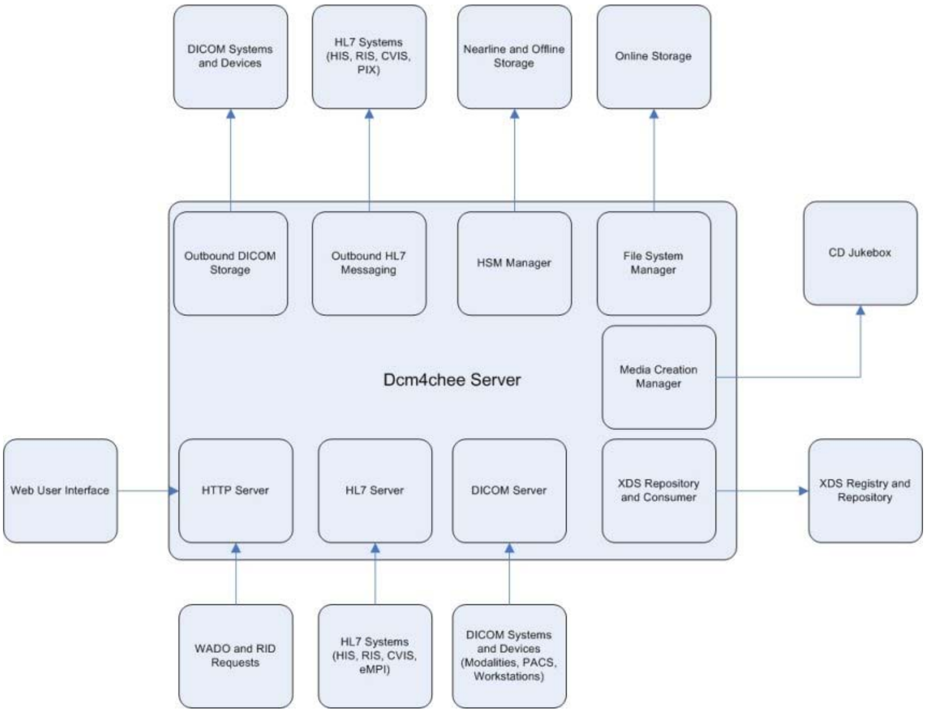

Figure 4.1: Overview of DCM4CHE components

4.3.4.2 Interface for Image Archive Management

DCM4CHE comes equipped with two web-interfaces for Image Archive Management. The first interface allows among others for

- Making queries about patient studies in the DB
- Editing Patient information e.g. for anonymization purposes
- Visualization of images by WADO
- User administration for the management of user name, group, password
- Management of recognized DICOM entities (that is for example name and IP address of DICOM clients that are allowed to retrieve information)
- Audit Record, to monitor the jobs required to the Dicom server

This first interface should be easily modified and integrated into HFP. Harmonization of Patients demographics and user data may be, for example, directly obtained through queries to the DB.

The second interface is a standard jmx-console *Mbean view*, that allows for invoking Mbean operation for internal server configuration and WADO services plus archive management procedures. As such, it is not necessary to integrate it into the platform, since it mainly addresses archive administrators.

4.3.4.3 Interface for Data Transmission

Clinical partners should be able to upload image to the image archive. If the echo lab is equipped with a PACS connected to the network, connection may be directly established with HEARTFAID Image Archive. However, since this seems not to be feasible in the validation sites, an interface dedicated to image upload should be provided.

The current implementation has been tested with K-pacs and Conquest (both acting as client) to upload images to the Image Archive.

Since K-pacs is free, it could be eventually used for this purposes, setting up a workstation running it in every validation site. Optionally, it is conceivable to develop a web interface calling the standard DICOM C-STORE method (implemented for example in DCM4CHE Toolkit) to upload DICOM images (or more general DICOM media) to the platform from anywhere.

4.3.4.4 Interface for Image Display

Image display interface should answer to the following needs of HFP:

- Reviewing of images by the referent physicians
- Reviewing of images for second opinion
- Quick access to image data (for example access to data of the previous examination in the same room where the new examination is carried out to appreciate changes in the clinical situation)
- Quick selection of images for post-processing workflow. For example, a physician may want to compute again a) left ventricle ejection fraction or b) end diastolic LV diameter. In case a) very likely he will select an image sequence taken from an apical view, while in case b) he will select a particular M-mode image. In any case, he needs to select quickly and easily a suitable image from the bunch of images in the patient’s study.

WADO services, implemented in DCM4CHE, are of course useful, but are not sufficient to deal with image sequences, since no kind of streaming is implemented.

It would be useful to add some features to WADO services, so as to include video streaming in some format or at least frame navigation (that is buttons to move forward and backward in the image sequence). Of course the images displayed in this way, besides being suitable for quick identification, are not suitable for diagnostic purposes, since the compression rate could be too high.

4.3.4.5 Final remarks

As a final remark, it is worthwhile to point out that DCM4CHE community is pursuing a new child project, called Xero, that provides a new web interface for clinical access to patients and studies (as opposed to the Web-based user interface described above which was mainly intended for administrators). This component is intended for users such as nurses, doctors and perhaps patient’s relatives who can’t easily install a full radiology client station. This web-interface should in principle give an answer, among others, to the interface problems described in the previous subsections, i.e. user administration, data query/retrieve, data transmission, consistent display of images, display of multiframe images (at least through frame navigation), numeric image reports and final reports. See [10] for further information.

5 References

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[9] DCM4CHE: http://www.dcm4che.org/

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