KardiaSoft Architecture – A Software Supporting Diagnosis and Therapy Monitoring of Heart Failure Patients Exploiting Saliva Biomarkers*

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***Abstract*— The aim of this work is to present the architecture of the KardiaSoft software, a clinical decision support tool allowing the healthcare professionals to monitor patients with heart failure by providing useful information and suggestions in terms of the estimation of the presence of heart failure (heart failure diagnosis), stratification-patient profiling, long term patient condition evaluation and therapy response monitoring. KardiaSoft is based on predictive modeling techniques that analyze data that correspond to four saliva biomarkers, measured by a point-of-care device, along with other patient's data. The KardiaSoft is designed based on the results of a user requirements elicitation process. A small clinical scale study with 135 subjects and an early clinical study with 90 subjects will take place in order to build and validate the predictive models, respectively.**

I. Introduction

Heart Failure (HF) is a common clinical syndrome that affects approximately 2% of the adult population, ranging from less than 2% in population younger than 60 years old to 10% at ages over 75 years. Patients with HF have a poor prognosis with high short- and long- term mortality, high re-hospitalization rates and severely impaired quality of life [1-3].

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The diagnosis of the HF is primarily clinical and despite recent scientific guidance, it frequently poses a challenge in many clinical settings. Although clinical symptoms and signs of HF are essential for the diagnosis of HF, the documentation of structural and/or functional cardiac abnormalities by echocardiography, as well as the measurement of natriuretic peptides are also necessary to establish the final diagnosis [3, 4]. The therapy monitoring of HF is currently based on a holistic patient approach that takes into account all clinical information that may derive from the patient's history and detailed physical examination (symptoms and signs), also accompanied by the use of echocardiography and biomarkers that may reveal an early deterioration or improvement prior to overt clinical presentation. Therefore, therapy monitoring in HF is equally challenging and remains an important clinical problem that requires further research, while the use of novel biomarkers in clinical practice, although promising, has not yet been fully/globally established. This research would provide better, more accurate and objective, widely applicable monitoring methods to prevent recurrent admissions and optimize patient care in HF.

A number of studies have revealed that the application of intelligent approaches in the analysis of characteristics and data, collected during the clinical practice for the management of patients with HF, contributes significantly to the early detection of HF, the estimation of the severity of HF, the identification of subtypes of HF, as well as the prediction of adverse events. An extended review of these studies along with a qualitative and quantitative comparison of them is presented in [5]. In the majority of the studies biomarkers extracted from blood, such as NT-proBNP and troponin, contribute significantly towards the HF diagnosis and prognosis. The transformation of the diagnostic and prognostic models, developed in the abovementioned studies, to decision support software tools has been achieved within the implementation of EU funded research projects like SensorArt [6], SmartTool [7], HeartMan [8] and HEARTEN [9].

The most recent studies have revealed the strong correlation of saliva biomarkers with HF severity, progression and mortality through statistical analysis methods, as well as methods developing computational models [9 -11]. Hart *et al.* [12] point out several advantages in using saliva instead of blood. The most prevalent one is that sample extraction is easier than blood sampling. Medical operators non-qualified for blood sampling can also be involved in the sampling procedure. Additional advantages include easier handling, greater acceptance by the patients as

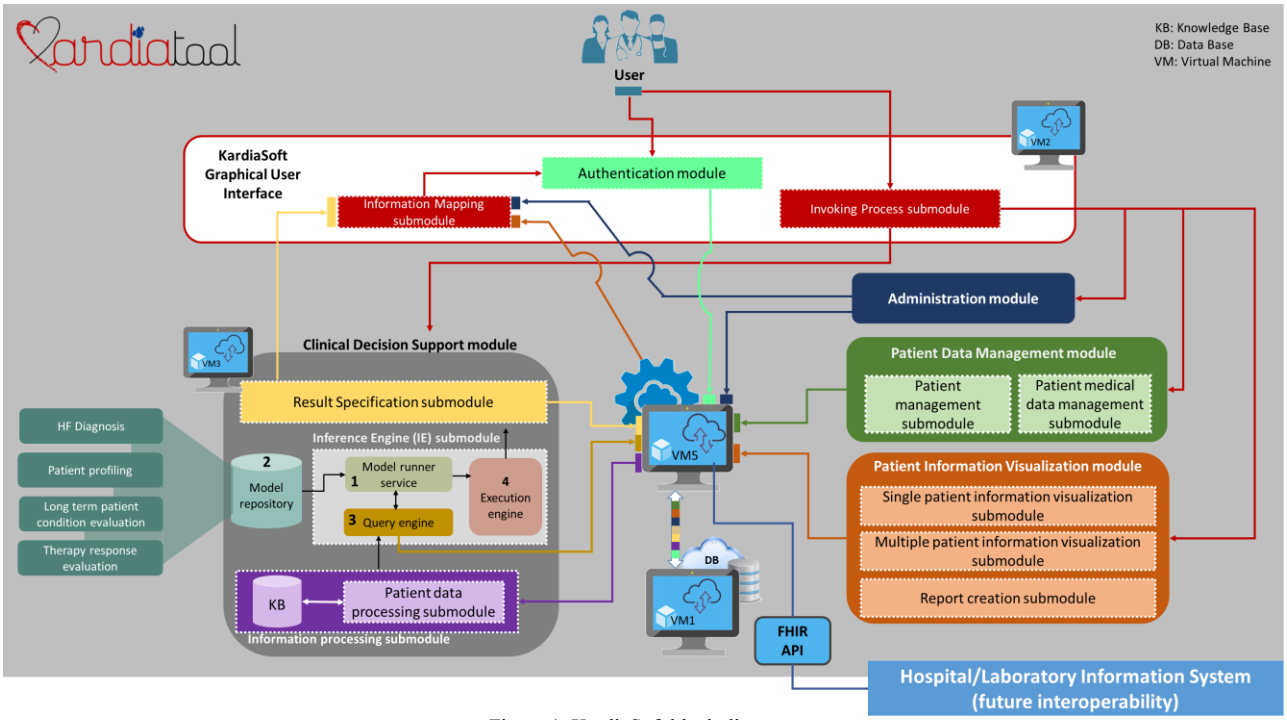

Figure 1. KardiaSoft block diagram.

saliva sampling is not invasive, lower contamination risk and the lack of need of venepuncture (which is sometimes very difficult for some elderly or frail patients). Despite these advantages, saliva detected biomarkers remain unexploited for HF management.

Besides early diagnosis and prognosis of HF, therapy monitoring of patients with HF is of critical value for healthcare professionals and could assist in the identification of subgroups of patients that would benefit from a more intensive follow-up to avoid frequent re-hospitalizations or delay disease progression to the end-stage of HF. In [13] HF monitoring models have been published as mathematical equations with complex formulas which are not suitable for clinical application. The relevant models had acceptable-to-good discriminatory ability (c-statistics >0.70) in the derivation sample. Only two models were externally validated more than once, displaying modest-to-acceptable discrimination (c-statistics 0.61-0.79). Impact analysis found none of the models recommended for use in any clinical practice guidelines. The limitations for the use of these risk scores in clinical practice (besides the limited validation process) include also the lack of an easily accessible platform that could provide direct feedback with the potential benefits gained from various interventions, as well as individualization of the risk for each patient or each HF phenotype observed. There is ample room for improving the usability of risk prediction tools while searching for improvement in the performance of these models at the same time.

KardiaSoft is a multi-purpose and multifunctional computational tool that is based on a variety of HF related data. Decision support processing is a critical component of KardiaSoft tool since it provides valuable clinical information to the healthcare professionals and assists them in the diagnostic and therapy monitoring judgment. KardiaSoft consists of trained predictive models, correlating the output of a novel point of care device (namely the KardiaPOC), measuring four saliva biomarkers (N-terminal pro b-type natriuretic peptide, Tumor Necrosis Factor –a, Interleukin- 10, Cortisol) at the same time, with heterogeneous data sources to allow for the extraction of patterns and rules towards efficient HF diagnosis and therapy monitoring in real time.

II. KARDIASOFT ARCHITECTURE

The process that was followed for the design of the KardiaSoft architecture consists of three steps described below.

User requirements elicitation. For the user requirements elicitation process three groups of ecosystem actors, who may influence or be influenced by the KardiaSoft, were identified: (i) *Users* including doctors and nurses, which are the main actors of the KardiaSoft tool, (ii) *Customers* where clinical laboratories, private or public hospitals and clinics, private cardiologists and general practitioners belong to and (iii) *Stakeholders* including patients, ICT infrastructure engineers, Clinical IT experts, Researchers, Industry, Regulatory bodies and Public Health Authorities. Additionally, secondary market research took place, in which analysis of official reports and documents, review of related international scientific literature and collection of the experience of past projects and related ongoing ones were performed. Finally, context of use analysis was achieved through the inclusion of questions to the questionnaire capturing the skills and experience of the users, their tasks in their daily practice, as well as technical, physical and organisational characteristics of their current working environment. The information that was gathered during the first step was the basis for the preparation of the questionnaire that was circulated, by three clinical centres, to 60 users. Simultaneously, an interview with three focus

groups (one from each clinical centre) was performed through physical or conference call meeting.

Functional and non- functional specifications identification. For the identification of the functional and non-functional specifications the FURPS+ model [14] was followed (Functionality, Usability, Reliability Performance, Supportability). The sign "+" in the FURPS+ model refers to constraints (design, implementation, interface and physical).

Architecture design. For the documentation of the software architecture the Software Engineering Institute's (SEI) approach, called Views and Beyond or V&B [15], was followed. In this way the software architecture is also compliant to the ISO/IEC/IEEE 42010:2011 standard.

As shown in Fig. 1, the KardaSoft is composed of six distinct modules as follows: (i) the Patient Data Management (PDM) module, (ii) the Patient Information Visualization (PIV) module, (iii) the Clinical Decision Support Segment (CDSS) module, (iv) the Authentication module, (v) the Administration module and (vi) the KardiaSoft Graphical User Interface (KGUI). The Fast Healthcare Interoperability Resources (FHIR) [16] standard is followed in order to ensure the linking of the KardiaSoft to hospital/laboratory information systems.

A. Patient Data Management (PDM)

The PDM module is responsible for adding a new patient, updating patients' basic profile and deleting a patient. It is also responsible for adding patients' clinical data and measurements, updating and deleting them. Using the PDMS all information related to the patient, apart from the KardiaPOC measurements, can be accessed, updated and stored to the cloud database.

B. Patient Information Visualization (PIV)

The PIV module offers a visualization of the patient information in different ways: single or multiple patients view. Single patient view allows the user to monitor the progress of the patient's health (through specific measurements) along different time periods (through the Single Patient Information Visualization submodule), while the multiple patients view allows the comparison of different patients or patient groups (through the Multiple Patient Information submodule). In this way the user (i.e. the doctor) can have a very good view of patient measurements and their progress. Additionally, pre-defined shareable reports can be produced (using the Patient report creation submodule) summarizing patient measurements. Reports are also stored in the cloud database.

C. Clinical Decision Support Segment (CDSS)

The CDSS module is responsible for processing relevant data and providing decision support for estimation of the presence of HF (HF diagnosis), stratification/patient profiling, long term patient condition evaluation and therapy response monitoring. According to the selected type of the decision support, the Inference Engine (and more specifically its model runner engine) loads the relevant model from the Model repository along with the relevant data from the cloud database. For the latter functionality, a query engine retrieves the data from the cloud database and passes it to the Information processing submodule which is responsible for data calculation and representations (according also to experts/clinical knowledge existing in the Knowledge Base). The model runner service then forwards the final data and the model to execution engine which is responsible for running the chosen model. The obtained results are transformed to a meaningful outcome for the decision type in question by the Results specification submodule. The cloud database is updated with the results accordingly.

The predictive models will be built using data from 135 subjects to be enrolled: 30 subjects of Group I-patients with symptoms of HF and known HF, 60 subjects of Group II - with hypertension or obesity and symptoms resembling HF but without HF, 45 subjects of Group III - patients with acute HF) will be collected within three clinical centers (University Of Ioannina Greece- UOI, Consiglio Nazionale Delle Ricerche Italy - CNR, University College Dublin Ireland - UCD). The accuracy of the CDSS will be validated through early clinical testing. More specifically, 90 further subjects (15 subjects from Group I, 30 subjects from Group II, 45 subjects from Group III) will be used for the validation of the KardiaSoft tool.

D. Authentication module

Initially the user logs-in through the Authentication module using his/her credentials. According to the information existing in the cloud database, the user is logged in and roles are assigned to him/her (controlled access). In case of a forgotten password a special mechanism is used to re-issue the password. The Authentication module is also responsible for keeping a log file with access to the system.

E. Administration module

The Administration module is responsible for managing sites, managing POCs (registering POCs, assigning POCs to sites), managing LOCs (assigning LOC to sites) and users. All relevant information is stored to the cloud database.

F. KardiaSoft Graphical User Interface (KGUI)

All the information is accessed and viewed through the KardiaSoft Graphical User Interface which is responsible for the visual representation of the different modules, the invocation of the respective module and the interaction with the user. It consists of six main segments which are the navigation GUI, the Patient data Management GUI, the Patient Information GUI, the CDSS GUI, the Authentication-Login GUI and the Administration GUI.

A summary of the modules of the KardiaSoft system, as well as the segments of each module is presented in Table I. The interaction between the modules is depicted in the context diagram in Fig. 2.

G. Cloud infrastructure

The KardiaSoft tool will be deployed in a cloud infrastructure. This infrastructure consists of five Virtual Machines (VMs) where different parts of the KardiaSoft are deployed: (i) *VM1: KardiaTool Database server* where the database is hosted. The database is designed in order to store: (a) demographic and clinical data of the patients, (b) information of the KardiaPOC and KardiaSoft users, (c) KardiaPOC devices information, (d) LOC information, (e) KardiaPOC measurements and (f) output of the KardiaSoft. (ii) *VM2: KardiaSoft GUI* where Navigation GUI, Patient

TABLE I KARDIASOFT BASIC MODULES AND THEIR SEGMENTS.

KardiaSoft	
Module	**Segments**
Patient Data Management Segment	Patient management submodule
	Patient medical data management submodule
Patient Information Visualization Segment	Single patient information visualization submodule
	Multiple patient information visualization submodule
	Report creation submodule
Clinical Decision Support Segment	Inference engine
	Information processing submodule
	Model repository
	Result specification submodule
Administration Segment	User Management submodule
	LOC Management submodule
	POC Management submodule
KardiaSoft Graphical User Interface Segment	Navigation GUI
	Patient data Management GUI
	Patient Information GUI
	CDSS GUI
	Authentication-Login GUI
	Administration GUI
Authentication Segment (AUTHS)	Login segment
	Access logging segment
	Password reminder segment

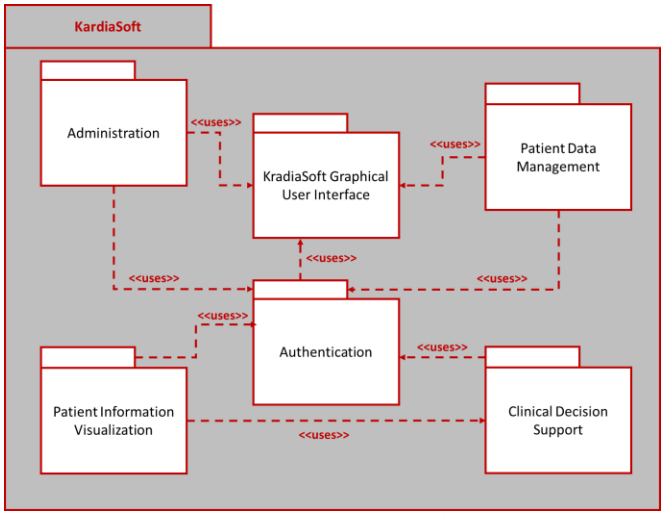

Figure 2. KardiaSoft context diagram representing the "use" relation between modules.

data Management GUI, Patient Information GUI, CDSS GUI, Authentication-Login GUI, Administration GUI are hosted. (iii) *VM3: KardiaSoft Engine* where the models and the mechanisms supporting the functionality of the KardiaSoft is deployed. (iv) *VM4: POC data manager* that is responsible for transferring the measurements received by the KardiaPOC device to the database server. (v) *VM5: Rest data server* that hosts all the services in order the proper communication of the KardiaSoft GUI, KardiaSoft Engine and POC data manager to be performed.

III. CONCLUSION

The KardiaSoft is a novel tool supporting a variety of functionalities allowing the effective and efficient monitoring of the heart failure patients by correlating saliva biomarker values with other clinical data of the patients in real time. The main novelties of the KardiaSoft tool rely (i) on the exploitation of the saliva biomarkers, (ii) the combination of heterogeneous data for patient monitoring and (iii) the application of machine learning techniques for decision support. The KardiaSoft tool aims at increasing the accuracy of diagnosis of HF, enabling therapy monitoring and decision making, supporting HF patients to prevent decompensation and/or hospitalization, improving health outcomes for HF patients and provide healthcare professionals with patient specific information. Patients are expected to receive a personalized treatment prescription and earlier screening of HF. Furthermore, improvement in disease management (e.g. waiting time and length of stay in the hospital can be reduced,), decrease of visits and improved satisfaction by the health services are going to be achieved. The above clinical impact is to be accompanied by significant social impact such as decreased mortality, improved quality of life, reduced emergency hospitalizations etc.).

REFERENCES

[1] "Cardiovascular diseases statistics - Statistics Explained." [Online]. Available:http://ec.europa.eu/eurostat/statisticsexplained/index.php/Cardiovascular_diseases_statistics.

[2] M. R. Cowie, "The heart failure epidemic," *Medicographia*, 2012.

[3] S.F. Nagueh, *et al.*, "Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging", *J Am Soc Echocardiogr* vol. 29, no. 4, pp. 277-314, 2016.

[4] P. Ponikowski *et al.*, "ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC", *Eur Heart J,* vol. 37, no. 27, pp.2129-2200, 2016.

[5] E.E. Tripoliti, T.G. Papadopoulos, G.S. Karanasiou, K.K. Naka, D.I. Fotiadis, "Heart Failure: Diagnosis, Severity Estimation And Prediction Of Adverse Events Through Machine Learning Techniques", *Computational and Structural Biotechnology Journal*, vol. 50, pp. 26-47, 2016.

[6] SensorArt – http://www.sensorart.eu/index.php?option=com_content&view=article&id=1&Itemid=11.

[7] SmartTool - http://www.smartool.eu/.

[8] HeartMan - http://cordis.europa.eu/project/rcn/199014_en.html.

[9] HEARTEN - http://www.hearten.eu/.

[10] E.E. Tripoliti *et al.*, "A Computational Approach for the Estimation of Heart Failure Patients Status Using Saliva Biomarkers", *Proceedings of the 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2017, Korea.

[11] E.E. Tripoliti et al., "Predicting Heart Failure patient events by exploiting saliva and breath biomarkers information", *Proceedings of the 17th annual IEEE International Conference on BioInformatics and BioEngineering (BIBE2017)*, 23-25 October Washington, USA.

[12] R.W. Hart, M.G. Mauk, C. Liu, X. Qiu, J.A. Thompson, D. Chen, D. Malamud, W.R. Abrams, H.H. Bau, "Point-of-care oral-based diagnostics", *Oral Diseases*, vol. 17, no. 8, pp. 745-752, 2011.

[13] J.B. Echouffo-Tcheugui et al., "Population risk prediction models for incident heart failure: a systematic review", *Circ. Heart Fail.*, vol. 8, no. 3, pp. 438–447, 2015.

[14] FURPS+ model - https://www.ibm.com/developerworks/rational/library/3975.html.

[15] P. Clements *et al.*, J. Stafford, Documenting Software Architectures: Views and Beyond (2nd Edition), Addison-Wesley.

[16] Fast Healthcare Interoperability Resources (FHIR) - https://www.hl7.org/fhir/overview.html.