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Decisional DNA for modeling and reuse of experiential clinical assessments in breast cancer diagnosis and treatment

Eider Sanchez [a,b,c,*], Wang Peng [d], Carlos Toro [a,b], Cesar Sanin [d], Manuel Graña [c], Edward Szczerbicki [d,e], Eduardo Carrasco [a,b], Frank Guijarro [f], Luis Brualla [g,h]

[a] Vicomtech-IK4 Research Centre, Mikeletegi Pasealekua 57, 20009 San Sebastian, Spain
[b] Biodonostia Health Research Institute, eHealth Group, Bioengineering Area, P. Doctor Begiristain s/n, 20014 San Sebastian, Spain
[c] University of the Basque Country UPV/EHU, Computational Intelligence Group, Computer Science Faculty, P. Manuel Lardizabal 1, 20018 San Sebastian, Spain
[d] School of Engineering, Faculty of Engineering and Built Environment, The University of Newcastle, University Drive, Callaghan NSW 2308, Australia
[e] Gdansk University of Technology, Narutowicza 11/12, 80-952 Gdansk, Poland
[f] Bilbomatica, C/ Santiago de Compostela 12 4 A, 48003 Bilbao, Spain
[g] ERESA SA, Avda. de Campanar 114 bajo, 46015 Valencia, Spain
[h] Valencia General University Hospital, Avenida Tres Cruces 2, 46014 Valencia, Spain

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ABSTRACT

Clinical Decision Support Systems (CDSS) are active knowledge resources that use patient data to generate case specific advice. The fast pace of change of clinical knowledge imposes to CDSS the continuous update of the domain knowledge and decision criteria. Traditional approaches require costly tedious manual maintenance of the CDSS knowledge bases and repositories. Often, such an effort cannot be assumed by medical teams, hence maintenance is often faulty. In this paper, we propose a (semi-) automatic update process of the underlying knowledge bases and decision criteria of CDSS, following a learning paradigm based on previous experiences, such as the continuous learning that clinicians carry out in real life. In this process clinical decisional events are acquired and formalized inside the system by the use of the SOEKS and Decisional DNA experiential knowledge representation techniques. We propose three algorithms processing clinical experience to: (a) provide a weighting of the different decision criteria, (b) obtain their fine-tuning, and (c) achieve the formalization of new decision criteria. Finally, we present an implementation instance of a CDSS for the domain of breast cancer diagnosis and treatment.

1. Introduction

The human factor is decisive in the success of clinical decisions, as the reasoning capabilities and prior knowledge on the problem are important at the time where decisions are made [60]. Recently, several studies have discussed human errors in medicine and their impact to the health system [19,20,36,10,33]. According to [36] it is estimated that between 44.000 and 98.000 patients died every year in the 1990s in US due to medical errors, with costs exceeding the 17 and 29 billion American dollars. Brennan et al. [10] argued that about 50% of those errors were preventable. At the beginning of the 2000s,a patient safety movement became stronger, influenced by other sectors such as aviation or nuclear power, where the tolerated failure rates were in comparison extremely lower [33], while, at the same time, human error in the health system was becoming to be accepted as inevitable. Since then, efforts have been made towards the development and the implementation of solutions aimed at the reduction of the incidence and impact of preventable medical errors [33]. In this context the development of Clinical Decision Support Systems (CDSS) has been encouraged, due to their expected ability of highlight errors, thus increasing error prevention [32,7].

By definition, CDSS are active knowledge resources that use patient data to generate case specific advice at the space-time point where decisions are made [7,40]. They provide several modes of decision support, including alerts, reminders, advice, critiques, and suggestions for improved care [32]. CDSS have been successfully proven at the academic level [8], without reaching transference to real clinical environments yet. Factors affecting this lack of success have been analyzed recently [40,47,62,35]. In particular, difficulties in knowledge base maintenance and updating have been identified as a key factor [62,4].

In order to provide recommendations, CDSS need to incorporate knowledge about the different domains, disease mechanisms,

* Corresponding author.
E-mail addresses: esanchez@vicomtech.org (E. Sanchez), ctoro@vicomtech.org (C. Toro).

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considered intervention details and/or decision criteria. This knowledge is generated from various sources, such as Clinical Practice Guidelines (CPG), medical journals, conferences, books and hospital internal reports.

In general, specification of a knowledge domain is usually made by a group of domain experts, who share their knowledge and reach an agreement [71]. The process steps are as follows [45]: (i) literature review, (ii) evidence evaluation, (iii) drafting of the domain knowledge and decision criteria, (iv) consultation and peer review between different domain experts, and (v) approval of contents. Two main issues arise at this point:

- New findings and discoveries take place each and every day in the clinical domain. Therefore content updating should be redone periodically. Medical teams cannot assume the effort because they lack the resources needed for such tasks, and thus the CDSS supporting knowledge may easily become out-dated, and even obsolete.
- The manual updating of domain rules has a great risk of introducing inconsistencies and semantic noise. On the other hand, we need that the relevant-to-the-domain rulesets are as extensible as possible. Therefore, tools for rule handling are required to facilitate the addition of new rules ensuring the correctness of the updated system. Additionally, each rule has a different weight or importance in a decision (i.e. in diagnosing flu, having fever is more decisive than having cough and mucosity). When the process of rule generation is performed by hand, rule weighting becomes subjective. Objective metrics that could lead in the future to rule comparison are hence required for standardization.

In this paper, we propose a technological solution that allows a (semi-)automatic updating of the underlying knowledge bases and decision criteria of CDSS. We hypothesize that they can be updated by following the same continuous learning paradigm followed by clinicians in real life, which is based on the knowledge acquired along with real life experience. In order to achieve that, in our system clinical Decisional Events are acquired and formalized by the use of experiential knowledge representation techniques, such as Set Of Experience Knowledge Structure (SOEKS) [13] and Decisional DNA (DDNA) [53].

We present specifications of the experience model, as well as of the experience acquisition and consolidation process. Based on those techniques, we propose three different algorithms processing experience in order to evolve the initial ruleset of a CDSS: rule weight evolution, rule fine-tuning, and rule generation. We also present an implementation of our approach within a Semantically steered CDSS (S-CDSS) for the domain of breast cancer diagnosis and treatment.

The structure of the paper is as follows: in Section 2 we present relevant concepts about the state of the art in clinical decision making, experience acquisition and experience modeling techniques; in Section 3 we give the specification of the experience modeling structure and describe the experience acquisition and consolidation process; in Section 4 we present three different rule evolution algorithms: rule weight evolution, rule fine-tuning, and new rule generation; in Section 5 we present a case study of the system for the breast cancer domain, and finally, in Section 6, conclusions and future work are summarized.

2. Background concepts

In this section we describe relevant concepts regarding clinical decision-making. First, we introduce clinical reasoning. Prior experiences of medical professionals play an important role in this context, thus our CDSS should consider the management of clinical experience. Then, a brief introduction to experience acquisition and experience modeling techniques is presented. Following our applied Decisional DNA and Set of Experience Knowledge Structure technologies are introduced. Finally, a brief state of the art is presented, including a critical discussion of other approaches for knowledge adaptation and learning, which could be competing or complementary to our work.

2.1. Clinical decision making and decision support

The process of clinical decision-making was not studied in deep until the late 1990s, when concerns on avoiding medical errors arose. Before, clinical decision-making was widely accepted as an esoteric matter that only concerned physicians, and no systematic effort was done to analyze possible errors and their causes [19]. Recently, the underlying processes have been studied and a consensus has been reached acknowledging the Dual Process Theory [19,44,23,24,48] as a valid model which differentiates two types of clinical reasoning: analytical and intuitive [19]. The former consists of testing hypotheses and concluding the most likely one [23]. It is focused on scientific rigor following a rule-based approach (deductive reasoning).

Nevertheless, the analytical approach requires a high effort from the doctors [24,44,48,66], therefore most of them follow an intuitive clinical reasoning based on their previous experiences on similar situations [49,17]. Intuitive reasoning requires much less effort to decision makers, but is subject to a higher error rate [19]. In fact, if the clinical case is not correctly identified and the similarity based reasoning process with prior experiences does not take into account all relevant parameters, the final decision may not be adequate. In general, everyday clinical practice is heavily influenced by previous experiences. This fact is reflected in medical learning and training programs, which emphasize the continuous acquisition of new experiences to enrich the knowledge of trainees [66,70,34].

Increasingly, the reasoning processes of CDSS are becoming similar to those followed by physicians in real life. In fact, recent approaches on CDSS follow both reasoning types. The intuitive approach is followed by Case-Based Reasoning systems [11,21,27,74,2,1]. Their major limitation is that the quality of the output depends on the previous cases included in the knowledge base. Examples of CDSS following the analytic approach [39,38] generate recommendations based on knowledge that is extracted from medical literature and evidence. Their major weakness is the difficulty for continuously updating the knowledge and decision criteria applied for the reasoning.

We hypothesize that, in the same manner as with physicians, a combined approach of analytic and intuitive modes for the CDSS reasoning processes could support both the production of recommendations and the update of the knowledge in the system. Thus, in our proposed mixed approach (i) recommendations are generated based on a set of production rules given by medical experts and (ii) those rules are updated by the system with the acquired experience. Next we review the state of the art techniques for CDSS acquisition and modeling of decisional experience.

2.2. Experience acquisition and experience modeling

Experience, as a general concept, comprises previous knowledge or a skill obtained through daily life [68,67]. Experience is understood as a kind of knowledge gained from real world practice rather than books, research, and studies [61]. In this way, experiential knowledge can be regarded as a specialization of knowledge that includes information and strategies obtained from performing previous tasks. When these tasks involve making decisions, we talk about gaining *decisional experience*.

The importance of decisional experience in knowledge engineering, and especially in knowledge sharing, has been recognized at least since the last ten years. European and Australian studies reported in [9] have established that the primary research aim of knowledge management (KM) should be to use the vast experience accumulating each day within organizations and systems, as far as true knowledge is developed through learning from current and past experiences [25,6]. Experience management (EM), its formalization, representation, and experience based systems development are capturing increasingly growing attention of researchers and practitioners. However, formulating the underlying problems and their solutions has not shown much progress yet. The fundamental limitation of current research in this area is that none of the proposed approaches uses experience as ongoing, real time knowledge source along the decisional process as happens naturally when humans make decisions to answer a new situation.

In summary, we require experience based modeling systems to store and reuse experience in an ongoing, real-time representation system endowed with the following critical features:

- Adaptability and cross-platform portability.
- Compactness and efficiency.
- Configurability and shareability.
- Security and trust.
- Being exclusively experience oriented.

2.3. Decisional DNA

We follow an approach to experience acquisition inspired in the way DNA stores and transmits information and knowledge. In nature, DNA contains "…the genetic instructions used in the development and functioning of all known living organisms. The main role of DNA molecules is the long-term storage of information. DNA is often compared to a set of blueprints and the DNA segments that carry this genetic information are called genes" [22]. The contribution of this approach is an architecture to support discovering, adding, storing, improving and sharing information and knowledge among agents, machines, and organizations through experience. We introduce a novel Knowledge Representation (KR) approach in which experiential knowledge is represented by Set of Experience (SOE), and is carried into the future by Decisional DNA (DDNA) [13,53] (see Fig. 1). The expressions "Set of Experience – SOE" and "Decisional DNA – DDNA" were coined during works in the period 2006–2007 [12,56,55,54]. Since then, our research efforts resulted in multi-technology shareable knowledge structure for decisional experience with proven portability, adaptability, shareability, security, and trust [57] and clinical decision-making environments [3,52,72].

2.4. State of the art approaches

Most current Computational Intelligence techniques for decisional system require quantified data that can be processed by analytically sound methods. When dealing with imprecise knowledge, as in CDSS, the basic requirement of quantified noise-free data may be an overwhelming condition. Following we present some relevant state of the art approaches, discussing their limitations for experience based knowledge modeling in the context of CDSS.

Support Vector Machines (SVM) [73,26,69] are supervised learning models for classification and regression analysis. In essence, they find a discriminating surface as a (non-)linear

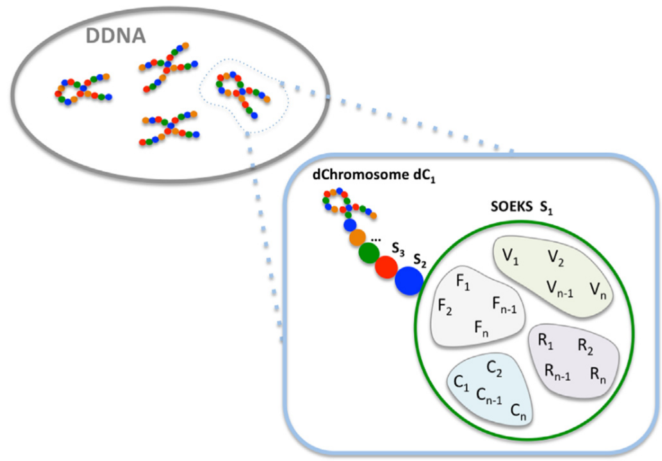

Fig. 1. SOE is combination of four components that characterize decision making actions (variables, functions, constraints, and rules) and it comprises a series of mathematical concepts (a logical component), together with a set of rules (a ruled based component), and it is built upon a specific event of decision-making (a frame component); Sets of Experience (Decisional Genes) are grouped according to their phenotype creating Decisional Chromosomes and groups of chromosomes create the Decisional DNA.

combination of support vectors providing the maximal separation (margin) between the classes, providing the greatest generalization of the classifier to unseen new data samples. The learning process consists of a dual minimization of a cost function, in which the classification error and some ad hoc regularization parameters are involved. In order to obtain good performance, hyperparameter optimization is needed, and therefore each learning experiment in SVM needs to be wrapped with a grid search procedure [42]. Though SVM have become a kind of de-facto standard for classification problems in many application domains, it is well known that they are very sensitive to data normalization, imbalanced distributions, and variations of the distributions which imply dramatic variations of the SVM hyperparameters when the data sample is changed. In summary, SVM would be rather inadequate as the basis for a CDSS which tries to follow the changes in clinical experience, where data may be unstable and imprecise, some problem instances have scarce samples, and decisions have some risk of noise.

Artificial Neural Networks (ANN) [51,29,28] are a collection of simple computational units interlinked by a system of connections [16] whose computation and training follow an early biological inspiration. Perceptrons are the basic ANN. Examples of more complex ANN approaches are Radial Basis Function networks (RBF) [15,29] whose neuron activation function is a radial basis function, and Probabilistic Neural Networks (PNN) [65], which in the context of classification use a kernel-based approximation to build an estimation of the probability density function of each class. Learning vector quantization (LVQ) [37,64] provides a method for supervised training competitive networks [58]. The input space is partitioned by an unsupervisedly trained competitive layer, and according to crisp clustering (input region) and/or soft clustering (degree of membership) input data is labelled by a supervisedly trained output layer. Extreme learning machine (ELM) [31,30] is a fast training approach for the single layer feed-forward neural networks (SFLN), providing on average good quality classification and regression results whose computation burden is orders of magnitude lower than conventional backpropagation training. However, ELM major criticism is the uncertainty of its performance due to the random generation of the hidden layer weights. Ensemble methods [5,14] may overcome such criticism with increasing computational cost. In general, ANN have sound and robust, though some of them are very time consuming, training algorithms. In some problem instances they retain their appeal because of their resilience. However, in the context of CDSS, one important criticism to ANN is their lack of explanation capacity, because there is no explicit representation of knowledge, as it is implicitly represented in the patterns of interactions between network components [43].

In a broad characterization, Computational Intelligence approaches as discussed above require the specification of a dataset which is assumed as a sample of the real process. Training algorithms may or not be sensitive to some numerical conditions, such as missing data and data scarcity, but they are definitively dependent of this dataset, and they often lack adaptability to new data or non-stationary environments. In general, they cope with this problem by retraining the system from scratch. Moreover, the bare data representation of the decisional event may not be enough in CDSS which require also to take into account the decision context. In fact, the context of a decisional event provides relevant information on how and why such decision was made, rather than only focusing on the final decision value. In order to represent the context of a decision, relations between data should be included in the experience representation model (such as restrictions, rules and functions in general). Such needs are not easily satisfied by SVM or ANN approaches.

The Case-Based Reasoning (CBR) approach [59,50] represents each decisional event independently as a case, and stores them into a previous case database. For each new case inputed to the system, (i) first, the relevant previous cases are retrieved; (ii) following, the knowledge in the cases retrieved is reused to propose a solution (classification) for the new one; (iii) the proposed solution is then revised by external means; and (iv) finally, the system learns by retaining the new case in the previous case base. The CBR allows some incremental learning, however the main limitation of current works on CBR [11,21,27,74,2,1] is their need to rely on static quantitative case characterizations in order to compute some kind of distance among cases to perform the search in the case database. The development of CDSS deals with imprecise and evolving characterizations of the decisional events that may not easily be dealt with by CBR.

3. Specification and reutilization of the experience model

Decisional experience is gathered by means of acquiring a historic file of Decisional Events that take place. Elements that conform a Decisional Event are captured into a SOEKS object every time a decision is made. We assume the clinical environment in the following.

Let a SOEKS be specified as a tuple $\mathbb{S}_t = \langle \{\mathcal{V}_n\}, \{C_m\}, \{\mathcal{R}_k\}, \{\mathcal{F}_p\} \rangle$, where

(i) $\{\mathcal{V}_n\}$ is a set of variables involved during the Decisional Event happening to a patient instance $I_i \in I$ to which the decision is oriented. Variables formally describe experience-based knowledge structure using an attribute-value language [12,46]. Let $\{\mathcal{V}_n\}$ be the set of variables of a domain, where a variable $\mathcal{V}_n = \langle V_n, v_n \rangle$ is composed by a variable specification V_n and a value v_n. Let a variable specification be the tuple $V_n = \langle t_V, \{\mathcal{C}_m\} \rangle$, where t_V is the type of variable (i.e. Integer, Float, Double, String) and $\{\mathcal{C}_m\}$ is a set of constraints, as defined below.

(ii) $\{\mathcal{C}_m\}$ is a set of constraints selecting a subspace ϕ_m of the value range of variables $\mathcal{V}_n$. Constraints describe relationships among variables, restricting the possibilities of feasible values. Each constraint is specified as a predicate, which can be expressed as follows: $\phi_m = \{v | C_m(v).\}$.

(iii) $\{\mathcal{R}_k\}$ is a set of rules that apply for the decision. Rules are used to express logical relationships among variables. They are specific evaluations of variables under a given fact. They are suitable for representing inferences, or for associating actions with conditions under which actions should be performed [46]. Each single rule describes a relationship between a condition and a consequence linked by the statements IF-THEN-ELSE. Let us specify a rule as a tuple $\mathcal{R}_k = \langle A_k, S_k, L_k, W_k, B_k \rangle$, where A_k denotes the antecedent clauses (IF-part), Q_k and L_k the consequent actions of the rule (THEN- and ELSE-parts, respectively), W_k the weight of the rule such that $W_k \in [0,1]$, and B_k is an auxiliary parameter. A_k sets value intervals for a subset of variables $\{\mathcal{V}^c_{n_k}\}$, that we call the conditional variables. Let us denote $M(A_k, \mathbb{S}_t)$ the matching predicate, which is true when values of a SOEKS $\mathbb{S}_t$ are within the value intervals set by the antecedent A_k. Q_k and L_k set action values to a different subset of variables $\{\mathcal{V}^s_{n_k}\}$, that we call consequent variables. Each consequent variable establishes a decision category d_i to which a rule $\mathcal{R}_k$ can provide recommendations.

(iv) $\{\mathcal{F}_p\}$ is a set of functions that evaluate variables. Functions describe associations between a dependent variable and a set of input variables. Abusing the notation, we can say that $\mathcal{F}_p : \times_{n \in N} \mathbb{V}_n \rightarrow \mathbb{V}_p$, that is, $v_p = \mathcal{F}_p(v_{n_1}, \ldots, v_{n_N})$, where $\mathbb{V}_n$ denotes the range of values of variable $\mathcal{V}_n$. Functions can be applied to reduce ambiguity between the different possible states of the variable set and to reason optimal states.

A sequence of SOEKS on the same decision category d, indexed by their time of occurrence, are stored, together with the corresponding final decision f_t carried out by the decision maker, in a Decisional Chromosome (DChromosome) $\mathbb{C}_d = \{(\mathbb{S}^t, f_t)\}$. A Decisional DDNA (DDNA) is a collection of DChromosomes $\mathbb{D}_m = \{\mathbb{C}_d\}$, which is specific for each decision maker m.

3.1. Experience acquisition and consolidation process

In our approach, a Decisional Event represents a decision made on an individual I_i, and a decision category d_i, for which a set of recommendations have been generated based on a given set of rules. The action of making the decision implies the selection of a final decision $f \in \mathbb{F}$ by the decision maker m_i. Such final decision can be made according to the provided recommendations or not. In a very general setting, a Decisional Event is stored into a SOEKS as follows:

1. Data associated with I_i is mapped into variables $\{\mathcal{V}_n\}$. Variable values v_n and constraints $\{\mathcal{C}_n\}$ are also mapped into $\{\mathcal{V}_n\}$.
2. Rules applying to decision domain d_i are stored in $\{\mathcal{R}_k\}$.
3. Applying functions are stored in $\{\mathcal{F}_p\}$.

The set of SOEKS stored into DChromosomes and DDNA will follow a temporal succession. Once Decisional Events are acquired into a SOEKS structure, the information they contain can be used by ruleset evolution algorithms. In the next sections, some of those algorithms will be presented, allowing to (i) gradually and repeatedly correct rules as well as deprecate them relying on the existing experience, and (ii) generate new rules. In particular, three different algorithms will be presented, two for rule edition/deprecation (i.e. rule weight evolution and fine-tuning of rules), and a case based reasoning algorithm for new rule generation.

Suggested changes on rules resulting from those methods will be provided at a secondary rule set. Such secondary ruleset will then be analyzed by a committee of domain experts, that will agree which of those changes to include in the primary ruleset.

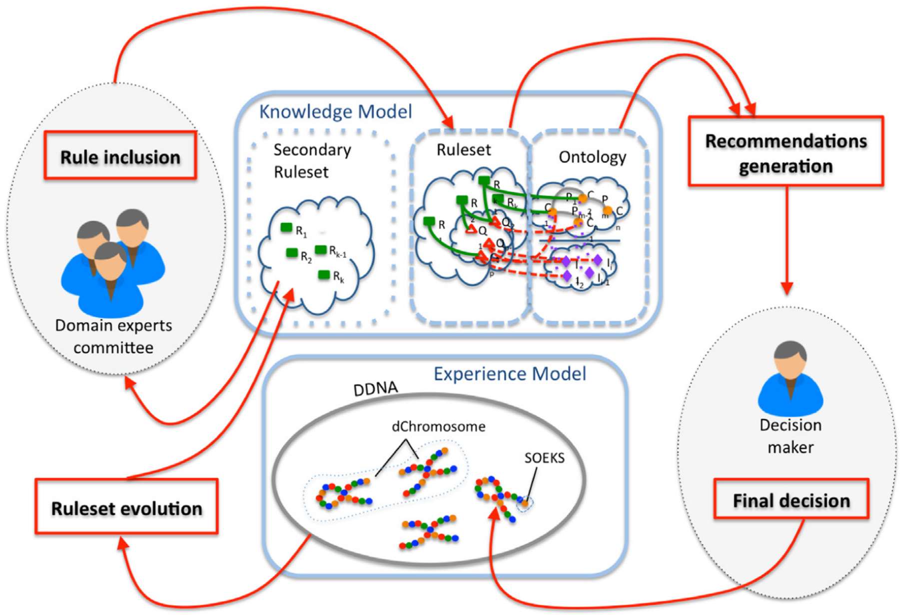

Fig. 2. Experience acquisition process.

Fig. 2 illustrates the complete experience acquisition process, including the generation of SOEKS and the evolution of the ruleset.

4. Rule evolution algorithms

In this section three different rule evolution algorithms will be presented: first, a rule weight evolution algorithm based on quantitative and qualitative criteria; additionally, an algorithm for the fine-tuning of rule conditional query clauses based on a qualitative measure, and finally, a case based reasoning algorithm for new rule generation.

4.1. Rule-weight evolution

Rule weight is a core feature of each rule in the SOEKS, used to indicate its importance with regard to other rules that provide recommendations for the same decision. The weight of a rule, W_k, objectively measured, is influenced by three distinct aspects:

1. *Quantitative measure*: The number of times a rule matches conditions of individuals, and, thus, its consequent value is recommended by the Decision Support System (DSS).
2. *Qualitative measure*: The number of times that, when a rule matches conditions of individuals, its consequent value coincides with the final value chosen by the decision maker.
3. *Trust/reputation of decision*.

Let $\mathbf{X} = \{X_1, X_2, \ldots, X_t, \ldots, X_T\}$ be a condition matching vector and $\mathbf{E} = \{E_1, E_2, \ldots, E_t, \ldots, E_T\}$ an error vector, such that

$$X_t = \{x_{t1}, x_{t2}, \ldots, x_{tk}, \ldots, x_{tK_t}\},$$
$$E_t = \{e_{t1}, e_{t2}, \ldots, e_{tk}, \ldots, e_{tK_t}\},$$

where T is the number of SOEKS in a dChromosome $\mathbb{C}_d$, and K_T is the number of rules in a SOEKS $\mathbb{S}_t$. Entries x_{tk} and e_{tk} in these matrices have two possible values, 1 or 0, defined as

$$x_{tk} = \begin{cases} 1 & \text{if } M(A_k, \mathbb{S}_t) \\ 0 & \text{otherwise} \end{cases},$$

$$e_{tk} = \begin{cases} 1 & \text{if } (x_{tk} = 1) \text{ and } (S_k = f_t) \\ 0 & \text{else} \end{cases}.$$

Let us define a collection of trust parameters associated to each decision made by decision maker $m : \boldsymbol{\alpha}_m = \{\alpha_{mt}\}$ where each $\alpha_{mt} \in [0, 1]$ is associated to a different decision maker. Let α_{m_t} be the trust of the final decision associated to a $\mathbb{S}_t$. We define the weight W_k of a rule r_k in the following expression:

$$W_k(\alpha) = \frac{\sum_m \sum_t (x_{mtk} - \alpha_{mt} e_{mtk})}{\sum_m \sum_t \sum_k (x_{mtk} - \alpha_{mt} e_{mtk})}.$$

4.1.1. Trust

In the expressions above, $\boldsymbol{\alpha}_m$ are subjective parameters which measure the perceived trustworthiness of a set of decisions. Trust indicates the level of supervised learning of the process of rule evolution, where a higher α_i implies higher supervision:

(i) When $\alpha_{mt} = 0$: no trust is put on decision maker m, and thus an unsupervised learning is used (quantitative-driven evolution only).
(ii) When $\alpha_{mt} > 0$: the trust level on decision maker m influences the level of supervised learning applied (quantitative- and qualitative-driven evolution).

Each α_{mt} can either be agreed by the team of decision makers, or be set up by every decision maker independently. In the latter case, different weights will be assigned to the same rule, depending on which decision maker sets α_m. The assignment of α_{mt} is done previous to rule weight evolution, and new values can be assigned in the future, if trust on the different decision makers changes.

4.1.2. Recalculation of W_k and convergence of the algorithm

Recalculation of rule weights can be performed either (i) automatically, after a decision occurs or following a certain pre-established frequency such as daily or weekly, or (ii) manually, on demand. When W_k is calculated all SOEKS $\mathbb{S}_t$ for the complete time interval that contain rule r_k are taken into account. Rule-weight evolution algorithm converges towards weights that provide recommendations that correspond either

(i) to the more frequently chosen decisions, in the case of quantitative-driven evolution only, or

(ii) to the ones that are more similar to the final choices of the decision maker, in the case of quantitative- and qualitative-driven evolution.

4.1.3. Weight zero meaning

Weight zero $W_k = 0$ has two different meanings:

(i) Rule r_k has not matched yet any individuals data.
(ii) Rule r_k has matched some individuals, and at the 100% of the matches the final decision of the decision maker has been different to the recommended.

At the second case, rules r_k such that $W_k = 0$ and $\exists x_{tk} | x_{tk} = 1$ are recommended to deprecation.

4.2. Fine-tuning of rules

Fine-tuning of rules consists of adapting rule condition intervals to reduce the difference between recommendations and the final decisions. Let the antecedent of a rule, A_k, be specified by a set of simple query clauses $q^s_{kl} = \langle V, o, v \rangle$, where V is a variable, o is the comparison operator (i.e. $>, <, =$), and v a value of the range of V. Let us recall the matching predicate $M(A_k, \mathbb{S}_t)$ and extend it as $M(q_{kl}, \mathbb{S}_t)$, which is true (active) when the simple query clause q^s_l matches the values of a SOEKS $\mathbb{S}_t$. Without loss of generality, we consider only categorical variables V_n. Let us define two parameters (i) μ_{kl}, counting the total amount of times that a query clause is active in a rule whose antecedent matches some SOEKS, and (ii) ρ_{kl}, counting the total amount of times that the query clause is active in a rule that matches a SOEKS and the final decision of the decision maker is the same as the recommendation of the rule consequent S_k. Formally,

$$\mu_{kl} = \sharp\{\mathbb{S}_t | M(A_k, \mathbb{S}_t) \text{ and } M(q^s_{kl}, \mathbb{S}_t),\ q^s_{kl} \in A_k\},$$
$$\rho_{kl} = \sharp\{\mathbb{S}_t | M(A_k, \mathbb{S}_t) \text{ and } M(q^s_{kl}, \mathbb{S}_t) \text{ and } (S_k = f_t),\ q^s_l \in A_k\},$$

where $\sharp$ denotes the cardinality of the set.

We define error prone query clauses as those having an error rate $e_{kl} = \rho_{kl}/\mu_{kl}$ greater than a threshold θ. Error prone query clauses are recommended for revision, by a domain experts committee that will decide whether to keep them, change them or remove them. Particularly, query clauses with error rates equal to 100% are recommended for deprecation. Algorithm 1 contains the pseudo code of the rule fine tuning algorithm.

4.2.1. Evolution activation and convergence of the algorithm

The process of fine tuning of rules is activated (i) automatically, after a decision occurs or following a certain pre-established frequency such as daily or weekly, or (ii) manually, on demand.

When fine tuning is calculated all SOEKS $\mathbb{S}_t$ since last change of rules are taken into account.

Algorithm 1 converges towards rules that provide recommendations more similar to the final choices of the decision maker.

Algorithm 1. Pseudocode for rule clause evolution.

Set θ
for $\mathbb{S}_t = 1$ to Number of SOEKS
{
  for $k = 1$ to Number of rules
  {
    if $M(A_k, \mathbb{S}_t)$ **then**
    {
      for $l = 1$ to Number of query clauses in rule k
      {
        if $M(q_{kl}, \mathbb{S}_t)$ **then**
        {
          $\mu_{kl} = \mu_{kl} + 1$
          if $S_k \neq f$ **then**
          {
            $\rho_{kl} = \rho_{kl} + 1$
          }
        }
      }
    }
  }
}
for $\mathbb{S}_t = 1$ to Number of SOEKS
{
  for $k = 1$ to Number of rules
  {
    for $l = 1$ to Number of query clauses in rule k
    {
      $e_{kl} = \frac{\rho_{kl}}{\mu_{kl}}$
      if $e_{kl} > \theta$**then**
      {
        if $e_{kl} = 1$ **then**
        {
          Recommend deprecation of query clause q_{kl} in rule r_k
        }
        else
        {
          Recommend revision of query clause q_{kl} in rule r_k
        }
      }
      else
      {
        Recommend no revision of q_{kl}
      }
    }
  }
}

4.3. Rule generation

To generate new rules we propose to follow a case based reasoning approach. Let us assume that a final decision has been made after analyzing a set of recommendation provided by a CDSS. Let $\{V_s\}$ be the set of variables that are relevant for such final decision stored in SOEKS $\mathbb{S}_t$, such that V_s is a variable included in query clauses of A_k and $M(A_k, \mathbb{S}_t)$. Every time a final decision is made decision makers are then asked to validate the set of $\{V_s\}$. They are asked to include the variables V_s that they considered during decision making and to remove the non-relevant ones, generating a new set of relevant variables $\{V'_s\}$.

Changes in $\{V_s\}$ mean that the recommendations that generated the CDSS are not complete. Thus, we generate a new rule where the antecedent equals to the values contained in the new set of relevant variables $\{V'_s\}$ and the consequent equals the final decision f (generated rules are of type IF/THEN).

4.3.1. Ruleset post-processing

The generation of new rules is performed on a secondary ruleset. They are introduced on the ruleset of the Decision Support System (DSS) when analyzed by a committee of domain experts, that will agree which of those rules to include. Thus a post processing of the generated secondary ruleset is needed, in order to detect

(i) spurious rules,
(ii) rules already included in others and
(iii) rules that generate inconsistencies

Such post-processing is done before the analysis of the domain experts committee.

5. Case study: breast cancer diagnosis and treatment

We have implemented a S-CDSS for the domain of diagnosis and treatment of breast cancer, presented in Sanchez et Al [52], under the framework of the Spanish research project LIFE [18]. It is aimed at supporting the Breast Unit of the Valencia University General Hospital (BUV), formed by eight different services of the hospital: (i) radiodiagnosis, (ii) nuclear medicine, (iii) radiation oncology, (iv) rehabilitation, (v) anatomical pathology, (vi) surgery, (vii) medical oncology, and (viii) psychology.

Let us recall the ontology and the ruleset we developed for the LIFE S-CDSS:

- *The LIFE Ontology, depicted in* Fig. 3:
  It is formed by three main classes: *Patient*, *Doctor* and *EHR*. *EHR* stands for Electronic Health Record and contains all patient-related general, sociological and clinical information. These three types of information are reflected in the three subclasses of *EHR*: *General_Information*, *Socio_Demographic_Information*, and *Medical_Tests*.
  Two main object type properties relate the three main classes: *correspondingPatient*, linking an *EHR* instance with a *Patient*, and *orderingDoctor*, linking an *EHR* instance with a *Doctor*.
  Subclass *Medical_Tests* contains eight different subclasses, one for each medical service of the BUV: *Radiodiagnosis*, *Nuclear_Medicine*, *Radiation_Oncology*, *Rehabilitation*, *Anatomical_Pathology*, *Surgery*, *Medical_Oncology*, and *Psychology*.
  The variables contained in the LIFE Data Model are reflected in the LIFE Ontology, by means of data type properties whose domains are these eight classes. An example is depicted in Fig. 3, where two data type properties related to the Radioagnosis service are shown: the BIRADS value for the mammography ("*RD_Mammography_BIRADS*") and the BIRADS value for the ultrasonography ("*RD_Ultrasonography_BIRADS*").
- *The LIFE ruleset, containing decision criteria for diagnosis and treatment of breast cancer*:
  In order to facilitate the creation of the ruleset, the medical team has proposed a new rule generation methodology:
  1. First, for each variable included in the LIFE Data Model (e.g. radiotherapic protocol type, from the radiotherapic oncology service), physicians identify whether it depends on other variables (e.g. the type of radiotherapic protocol applied to each patient depends on the type of surgery applied, the size of the surgical piece of pathologic anatomy, the number of lymph nodes found in the patient during radiodiagnosis and the existence of hypersensibility).
  2. Then, the dependence conditions for every different possible value of the former variable are established (e.g. radiotherapic protocol MAMA-50 is recommended when the type of surgery applied is conservative, there are no lymph nodes, there exists hypersensibility, and the size of the surgical piece of pathologic anatomy is T0, T1mic, T1a or T1b). The different rules will be formed by these conditions.
  3. Finally, each rule is introduced to a web based rule generator tool, integrated within the CDSS application and designed to easily create rules, without dealing with rule syntax. Fig. 4 depicts an example rule generated by the system after it is introduced in the rule generator tool, rule RT0001.

The LIFE S-CDSS allows physicians to request decision recommendations for a certain decision domain. As decision aids for doctors, three different features are provided by the system: (a) patient relevant data summary, (b) recommendation options with their corresponding percentages and a graphical pie chart plot, and (c) bibliography attached to each recommendation option. Finally, physicians select a final decision value, included or not in the set of recommended options. Such Decisional Event is formalized to a SOEKS serializing variables and rules into such structure, and the SOEKS is added to the DDNA of the system.

We evaluated the aforementioned rule evolution algorithms. We selected 62 rules, covering decision criteria for radiation

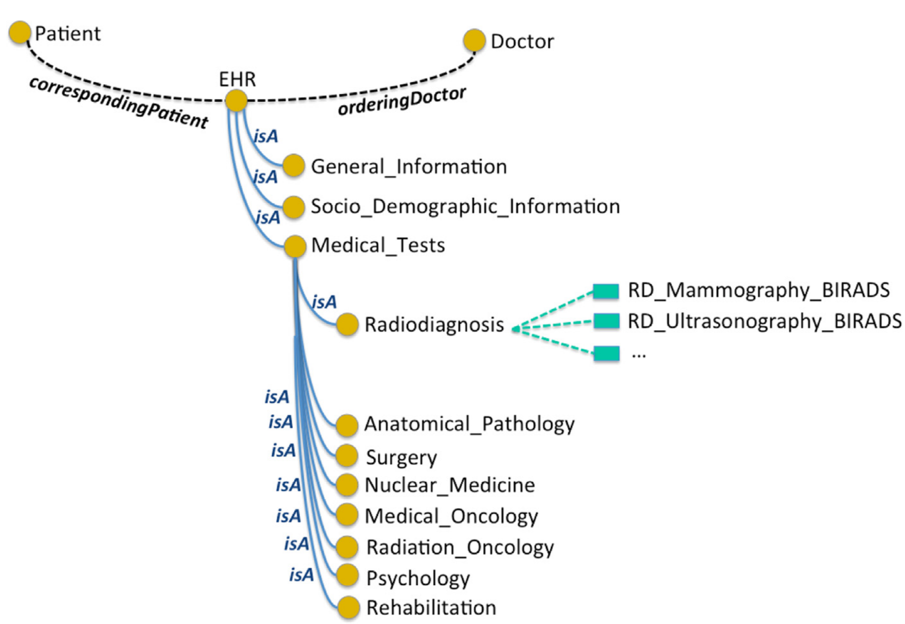

Fig. 3. The LIFE ontology.

```
<?xml version="1.0" encoding="ISO-8859-1"?>
<RuleSet>
        <LoadRule>
                <RuleID>RT0001</RuleID>
                <Rule>If (( CLASS Anatomical_Pathology with the PROPERTY AP_SurgicalPiece_Size EQUALS TO T0 )
OR ( CLASS Anatomical_Pathology with the PROPERTY AP_SurgicalPiece_Size EQUALS TO T1mic )
OR ( CLASS Anatomical_Pathology with the PROPERTY AP_SurgicalPiece_Size EQUALS TO T1a )
OR ( CLASS Anatomical_Pathology with the PROPERTY AP_SurgicalPiece_Size EQUALS TO T1b )
AND ( CLASS Surgery with the PROPERTY S_InterventionType EQUALS TO Conservative )
AND ( CLASS Radiation_Oncology with the PROPERTY RO_hypersensitivity EQUALS TO Yes )
AND ( CLASS Anatomical_Pathology with the PROPERTY AP_SurgicalPiece_LymphNodes EQUALS TO 0 ))
then ( CLASS Radiation_Oncology with the PROPERTY RO_ProtocolName EQUALS TO MAMA-50 ) </Rule>
                <weight>100</weight>
                <AccordingTo>
                        <classes>
                                <class>GivenBySpecialist</class>
                        </classes>
                        <specialist>
                                <specialistType>Radiotherapist</specialistType>
                                <specialistPlace>Hospital General Universitario de Valencia</specialistPlace>
                                <reportTitle>NE</reportTitle>
                        </specialist>
                </AccordingTo>
        </LoadRule>
</RuleSet>
```

Fig. 4. Generated rule example.

oncology, and we introduced in the system 71 example patients. Particularly, the patients introduced in the system only match conditions of a subset of 7 of the rules included in the complete set: rules RT0001, RT0002, RT0011, RT0017, RT0045, RT0061, and RT0062. For each patient a final decision was introduced into the system about the assigned type of radiotherapic protocol. The corresponding SOEKS object was stored into the DDNA of the system.

During the introduction of each final decision the proposed case-based approach for new rule generation was followed. New rules were generated when according to the decision maker the set of variables relevant for such final decision were different from those proposed by the system. The new rules were introduced into a secondary ruleset of the system for a future revision by a domain experts committee.

After the 71 patients were introduced, both the rule weight evolution algorithm and the fine tuning of rules have been executed. Table 1 contains the weights of the 7 rules that match conditions, the percentage of error prone rules, as well as the number of query clauses per rule (NQC) and the number of error prone query clauses (Error NQC) that have an associated change recommendation.

The highest rule weight values when α is set to 0 (i.e. quantitative evolution) are taken by rules RT0001, RT0002 and RT0061 (weight value: 19.14%). They are the most frequent matching rules for our set of 71 patients. However, when we consider $\alpha=1$ (i.e. qualitative and quantitative evolution) the highest rule weight values are taken by rules RT0001 and RT0062 (value: 33.02%). Rules RT0002 and RT0061 are highly error-prone rules (respectively, 87.5% and 100% of the times when a rule matches patient conditions, the final decision of the physician has been a different one), and thus their associated weights decrease with the qualitative mode. In particular, rule RT0061 loses completely its weight, due to a 100% associated error rate.

The fine-tuning of rules algorithm provides the change recommendation for 5 of the 7 rules: RT0001, RT0002, RT0017, RT0061 and RT0062. Particularly, the last column in Table 1 shows the number of query clauses that have an associated change recommendation. Fig. 5 shows an example screenshot of fine-tuning of of rule RT001, where the value T1mic for the surgical piece size is recommended to be removed from the rule (it has an associated error rate of 100%).

Table 1
Rule weights and error prone clauses.

Rule	Weight $\alpha=0$ (%)	Weight $\alpha=1$ (%)	Error prone rules (%)	NQC	Error NQC
RT0001	19.14	33.02	12.5	7	1
RT0002	19.14	4.72	87.5	7	3
RT0011	3.83	7.55	0	3	0
RT0017	11.00	0	100	7	4
RT0045	11.00	21.70	0	6	0
RT0061	19.14	0	100	7	3
RT0062	16.75	33.02	0	1	0

6. Conclusions and future work

In this paper we have presented an experience-based approach that allows the (semi-)automatic maintenance and update of Semantically Steered Clinical Decision Support Systems (S-CDSSS). In our work we have proposed an experience-driven learning process that evolves the ruleset of a S-CDSS based on the previous Decisional Events experienced by physicians (their day-to-day expertise). Particularly, we have proposed three rule evolution algorithms:

(i) A rule weight evolution algorithm that allows the production of rule weights based on a non-subjective metric.
(ii) A rule fine-tuning algorithm that facilitates to the clinical experts committee the rule-maintenance by suggesting error prone rules and query clauses to be reviewed.
(ii) A new rule generation algorithm that extends the ruleset in an easy way, by considering the new cases that appear on the daily routine.

Such evolution process allows the discovery of new knowledge in the system (intrinsic knowledge) (a) facilitating the evaluation of the decisions made previously and the analysis of the actions followed, in order to improve the performance at clinical, ethical or economical levels, (b) allowing the training of new team members or facilitating current members to keep up-to-date, and (c) suggesting new knowledge that could be validated, driving clinical research activities or trials. In this sense, our approach could foster research activities of the medical team.

Our work is based on the experiential knowledge representation techniques SOEKS and Decisional DNA. These techniques have been applied to different domains, but in this work we have shown a successful case study for diagnosis and treatment of breast cancer.

As a future work, we will work on decision traceability, in order to allow analysis of the contribution of each link in the decision chain to the final results.

Also, we will work on the semantization of the Electronic Health Record (EHR), to allow direct integration of S-CDSS in the

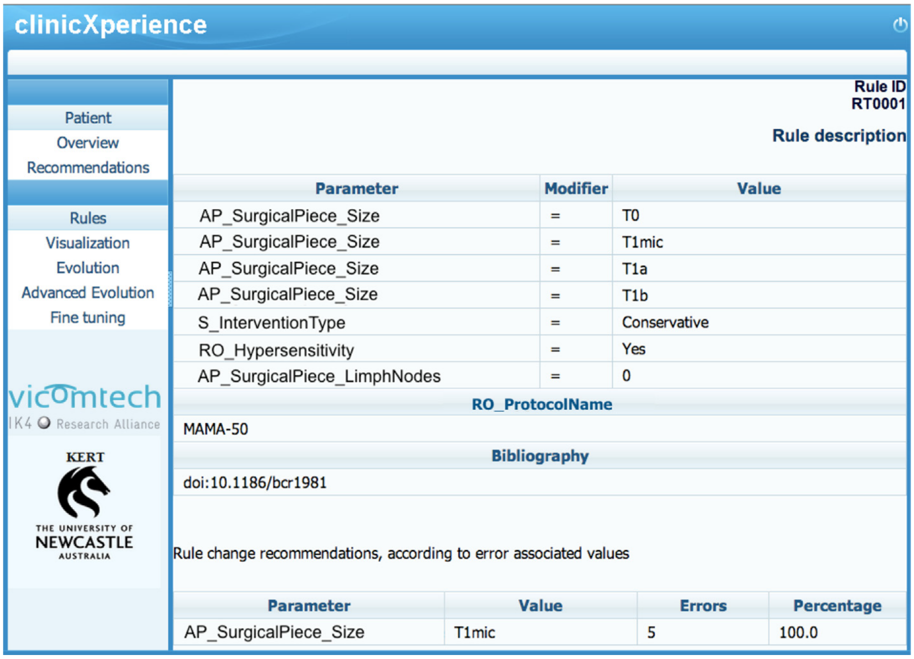

Fig. 5. Screenshot example of fine-tuning of rules.

clinical workflow. Some previous works [63,41] have stated current problems of EHR standards and we will continue our research line in semantic technologies to provide integration with our platform.

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Eider Sanchez studied Telecommunications Engineering in the University of Navarra. She made an internship in the Fraunhofer Institute of Integrated Circuits, in Germany, in 2008, and wrote her Engineering Final Project in CEIT, in 2009. Since 2009, she is working as a researcher in Vicomtech-IK4 in the area of eHealth and Biomedical Applications. Her research activities focus on the application of knowledge engineering to the medical domain. In 2011 she finished her Master in Advanced Computer Systems at the University of the Basque Country (EHU/UPV). Currently she is pursuing her Ph.D. on Semantic CDSS, in the Computational Intelligence Group of EHU/UPV.

Peng Wang is currently a Ph.D. student at the University of Newcastle, Australia. After graduating as a Computer Scientist in 1998 from North-eastern Normal Universality, he worked for 9 years in one of the world top 100 companies, China telecommunication Co., in Shanghai. His experience in different technologies and project manager took him to pursue Master studies in Information Technology at The University of Newcastle, graduating in 2010. Currently, his interests focus on using web and heuristics techniques to enhance the use of experience knowledge structure and DDNA.

Carlos Toro received his Ph.D. in Computer Science from the University of the Basque Country in the field of applied Semantics and his diploma degree in Mechanical Engineering with honors from the EAFIT University. He was invited as student researcher to the LSFA (University of Illinois, 1998) working in the field of virtual reality and industrial plant layout design. He was appointed as lecturer at EAFIT University in CAD/CAM Systems and Conceptual Design (2003–2004). Since 2003 he is a senior researcher at Vicomtech-IK4 within the Industrial Applications division. He was invited researcher at The University of Newcastle, Australia (2007 and 2011).

Cesar Sanin has been working in the field of knowledge engineering and intelligent technologies for the past 10 years. He obtained his Administrative Engineering Degree, in 2000, from the National University of Colombia and a Diploma in IT, 2003, at The University of Newcastle, Australia. Afterward, he pursued a Ph.D. degree at the School of Mechanical Engineering of The University of Newcastle, and received his degree in the field of Knowledge Engineering and Intelligent Technologies in 2007. Currently, he continues his work at The University of Newcastle as a co-director of the Knowledge Engineering Research Team – KERT. His research focuses on the areas of knowledge engineering, decision support systems and intelligent systems for engineering and business.

Manuel Graña is full professor at the Computer Science Department of the Universidad del Pais Vasco. His research interest include image processing, artificial neural networks architectures and applications, robotics and computer vision. He has co-edited several books, co-authored more than 100 journal papers and 200 conference papers. He has been the advisor of 24 Ph.D. Thesis.

Edward Szczerbicki has had very extensive experience in the area of intelligent systems development over an uninterrupted 30 year period, 20 years of which he spent in the top systems research centers in the USA, UK, Germany, and Australia. In this area he contributed to the understanding of information and knowledge engineering in systems operating in environments characterized by informational uncertainties and dynamics. He has published 300+ refereed papers which attracted close to 800 citations over the last ten years. His D.Sc. degree (1993) and the Title of Professor (2006) were gained in the area of information science for his international published contributions. His research contributes significantly to the area of smart information use in modeling and development of intelligent systems. His academic experience includes ongoing positions with Gdansk University of Technology, Gdansk, Poland; Strathclyde University, Glasgow, Scotland; The University of Iowa, Iowa City, USA; University of California, Berkeley, USA; and The University of Newcastle, Newcastle Australia.

Eduardo Carrasco is a graduate of the San Sebastian Higher School of Industrial Engineers where he read Electronic and Control Systems Engineering in 1998. After two years as Assistant Researcher at Centro de Estudios e Investigaciones Tecnicas de Gipuzkoa, in 2001 he held the position of Visitor Researcher at Fraunhofer Instituet fur Graphische Datenverarbeitung. From 2003 onwards he is a Staff Researcher at Vicomtech-IK4. His main interests are Human Computer Interaction, e-Inclusion and e-Health. Currently, Eduardo is the Manager of the Independent Living Group at Vicomtech-IK4 and he is also affiliated to the e-Health Group at Biodonostia Health Research Institute.

Frank Guijarro is a project manager with more than 20 years of experience in IT projects, including knowledge-based systems, semantic webs, ontology, mobility, GIS and GPS navigation & positioning systems. Since 2000 he works in Bilbomatica leading the R&D&I department and has a long experience on several areas such as health, electronic administration, SmartCities and Tourism.

Luis Brualla is a medical physicist since 2001 in Valencia University General Hospital working for ERESA. Specially dedicated to Radiotherapy, his main topics of research are intensity modulated radiotherapy, image guided radiotherapy and radiation dosimetry, with some publications in those fields. He has participated in different research projects related with these subjects, such as “development of a liquid chamber array for quality control in Radiotherapy treatments”, Neutor (development of a neutron radiation detector), Mert (Modulated electron radiotherapy) and Life (integral approach to breast cancer).