TRANSFORMING BONE MARROW TRANSPLANTATION DATA INTO A CASE-BASED REASONING SYSTEM FOR DECISION SUPPORT

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ABSTRACT

A case-based reasoning (CBR) decision support system (DSS) is well-suited to a clinical environment where there are novel problems and a low volume of cases, such as the Bone Marrow Transplant (BMT) Clinic in Halifax. The focus is experience management of the BMT patient to avoid post-transplant complications. We leverage Health Level Seven (HL7) Clinical Document Architecture (CDA) compliant, XML-based Electronic Medical Record (EMR) and National Cancer Institute (NCI) ontology to homogenize the structure and content of patient discharge summary. The EMR is transformed to operable clinical cases (OCC) formalism for CBR. Then, the R5 processes--repartition, retrieval, reuse, revise, and retain--are applied to implement the CBR DSS system. The DSS returns advice based on similar patients and their outcomes.

KEYWORDS

Case-Based Reasoning, Electronic Medical Records, Bone Marrow Transplantation, Knowledge Acquisition, Health Level 7 Clinical Document Architecture (HL7 CDA)

1. INTRODUCTION

An experience management system can be constructed using medical records of patients. Electronic health records are a cognitive artifact and shape the way in which clinicians obtain, organize and reason with knowledge [1]. Operalisation of electronic health record data allows us to derive decision-quality knowledge about what has been done and what have been the outcomes [2].

Knowledge that is learned through practice or experience is reused when solving a new case. This process is called case-based reasoning (CBR). A physician can solve problems more efficiently by associating new problems with previously encountered and solved cases [3].

A systematic capture of case information is required for patients registered with the Bone Marrow Transplant (BMT) Program in Halifax, Nova Scotia [4]. Patient data is shared with the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Bone and Marrow Transplant Registry (ABMTR). There are over 400 centers participating in the IBMTR and ABMTR and they receive statistical reports on outcomes of the patient population that undergoes autologous and allogeneic blood and bone marrow transplants.

According to the IBMTR/ABMTR Pre-Registration/Registration Manual, for a procedure to be classified as a transplant there must be the aim of:

- Repopulating the bone marrow with the infused stem cells and/or
- Treating persistent/relapsed disease by the infusion of the stem cells

While the IBMTR/ABMTR data addresses what is deemed essential information for the patient population, our data is not yet in that form. Our system design describes transformation from clinical narratives in the discharge summaries into an HL7 Template for BMT structured discharge summary that will serve data needs of IBMTR/ABMTR and produce operable clinical cases (OCC) for a CBR system.

2. HEALTH CARE-RELATED KNOWLEDGE MANAGEMENT ISSUE

2.1. Complications Following Bone Marrow Transplant

It takes two to four weeks following Bone Marrow Transplantation (BMT) for the stem cells to begin producing enough blood cells.

2.1.1. Early direct chemoradiotoxicities

The early or acute direct toxicities are nausea, vomiting and mild skin erythema. Usually the patients would have oral mucositis and hair loosing in the first month after the chemo-radiotherapy.

2.1.2. Late direct chemoradiotoxicities

The late direct chemotherapy and radiotherapy effects are usually because of their affect on the cell regeneration process.

2.1.3. Graft-versus-host disease (GVHD)

GVHD is the result of the allogeneic (donor) T cells (immune system cells) in the graft, reacting against the recipient's body. Acute GVHD occurs within the first 3 months after the transplant, while chronic GVHD happens after this time period.

- ***Acute GVHD***: Despite prophylaxis, acute GVHD will develop in ~30% of patients from matched siblings and in ~60% from unmatched donors.
- ***Chronic GVHD***: It is similar to the immune disorders and usually in most of the patients it resolves, but with highly susceptibility to significant infection during the disorder.

2.1.4. Graft failure

The occurrence rate is about 1-3%. In autologous transplantation is usually because of the damage of the bone marrow cells in the lab. In allogeneic BMT it is usually because of the remaining host immunity to reject the graft which could be the result of an incomplete immunosuppressive regime.

2.1.5. Infection

It happens mostly in allogeneic BMT because of the immunosuppressive regime that the patient has to receive it before the BMT. The infections are categorized as bacterial, fungal (Aspergillus) [5], and viral (CMV, VZV and HSV) [6]. The management of the patient who gets fever is a difficult challenge and is guided by individual aspects of the patient.

3. PROJECT OBJECTIVES

The project aims to describe the processes needed to create an EMR based on an HL7 template, transform the EMR to reasoning constructs in the knowledge modality of cases and their components, and then create a CBR system for post-transplant care of BMT patients.

4 LITERATURE REVIEW

4.1 Experience Management and CBR Systems

There is no gold standard for evaluating a case-based reasoning system in medicine. Research often shows that past clinical practices are ineffective and not necessarily based on objective scientific evidence [7] [8] [9] [10]. The CBR must be able to adapt to evidence that is open to different interpretations and subject to change as scientific knowledge advances.

In experience management, there is the organizational view and the cognitive sciences view [11]. In the clinical context, the electronic medical record is an experience collection. The computer-based representation of medical knowledge from electronic medical records can only attempt to formalize the current state of professional and scientific opinion.

4.2 CBR Systems Used In Medical Applications

The evolution of CBR systems are still in research and experimental phases.

4.2.1 Diabetic patients management exploiting CBR

Diabetic Mellitus type I patients have to be always under a physician supervision in order to manage their disease and adjust their daily activities with it. It is interesting to create a system that enables physicians in performing an intelligent consultation of the available data. To cope with this problem the designers tried to create a new tool for data base retrieval and knowledge management based on CBR technology which can produce solutions to problems by taking into account past experiences [12].

4.2.2 Web application for CBR in histopathology

The researchers used CBR approach to provide an intelligent access to a collection of illustrated medical cases through the Internet. They presented a Web interface for the CBR system IDEM (image and diagnosis from examples in medicine) in the domain of breast cancer histopathology. The advantage of adopting Web tools are limited by the difficulty in learning, how to issue queries and for what results. Particularly, in image databases querying the retrieval process depends on the representation of the image in the base. Therefore CBR could be suitable to be the solution as CBR derives from analogical research and can be considered as a form of intra-domain analogy [13].

4.2.3 CBR in antibiotic advise therapy in ICU

Severe bacterial infections in ICU patients who have encounter additional complications are still a life threatening issue. Since advice for such critical ill patients is immediately necessary and the laboratory process takes at least 48 hours to identify the pathogen and test it for antibiotic resistance and sensitivity, physicians usually predict a probable pathogen based on their background knowledge and treat the patient with a suitable antibiotic till the actual results come from the lab. This sort of antibiotic therapy is called “calculated” in contrast to a “selective” therapy. The researchers developed a decision support system called ICONS to apply for this issue which uses CBR, so previously documented cases can be used to solve current problems. This system also uses 4R CBR system cycle and don’t use the repartitioning part [14].

4.2.4 Recognition of critical lab results by CBR

Unfortunately normal ranges of lab results in many of medical settings can’t be defined as certain numbers and the normal ranges have to be defined based on each case by the physicians experience of the previous cases that they had before. This issue is also apparent when physicians will determine the probability of the kidney graft rejection in post transplant patients by the amount of their creatinine in their urine lad tests. Because the pathophysiology of transplant rejection is incompletely understood, simple algorithms or rule-based expert systems are not suitable for them. The best method to mimic the human technique of problem solving would be CBR that belongs to the ‘lazy learning’ algorithms. The crucial task in CBR is the definition of a similarity measurement for the case retrieval. Because in this study the researchers had to handle data in time series they used dynamic time warping (DTW) method which had been successfully applied to pattern recognition in time series. This study compared the efficiency of this method in CBR with the diagnostic accuracy of physicians experienced in nephrology [15].

4.3 CBR Systems Architecture

A CBR system requires a critical mass of diagnostic-quality operable clinical cases (OCC) to function. The procurement of OCCs for a CBR system is considered a bottleneck. The case acquisition and transcription info-structure technique produces OCCs for indexing, storage and retrieval in a CBR [16]. The main features of the operable cases are:

- A case which represents specific knowledge tied to a context. It records knowledge at an operable level.
- They can come in many different shapes and sizes, covering large or small time slices, associating solutions with problems, outcomes with solutions, or both.
- Operable cases record experiences that are different from what is expected and they are important to record.

CBR is a process of “Remember and Adapt” or “Remember and Complete” and this makes two styles of CBR [17].

- ***Problem Solving***: A solution could be proposed to solve a new problem, by extracting the solution from some retrieved case. This could be very useful in BMT complications’ diagnosis if it is followed by adaptation and criticism of the new solution.
- ***Interpretive:*** An interpretation could be proposed based on retrieved cases and followed by a justification. It would be very efficient for a clinician to propose a solution for BMT complications

In general, each CBR system comes up with a set of methodologies that are suitable for its domain of application environments to solve the problem [18]. There is no universal CBR method. The core problems addressed by CBR research can be grouped into five areas:

- ***Representation of a Case***: a primary problem of deciding what to store in a case, finding an appropriate structure for describing case contents, and deciding how the case memory should be organized and indexed for effective retrieval and reuse.
- ***Case Retrieval***: which strategy of retrieval should be used: syntactic similarity assessment - sometimes referred to as a "knowledge- poor" or semantically oriented approaches - referred to as "knowledge-intensive" which uses the contextual meaning of a problem description in its matching, for domains where the general domain knowledge is available.
- ***Case Reuse***: reusing a past case to solve the new case has two aspects: the differences among the past and the current case and what part of a retrieved case can be transferred to the new case. The differences are ignored because they are considered non relevant while the similarities are relevant for matching between cases. This is a trivial type of reuse. Another approach is the adaptation which is a transformational reuse of the past case solution and derivational reuse to construct the solution for a new case. There are at least two strategies for adaptation: tweaking and compositional adaptation. Tweaking means to adapt a returned case to make it more closely match the problem situation in which it will be applied. The similarity metric is goal-based. A user examines a suggestion from the system and critiques it. Different users have different goals and goal rankings, especially in a planning situation such as post-transplant management [19]. For

compositional adaptation, case components are amalgamated for a personalized solution [20].

- ***Case Revision***: revising a case solution using domain-specific knowledge when the reused case fails to solve the new problem. In a medical decision support system, a new solution may change with clinical experience and scientific investigation and it could take a long time to confirm the justification of the solution.
- ***Case Retain***: It involves selecting which information from the case to retain, in what form to retain it, how to index the case for later retrieval from similar problems, and how to integrate the new case in the memory structure. Sometimes an entirely new case will have to be constructed. The indexing is also a central problem in CBR such as what type of indexes to use for future retrieval and how to structure the search space of indexes.

5. MATERIALS

5.1 Domain Ontology

One of our healthcare issues is to match the terminology used in the BMT discharge summaries and IBMTR/ABMTR report forms with concept definitions. The National Cancer Institute (NCI) has developed an infrastructure for data management and integration [21]. They have produced a comprehensive biomedical terminology database that contains 850,000 concepts mapped to 1,500,000 terms by over 4,500,000 relationships. Transplant-Related diseases are the conditions that are the focus of our problem and the concepts are described in the NCI Thesaurus available via http://ncimeta.nci.nih.gov/indexMetaphrase.html.

Semantic Web researchers have produced technologies for ontology development and maintenance [22]. The Web Ontology Language (OWL) is a knowledge tool for ontology construction, and the formal semantics can be expressed using description logics (DL) for concept classification. The NCI Thesaurus is expressed in OWL DL.

5.2 IBMTR/ABMTR Report Forms

The forms that are completed by the BMT Program for the international registry are described in Table 1. The creation of an HL7 Template for BMT Discharge Summary used the data requirements of that system as part of the design.

Form Name	Description	Process
Pre-registration	1-page of essential data plus 7-page disease inserts	All cases 2 weeks prior to start of high-dose conditioning
Donor Information	12-page form for allogeneic	At registration
Day 100 Core Form	40-page form. Requested for approximately 1/3 of cases	At 100 days post-transplant
Modified 100 Day Report	2-page form. Used when Core Form not requested.	At 100 days post-transplant
Follow-Up Core Form	26-page Core Form.	Yearly after transplant
Transplant Essential Data Follow-Up Report	1-page form. Used when Core Form not requested.	Yearly after transplant

Table 1: Structured Data submitted to International BMT Registry

5.3 HL7 Template for BMT Discharge Summary

The HL7 Version 3 (V3) Templates are artifacts for unambiguous exchange of data. In its simplest sense, the HL7 Template indicates which clinical concepts are to be captured and whether they are to be captured as numeric, coded, text, or physicians' reasoning. The HL7 Templates are building blocks that constrain the HL7 Clinical Document Architecture (CDA), a document-based EMR standard. The BMT-dischrge-summary-template-0.1.doc, an HL7 Template for BMT Discharge Summary, has been released to the authors of this study for local validation and feedback. The aim is to achieve interoperability, which is the ability of two or more systems or components to exchange information and to use the information that has been exchanged. Both functional and semantic interoperability are required, and consensus with the IBMTR community is sought for HL7-approved coding scheme to use on a field-by-field basis (e.g., SNOMED CT). The BMT Unit in the QEII Health Sciences Centre is a member of the global BMT community and shares some data with the IBMTR. The HL7 Templates for CDA-based BMT documents, such as the Discharge Summary, function as boundary objects between the care and research communities of practice.

5.4 HL7 CDA for BMT Essential data

HL7 CDA is a derivative of the HL7 Reference Information Model and specifies the format of the information and the method for exchanging information between various systems. A CDA-based BMT document ontology was proposed [23] for the exchange of essential data contained in BMT patients' IBMTR report forms (Table 2). New work, the BMT-dischrge-summary-template-0.1.doc, uses a 'constrain then transform' approach.

Hospitalization date	Discharge date	Demography	List of diagnosis
Chief complaint	Current illness	Personal medical history	Family medical history
Allergies & habits	Physical examination results	Lab Results	Imaging & functional studies
Donor and match information	Conditioning	Transplantation	Engraftment
Post BMT therapy	Post BMT acute GVHD, complications and treatments	General summary and medications at discharge	

Table 2 Essential data in IBM BMT Discharge Summary CDA R2 Template

This CDA structure facilitates the implementation of CBR matching. First, its structured portions rely on standard HL7 classes, e.g. Observation, Procedure, Substance Administration and so forth. Next, it is composed of "IF … THEN…" conditional construct and suitable for Boolean Logic. It also involves the semantics of codes from HL7-approved coding schemes for standardization of preferred term for a concept.

5.5 Patient Records

The set of 92 BMT patient records from the Halifax BMT Program included all transplant procedures from 1994 to 1997. The data includes a subset of information that would be captured for IBMTR/ABMTR pre-registration, a flow sheet of temporal information captured on Day 0, Day 1, Day 5 and Day 10 post-transplant, discharge summaries that are a clinical narrative for patient's course in hospital, and autopsy records for those patients who died post-transplant. The coded data was stored in an electronic spreadsheet. A scanner is needed to capture the narrative text in the paper charts into an electronic form.

5.6 Decision Support Systems Licensed for Local Use

DxPlain, a diagnostic assistant system, is available to Nova Scotian Physicians via DoctorsNS website (www.doctorsns.com). The DxPlain application is an interactive program in which the user enters clinical findings and requests access to the DxPlain knowledge base, or asks DxPlain to provide a diagnostic decision. It provides references for each diseased based on user's inputs of signs, symptoms and laboratory examinations. Where there is overlap, DxPlain can provide case-based explanation for the associations between problems and solutions in our CBR system.

6. RESULTS

6.1 HL7 CDA Generation

The forty-page IBMTR (International Bone Marrow Transplant Registry) Report Core Form contains a BMT case's thorough BMT data and temporal information from various sources.

Comparing the medical records of our 92 BMT cases with the IBMTR Report Core Form, we classify the structure of each record into problem, solution, and outcome, and then extract essential elements from it to generate our HL7 CDA template.

We define problem as diseases leading to BMT. In IBMTR Report Core Form, the 4-page grouping of diseases is permutable and complex with specific insert form for each particular disease. To simplify the CDA generation, we group the diseases of our 92 BMT cases into two groups, cancer and non-malignance, using "IF … THEN …" to describe each group in our localized CDA template.

Solution is the result of a BMT and can be infection, graft versus host disease (GVHD), graft failure, late direct chemotherapy, early direct chemotherapy. Each has one particular section in CDA template. Outcome is the difference between before and after BMT ECOG scores. Success is indicated by a positive number.

We apply SNOMED as our terminology system, and National Cancer Institute (NCI) ontology, which is expressed in OWL DL, to our HL7 CDA template. XForm, comprised of separate sections that describe purpose and presentation and recommended by W2C, could provide support to form-derived data types in CDA. XSLT, a language for transforming XML documents into other XML documents, could be used to transform a specific XML schema into HL7 CDA format which can be accepted by MS InfoPath.

6.2 Dealing with Temporal Data

A problem related to IBMTR form-based OCC generation is how to transform domain of temporal abstraction into OCC. One solution is using middleware technologies to generate CDA instances with populated data from EMR and save them in repository after standardization and patient privacy information removal. Then, the temporal abstraction tool parses the CDAs in the repository, and applies temporal abstraction rules to create the IBMTR form-based OCC (Figure1).

Abstraction can be defined as the structure {<parameter, value, context>, interval} denoting "the parameter has a particular value given a specific interpretation context, is interpreted over a specific time interval." By evaluating and summarizing the state of a patient over a period, the output of abstractions should be beneficial to our clinical decision support purpose which is to get the best outcomes (ECOG scores) [24].

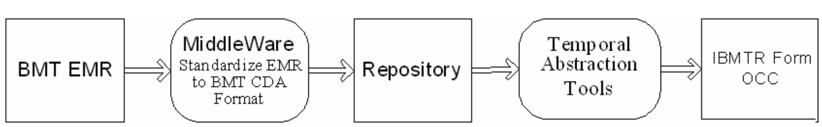

Figure 1: Generate IBMTR Form Based OCC

6.3 Terminological Standardization

The problems of coding clinical text for EMR is that there may not be a perfect match between the language used by the clinician and the coding scheme. The discharge summaries were processed by the Meta Map Transfer (MMTx) program for string based searching [25].The terminology used in the IBMTR/ABMTR report forms was mapped to NCI Thesaurus [26]. Terminology was standardized to SNOMED CT, if available, else NCI code.

A terminological system has two classical goals: standardization and communication. The prototype of France’s national information system for transplantation (EfG-TS) linked concepts using the Conceptual Graph formalism as the underlying knowledge representational model [27]. This project uses the OWL DL formalism as the underlying knowledge representational model.

7. THE PROPOSED SOLUTION

The overall solution for the bone marrow transplantation system design is given in Figure 2.

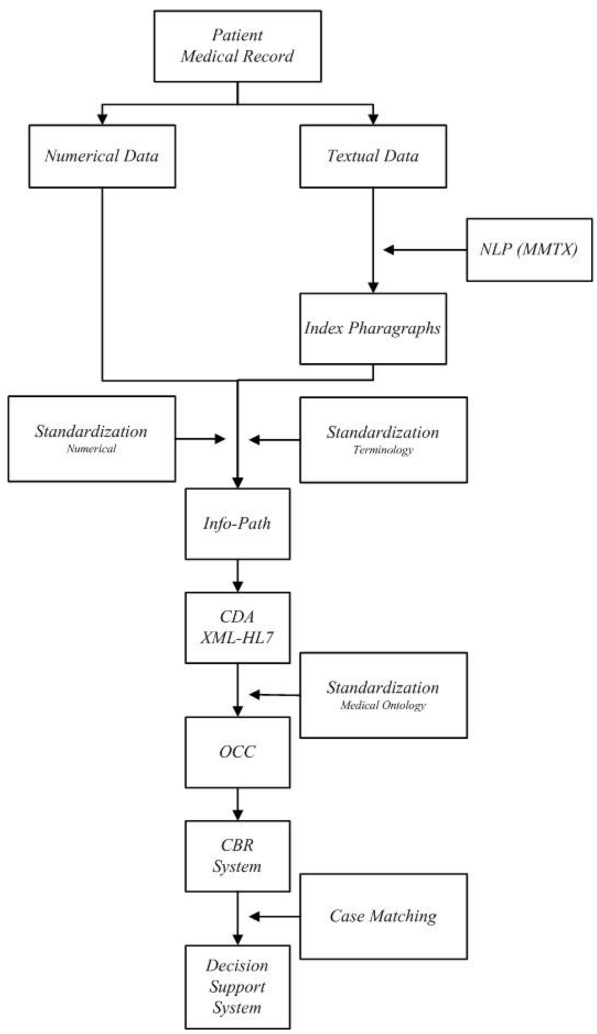

Figure 2: EMR OCC Transformation

7.1. Transforming the Medical Records into EMR and OCC

The operational layer requires building a localized IBMTR HL7 CDA-compliant EMR schema and a new case can be entered using MS InfoPath software for CDA. The standardization layer transforms the EMR for old and new cases into a more generalized OCC. In our design (Figure 3) we draw on the knowledge layer for the case components. We have designed the standardization layer and a new case can be entered into MS InfoPath for case based reasoning.

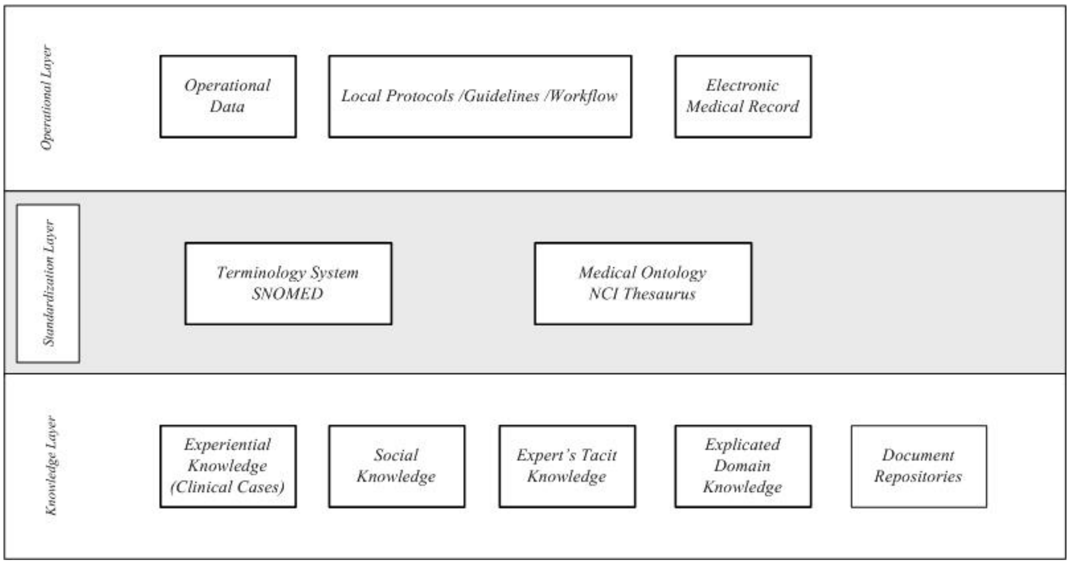

Figure 3: KM Solution Architecture

Once an OCC is created, it is indexed and stored in case base. We can compare an OCC generated from a new case to past cases stored in case base using utility-oriented matching [28] which does not depend on problem descriptions.

Utility-oriented matching is a new research direction for CBR. Instead of the traditional view of CBR "similar problems have similar solutions", it uses level of utility reasoning. When a new case comes out, it uses "similarity function" sim (p,si) to compare the problem p of the new case with a solution s_i which is a solution of an old case stored in the case base. While the new problem p is transformed into utility description d, utility description d_i is generated from solution s_i when the case base is retrieved. Then, d and d_i is compared to approximate the utility of a given solution s_i for a new problem. If there is a match, solution s_i is adapted and applied to the new case. After comparison, the OCC of the new case enters into the case base (Figure 3).

The case-based structure contains the description and solution in an EMR and the adaptation/ repartition case may contain the case-based and the outcome latest update of an EMR (Figure 4).

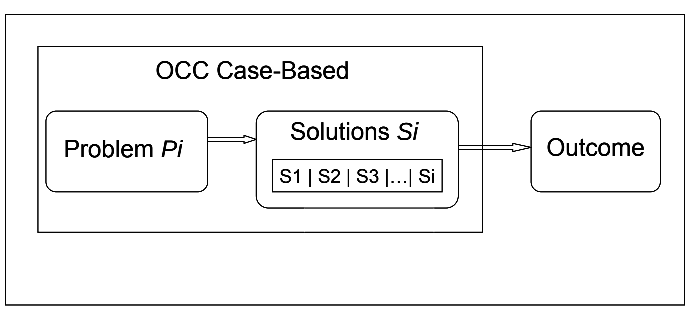

Figure 4. A Compositional-Solution OCC Structure

7.2 Knowledge Management Solution Strategy

In a CBR application, a new case usually depicts as a problem situation and a reasoning means using past cases to solve the new case. A past case, stored case, or retained case is a previously experienced or resolved solution which has been processed and learned in a way that it can be reused to solve of future problems. “Case- based reasoning is - in effect - a cyclic and integrated process of solving a problem, learning from this experience, solving a new problem, etc.” [29]

7.3 CBR R5 Process Model

The R5 model of CBR is comprised of five tasks [30] [31] (Figure 5):

- Retrieve the most similar cases
- Reuse the cases to attempt to solve the problem
- Revise the proposed solution
- Repartition the problem and solution domains
- Retain the new solution as part of a new case

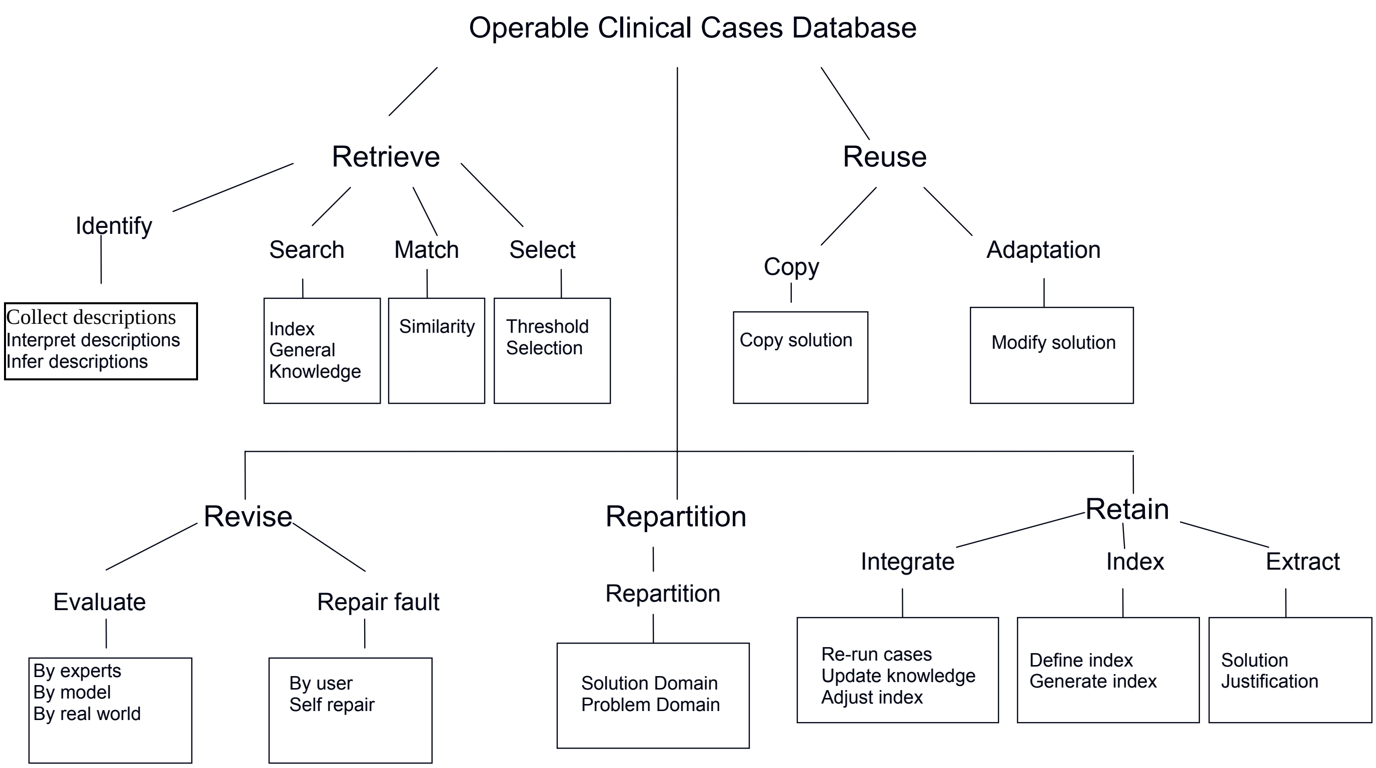

Figure 5. General CBR Methodologies

7.3.1 Case Retrieval

The process includes two phases: (1) Recalling the previous cases (2) Selecting the best subset of cases. Although it is usual for physicians to think in this way, but to implement it in computers it’s necessary to use matching or similarity assessments. The main problems would be “Indexing-Vocabulary” and “Situation-Assessment” which could be partially solved by “Retrieval & Matching Algorithms” to search a massive case library in an efficient way to find the appropriate cases (Figure 6) [32].

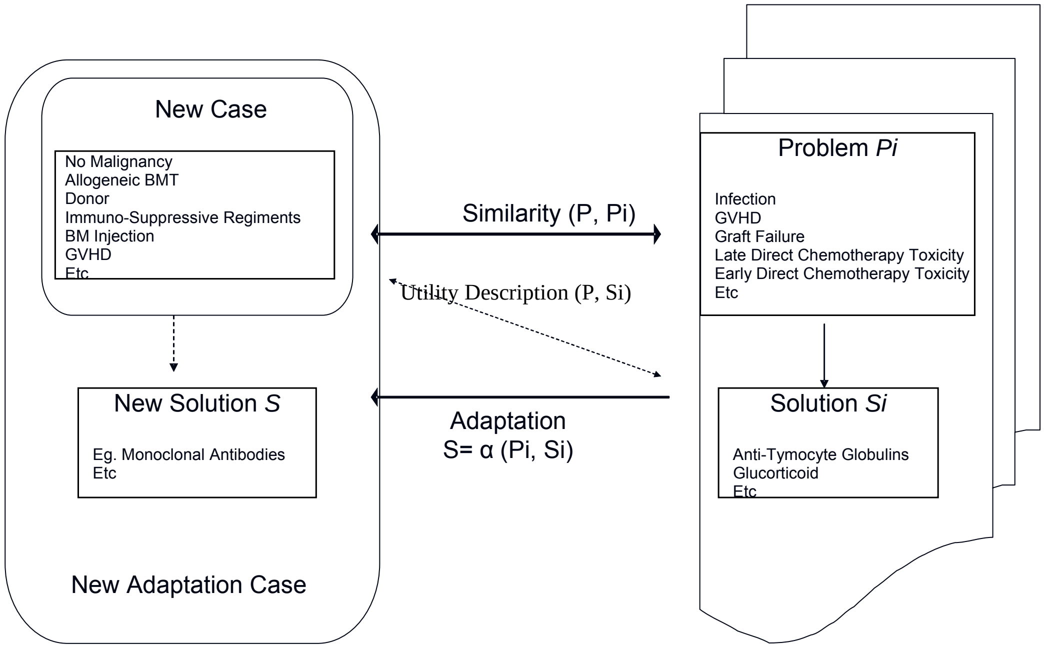

Figure 6. Retrieval Method of CBR Model

7.3.2 Case Reuse

When a retrieved case is used to solve a new case, there are two contexts being focused: differences among the retrieved and the current case which descriptions of a retrieved case are matched with the new cases' descriptions. When the retrieved solution is only partially used to solve the new case, there are two ways to reuse the past case solution: transforming the past solution to the new case's solution or deriving a new solution from the method that constructs the past solution. This is called an adaptation process in the CBR cycle. A new causal explanation will be built from the old causal explanations by rules with condition- partition indexing differences and with a transformational part of the rule. The case base will be updated by a new learnt case or by modification of retrieved case.

7.3.3 Case Revision

When a case solution generated during the reuse phase fails during validating (evaluating) the result, an opportunity for learning from failure or updating is considering. This phase is called case revision and consists of two tasks: evaluating the case solution generated by reuse. If successful, learning from the success case retains or repairing the case solution using domain-specific knowledge. The explanation-based learning technique can be used to repair the solution.

7.3.4 Case Repartition

If a previous case is found, there are two possibilities:

- If a solution for new case is also found in the domain of solutions, there is no need to store the new case.
- If there is no solution found or the solution is no longer appropriate for a new case problem, we need to repartition the domain of solutions and the domain of the problem descriptions. In this case, the new case problem is either added to a partition of previous

problems if it meets some certain degree of similarities of the class partition, or the new partition for the new case will be created in the cased-base domain (Figure 7).

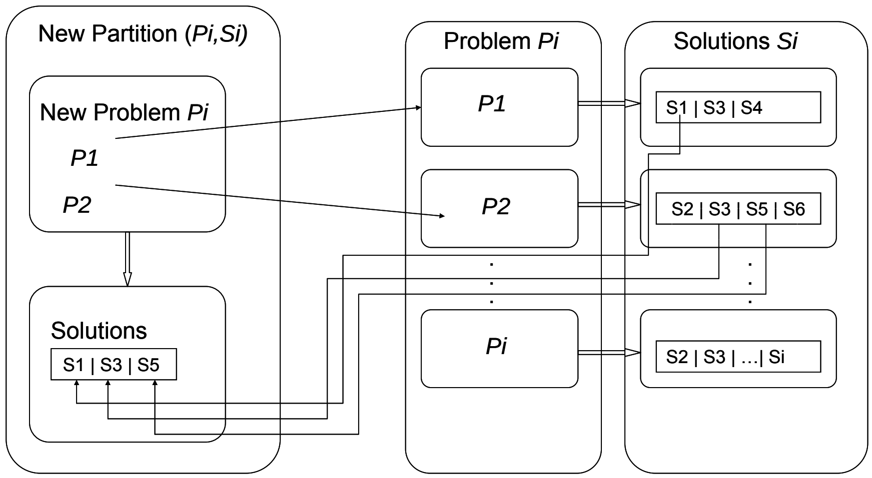

Figure 7. A Repartitioned Case in R5 CBR Model

7.3.5 Case Retain

It doesn't matter how the new problem is solved by using the retrieved case, the solution learning from the reuse and revision processes should be retained. That is because the proposed solution is triggered by the outcome of the evaluation and possible repair. It involves selecting which information from the case to retain, in what form to retain it, how to index the case for later retrieval from similar problems, and how to integrate the new case in the memory structure.

8. EVALUATING BMT CBR

CBR systems inherit real world's fuzziness and uncertainty which primarily come from [33]:

- Validity of the knowledge base content (rules, frames, etc.)
- Validity of a user's subjective response and feeling

To evaluate the BMT CBR system, we randomly select 2/3 BMT cases to establish the knowledge case and the other 1/3 cases as simulated cases to evaluate this system using a method similar to Iliad's Simulator Mode which is designed to provide a realistic problem-solving experience in "working up a patient" with a clinical diagnostic problem(s). [34].

In our case, experts' interventions are needed. We input data (findings) of these simulated cases to the CBR system and assess the outcomes (improvement of ECOG score) in the following ways [35], assuming each case has top 3 outcomes as outcome:

- The score for correct outcome- the proportion of the outcomes which is consistent with these cases' fact
- The score for rank- the average rank of the correct (or closely related) outcomes as it appears on the computer-generated list
- The comprehensiveness score- the average proportion of the appropriate evaluations (outcomes) which is considered reasonable by the experts but not necessary consistent with these cases' fact

9. DISCUSSION

Through analysis of the BMT clinical knowledge management dynamics we propose a CBR solution as a decision support system. The R5 architecture combined with the compositional adaptation is optimal for the complexity of the BMT data.

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REFERENCES

[1] Patel VL, Kushniruk AW, Yang S, Yale J-F, Impact of a Computer-based Patient Record System on Data Collection, Knowledge Organization, and Reasoning. *J Am Med Inform Assoc 2000*. Vol &(6), pp 569-585.

[2] Abidi, SSR & Manickam, S. Leveraging XML-based electronic medical records to extract experiential clinical knowledge: An automated approach to generate cases for medical case-based reasoning systems. *International Journal of Medical Informatics.* Vol. 68, 2002, pp. 187-203.

[3] Eshach H, Bitterman H. From case-based reasoning to problem-based learning. *Academic Medicine.* Vol 78(5), 2003, pp. 491-6.

[4] Couban S, Stewart AK, Loach D, Panzarella T, Meharchand J, Autologous and allogeneic transplantation for multiple myeloma at a single centre. *Bone Marrow Transplantation*, (1997) 19, pp.783–789

[5] Goodman JL et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *New England Journal Med* 326:845, 1992

[6] Goodrich M et al. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intem Med 118:173, 1993

[7] Althoff K-D, Nick M, *How to Support Experience Management with Evaluation - Foundations, Evaluation Methods, and Examples for Case-Based Reasoning and Experience Factory*. LNAI series, 2003, Springer Verlag.

[8] Nick M, Althoff K-D, Decker B, Tautz C, How to Go Online with an Experience Base. *In Proceedings of German Conference on Professional Knowledge Management - Experiences & Visions 2001*, Baden-Baden.

[9] Lees B, Hamza M, Irgens C, Managing Engineering Design Experience with Case-Based Reasoning. *In Proceedings of German Conference on Professional Knowledge Management - Experiences & Visions 2001,* Baden-Baden.

[10] Quality and safety of clinical decision support systems: A draft protocol for discussion. *OpenClinical Green Paper,* 2002. http://www.openclinical.org/docs/qands011.pdf

[11] Bartlmae K, Riemenschneider M, Case Based Reasoning for Knowledge Management in KDD-Projects. *In Proceedings of the 3rd International Conference on Practical Aspects of Knowledge Management (PAKM 2000),* Basel, Switzerland.

[12] Montani S, Bellazi R, Portinale L, D'Annunzio G, Fiocchi S, Stefanelli M, Diabetic patients management exploiting case-based reasoning systems, *Computer Methods and Programs in Biomedicine*, 12 May 1999

[13] LeBozec C, Jaulent MC, Zapletal E, Heudes D, Degoulet P, IDEM:A web applicaion of case-base reasoning in histopathology, *Computers in Biology and Medicine* vol 28, (1998) 473-487

[14] Schmidt R, Gierl L, Case-base reasoning for antibiotics therapy advice: an investigation of retrieval algorithms and prototypes, Artificial intelligence in Medicine vol 23, (2001) 171-188

[15] Fritche L, Schlaefer A, Budde K, Schroetter K, Neumayer H, Recognition of situations from time series of laboratory results by case-base reasoning, *JAMIA* vol9, Sep 2002 520-527

[16] Abidi, SSR & Manickam, S. Leveraging XML-based electronic medical records to extract experiential clinical knowledge: An automated approach to generate cases for medical case-based reasoning systems. *International Journal of Medical Informatics.* Vol. 68, 2002, pp. 187-203.

[17] Finnie G, Sun Z, R5 model for case-based reasoning. *Knowledge-Based Systems* 16 (2003) pp. 59–65

[18] Aamodt, A. Plaza, E. Case-Based Reasoning: Foundational Issues, Methodological Variations, and System Approaches. *AI Communications*. IOS Press, 1994, Vol. 7: 1, pp.39- 59

[19] Burke R, The Wasabi Personal Shopper: A Case-Based Recommender System, AAAI-99 *Sixteenth National Conference on Artificial Intelligence*, 1999 Orlando, Florida Proceedings. p. 844-849

[20] Abidi SSR, Designing Adaptive Hypermedia for Internet Portals: A Personalization Strategy Featuring Case Base Reasoning With Compositional Adaptation. In Garijo FJ, Riquelme JC & Toro M (Eds.) Lecture Notes in Artificial Intelligence 2527: *Advances in Artificial Intelligence* (IBERAMIA 2002). Springer Verlag: Berlin, 2002. pp. 60-69.

[21] Covitz PA, Hartel F, Schaefer C, De Coronado S, Fragoso G, Sahni H, Gustafson S, Buetow KH, caCORE: a common infrastructure for cancer informatics. *Bioinformatics.* 2003 Dec 12;19(18). Pp. 2404-12.

[22] Berners-Lee T, Hendler J, Lassila O, The Semantic Web. *Scientific American* May 2001, pp 35-43.

[23] Shabo, A. BMT (Bone-Marrow Transplantation) Document Ontology. Version 2, 2001. *IMR Project*. IBM Research Lab, Haifa, Israel.

[24] Yuval Shahar, et al. Knowledge-Based Temporal Abstraction in Clinical Domains, *Artificial Intelligence in Medicine*, 1996 8(3):267-298

[25] Aronson A, Effective Mapping of Biomedical Text to the UMLS Metathesaurus: *The MetaMap Program. Proceedings of AMIA 2001*, pp. 17-21.

[26] Hartel F, *NCI Metaphrase User Guide Version 2.0. 2002.* National Cancer Institute, National Institutes of Health, Bethesda, MD.

[27] Jacquelinet C, Burgun A, Delamarre D, Strang N, Djabbour S, Boutin B, LeBeux P, Developing the ontological foundations of a terminological system for end-stage diseases, organ failure, dialysis and transplantation. *Interntional Journal of Medical Informatics 2003*, 70, pp. 317-328.

[28] Robert Dolin, Peter L. Elkin, Charlie Mead. *HL7 Version 3 Templates*, September 18, 2002. Baltimore, MD.

[29] Aamodt, A. Plaza, E. Case-Based Reasoning: Foundational Issues, Methodological Variations, and System Approaches. *AI Communications*. IOS Press, 1994, Vol. 7: 1, pp.39- 59

[30] Kolodner, J. *Case-Base Reasoning*, Georgia Institute of Technology , Morgan Kaufman Publisher,1993

[31] A. Aamodt, E. Plaza (1994); AICom - *Artificial Intelligence Communications*, IOS Press, Vol. 7: 1, pp. 39-59. (http://www.iiia.csic.es/People/enric/AICom.html#RTFToC19)

[32] Bergmann, R., Richter, M.M., Schmitt, S., Stahl, A., Vollrath, I. Utility-Oriented Matching: A New Research Direction for Case-Based Reasoning. 9th *German Workshop on Case-Based Reasoning* (GWCBR'2001). (http://wwwagr.informatik.uni-kl.de/~bergmann/)

[33] KS Metaxiotis, J-E Samouilidis, JE Psarras, Expert Systems in Medicine: Academic Illusion or Real Power? *Journal of Informatics in Primary Care* 2000 (February):3-8

[34] Applied AI Informatics, *ILIAD Users Manual*

[35] Eta S. Berner, George D. Webster, Alwyn A. Shugerman, James R. Jackson, James Algina, Alfred L. Baker, Eugene V. Ball, C. Glenn Cobbs, Vincent W. Dennis, Eugene P. Frenkel, Leonard D. Hudson, Elliott L. Mancall, Charles E. Rackley, and O. David Taunton Performance of Four Computer-Based Diagnostic Systems, *The New England Journal of Medicine*, Volume 330, Number 25, June 23, 1994, 1792-1796