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オブジェクト指向データベースの概念に基づく先天異常症の臨床症例の記述

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Abstract

先天性顔貌異常症は疾患の頻度が稀であるため、臨床医が経験する症例数はきわめて少なく、先天性顔貌異常症の専門家でない限り、診断することは困難である。我々はこのような症例を蓄積し、診断支援に役立つような症例データベースの作成のために、オブジェクト指向データベースの形式を選択し、データベースを作成した。さらにこれを診断支援システムにて利用すべく、エキスパートシステム及び症例準拠型システムを含めた診断支援システム COBRA(COmputer-assisted Birth defect Recognition Aid) を開発した。このシステムでは症候の入力方法として症候を含んだ画像を選択する形式を選択、診断結果から典型的な症例を提示する形式となっており、我々は現在、当システムを評価中である。

Description of Clinical Cases of Congenital Anomalies based on Object-oriented Scheme

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Abstract

Medical data consist of many kinds of data from different resources, such as natural language data, sound data from physical examinations, numerical data from laboratory examinations, time-series data from monitoring systems, and medical images (for example, X-ray, Computer Tomography, and Magnetic Resonance Image). Therefore it has been pointed out that medical databases should be implemented as multidatabases. However, there have been few systems which integrate these data into multidatabases. In this paper, we report a system called COBRA (Computer-Operated Birth-defect Recognition Aid), which supports diagnosis and information retrieval of congenital malformation diseases and which also integrates natural language data, sound data, numerical data, and medical images into multidatabases on syndrome of congenital malformation. The results show that object-oriented scheme makes it easy to implement and integrate these knowledge-databases in COBRA, which suggests that these clinical databases should be implemented as object-oriented databases.

1. Introduction

There have been developed many medical decision support systems, such as MYCIN since the end of 1970's [2]. One of the most important problems of these decision support systems is that their input interfaces are based on verbal information and that they cannot handle multi-data, which causes the following two problems. First, users have to know the correct meaning of medical technical terms, such as symptoms, on the input screen. Usually, however, medical experts who major in respiratory diseases do not know technical terms in neurology precisely. Therefore it is hard even for medical experts to use a medical expert system, which makes them difficult to apply to real-world situations. Second, we often need non-verbal information, such as visual images in order to understand medical technical terms, since those technical terms are closely related to those kinds of data. For example, a neurological symptom "ptosis" can be explained in words as shown in Subsection 3.1 [1]. However, even medical experts cannot easily understand several technical terms in the explanation. Thus, if we can use visual images as shown in Fig. 6, then it may be easier to understand those terms[1].

Interestingly, those problems are also closely related not only to practical use, but also to medical education. Medical education needs both verbal information and non-verbal information, because substantial part of medical education is to teach the way how to describe non-verbal information by using technical terms. For example, medical students do not exactly know about ptosis. In order to understand this symptom, we need a picture or a photograph which shows a typical case of ptosis. In other words, medical education can be viewed as a process in which students learn the relations between verbal information and non-verbal information.

Therefore, the above problems in medical decision support and education suggest that medical intelligent systems should deal with many different kinds of data for practical use. Actually, medical data consist of many kinds of data from different resources, such as natural language data, sound data from physical examinations, numerical data from laboratory examinations, time-series data from monitoring systems, and medical images (for example, X-ray, Computer Tomography, and Magnetic Resonance Image). Furthermore, since medical technical terms are closely related to the characteristics of those kinds of data, we need to represent the semantic relations between medical terms and non-verbal information in order to understand medical terms and their meaning. Thus, it has been pointed out that medical databases should be implemented as multidatabases, although there have been few systems which integrates these data into multidatabases.

[1]The arrow in Fig. 6 shows the location where a symptom "Epicanthal Folds" can be observed.

In this paper, we report a system, called COBRA (Computer-Operated Birth-defect Recognition Aid), which supports decision-making using an expert-system module and a module of case-based reasoning. COBRA also supports information retrieval of congenital malformation diseases, based on an object-oriented scheme, and integrates natural language data, sound data, numerical data, and medical images into multidatabases on congenital malformation diseases [4].

This system is implemented on one kind of object-oriented databases, SuperCard in Macintosh [6]. It consists of the following four knowledge-bases, called *ontology*, which are implemented as object-oriented databases, and three modules, which are implemented by object-oriented programming language.

These knowledge-databases in COBRA are easily implemented in an object-oriented scheme, which suggests that these clinical databases should be implemented as object-oriented databases. In this paper, we present the present architecture of COBRA, and report how naturally we can implement medical databases as integration of object-oriented databases.

The paper is organized as follows: Section 2 discusses the characteristics of medical knowledge-bases from the viewpoint of heterogeneous knowledge-bases. Then, Section 3 gives an implementation of four types of knowledge-bases: concept ontology, task ontology, event ontology, and case-databases. Section 4 presents four kinds of integration of these heterogeneous knowledge-bases: information retrieval, expert-system module, case-based reasoning module, and case-follow-up module. Section 5 discusses the problems of COBRA. Finally, Section 6 concludes this paper.

2. Integration of Medical Knowledge

Medical knowledge can be classified with respect to the following three axes: verbal, temporal, and typical. In the following subsection, we discuss classification of medical knowledge with respect to the proposed attributes, and how to integrate these kinds of knowledge.

2.1 Verbal and Non-verbal Information

As discussed in Section 1, medical decision-making can be viewed as a process in which medical experts integrate verbal and non-verbal information using their experiences, whereas education can be regarded as a process in which students or residents learn the relations between verbal information and non-verbal information. Thus, the first axis to classify medical knowledge is whether an item is represented as verbal information or not. For example, verbal information on ptosis is the definition of this symptom, diseases in which this manifestation can be observed, the mechanism of this disorder, and so on. On the other hand, non-verbal information on ptosis is a typical medical image or illustration on this symptom. It is notable that these two kinds of knowledge are closely related with each other. In the above example, the definition of ptosis is linked to a typical medical image, where information on the patient, such as the final diagnosis, are attached. In other words, description on ptosis can be represented as integration of verbal and non-verbal information.

2.2 Temporal Information

The second axis is whether the content of information is temporal or not. For example, therapeutic processes can be viewed as temporal information on a patient. After the final diagnostic conclusion, medical experts make and perform a treatment plan. The plan is evaluated temporally, and will be changed if the decided treatment seems to be a failure. Each plan includes information on what type of therapy, such as medication and surgery, should be applied, and is also linked to non-temporal information on each therapy, such as knowledge on drugs. Thus, description on therapy can be viewed as integration of temporal information and non-temporal information.

2.3 Typicality and Atypicality

Finally, the third axis is whether knowledge is general or case-specific. As shown in Subsection 2.1, verbal information on a symptom is linked to a typical medical image. However, even if a typical knowledge can cover most of the cases, exceptions or atypical cases always exist. These atypical cases may be generalized in the future when more atypical cases are accumulated, but they should be stored as knowledge on atypicality in the present situation.

2.4 Integration of Medical Knowledge-Bases

According to these axes, medical knowledge is classified into four categories, each of which we call *knowledge unit*, by a decision tree shown in Fig. 1[2]. It is notable that the above classification is obtained from a viewpoint of medical reasoning and that these units are closely related to each other. Thus, integration of such heterogeneous knowledge-bases can be seen as how to gather information from the above four knowledge units.

In COBRA, we introduce three types of integration, based on an object-oriented approach [7]: first, nonverbal information and verbal information are gathered into three knowledge-bases, which we call *ontologies*. For example, concept ontology is a knowledge-base which describes relations between raw medical resources and concepts or between concepts and concepts, as discussed in Section 3.1.

[2] In this tree, further classification of non-verbal information is not given, for simplicity, although each non-verbal information can be classified with respect to the characteristics of each knowledge.

Verbal?
- *yes* : *Temporal?*
  - *yes* : *Typical?*
    - *yes* : Task
    - *no* : Event
  - *no* : Concept
- *no* : Raw Medical Resources

Figure 1: Classification of Medical Knowledge

Second, integration of three ontologies is introduced in order to describe medical decision support and clinical "case"-databases, as discussed in Section 4. Especially, each case includes medical decision-making processes, which consists of concept and task ontologies, and chronological description of the status, which consists of event ontologies and concept ontologies.

Finally, third, integration of "case"-databases, implemented as Case-Follow-Up module, is introduced to describe relations between "case"-databases, such as family linkage.

In the subsequent sections, we discuss the details of three types of integration.

3. Knowledge-Bases: Ontology

Based on the discussion on medical knowledge shown in Section 2, COBRA includes the following four knowledge-bases, called ontology: concept ontology, task ontology, event ontology, and case-databases. In the following subsections, we discuss the characteristics of these knowledge-bases further.

3.1 Concept Ontology

These knowledge-bases describe knowledge on diseases, clinical observations (symptoms), and other medical concepts, all of which are implemented as the object-oriented databases [7].

(1) Knowledge on Diseases

This knowledge-base represents information on diseases, such as the definition, typical clinical cases, examinations needed for diagnosis. If needed, sound data, such as voice or heart sound, are attached to this knowledge-base. For example, the description of Freeman-Sheldon syndrome consists of the following six items:

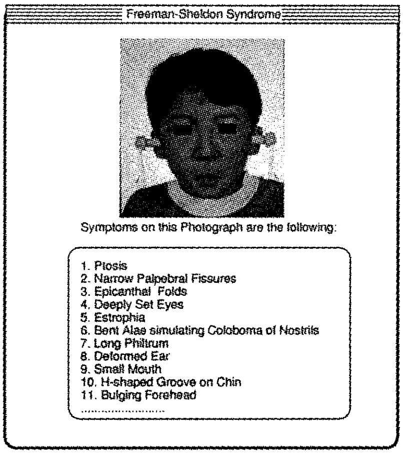

Figure 2: A typical Case-Database of Freeman-Sheldon Syndrome

1. Definition of Syndrome: this syndrome is symptomatologically defined as a set of the 19 symptoms, such as ptosis, narrow palpebral fissures and epicanthal folds, each of which is linked to its knowledge in concept ontology.
2. Typical Photograph of Syndrome: this item is linked to case-databases. For example, Fig. 2 shows a typical case of Freeman-Sheldon syndrome linked to this item, where its symptomatological description is attached.
3. Laboratory examinations: this item is linked to *task ontology*, which is discussed later.
4. Medical Images: this item is linked to *task ontology*, which is discussed later.
5. Mechanisms of Syndrome: although we have few knowledge on the causes of most of the congenital malformation, some diseases are said to be of genetic origin.
6. Genetics: there have been reported several famous families, some of whose members suffered from the same syndrome [1]. These genetic knowledge makes us understand the characteristics of this disease from the viewpoint of genetics, such as the family tree shown in Fig.3[3].
7. Diagnostic Rule: it is closely related with the definition of a syndrome. In the case of Freeman-Sheldon syndrome, the rule is defined as follows:

[3]Square and circle denote male and female respectively, and black square and circle denote a patient suffering from the same syndrome. Therefore this figure shows that his mother firstly suffers from Freeman-Sheldon syndrome and that her offspring inherits the genetic characteristics in a dominant way.

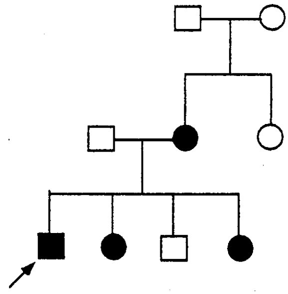

Figure 3: A Family Tree of Freeman-Sheldon Syndrome

> If a patient has the following 19 symptoms: ptosis, narrow palpebral fissures, epicanthal folds, deeply set eyes, estropia, exotropia, small nose, bent alae simulating coloboma of nostrils, long philtrum, deformed ear, small mouth, H-shaped groove on chin, bulging forehead, short stature, poor weight, scoliosis, ulnar deviation of fingers, whistling face, and mask-like face, then Freeman-Sheldon syndrome is suspected with probability 1.0.

(2) Knowledge on Clinical Observations

This knowledge describes the meaning of clinical observations, how to observe this manifestations, and statistical measures with a syndrome is suspected when this symptom is observed.

For example, ptosis is a symptom of the eyelids. In the normal individual, the eyelids on each side are at the same level with respect to the limbus of the cornea [1]. However, in the cases of ptosis, the upper eyelids are retracting and going down below the limbus of the cornea. Although this symptom is a characteristic feature of muscular dystrophies, myasthenia gravis and third nerve lesions, it can also be observed in congenital malformations: this symptom is not specific to any congenital malformations, since almost the all cases may have it. Therefore the statistical measure should be low for each disease.

In these knowledge-databases, the meaning of each clinical observation is linked to corresponding anatomical knowledge, and physiological knowledge. In the above example, anatomical knowledge on the third nerve is referred, because ptosis is closely related to the third nerve. Furthermore, the item which shows the way to observe manifestations is linked to the corresponding task ontology. In the above example, ptosis is linked to knowledge on neurological examinations, since ptosis can be observed by an ordinary neurological examination.

(3) Knowledge on Other Medical Concepts

It is not sufficient to implement only the concepts of diseases and symptoms. We also need anatomical knowledge, physiological knowledge, and knowledge on examinations, such as and laboratory examinations.

In the case of ptosis, we need to understand anatomical knowledge on the third nerve in order to understand ptosis. The third nerve cell is located in the midbrain and controlled by neurons in the upper region, such as encephaly. This nerve passes near the chiasma of optic neurons, and cartoid artery, and it connects with optical muscles. Thus, the malfunction of the third nerve may cause that of optical muscles, which results in ptosis, estrophia, and extrophia. Conversely, ptosis makes us suspect the malfunction of optical muscles or that of the third nerve: the former disorder can be observed in the cases of myathenia gravis, and the latter one can be observed in those of third nerve palsy. These symptoms are also included in a typical case of Freeman-Sheldon syndrome (Fig. 2), and in its diagnostic rule.

Actually, these kinds of knowledge-bases are indispensable to education of residents or students, since it is difficult for them to associate some disorders with anatomical knowledge. For this purpose, we implement such kind of knowledge as much as possible.

3.2 Task Ontology

This knowledge-bases describes the knowledge on laboratory examinations and medical images.

Laboratory Examinations

There are several syndromes caused by endocrinological disorders. For example, hypothyroidism, whose patient cannot generate enough thyroid hormone, causes several disorders, such as mental retardation. Therefore we need several kinds of laboratory examinations in order to make a differential diagnosis.

Each knowledge-base describes the way to make laboratory examinations, how to interpret the results, and statistical measures with which a syndrome is suspected when the specific results are observed. For the above example, when concentration of thyroid hormone is very low and when concentration of thyroid stimulating hormone is very high, hypothyroidism is strongly suspected with probability 0.99 [1].

Medical Images

Medical images consist of X-ray, Computer Tomography (CT), and Magnetic Resonance Image (MRI). Since these medical images have their own characteristics, medical experts use those images for their specific purpose. For example, when they would like to characterize whether a target region is rich in water or not, they will use MRI technique to focus on that region. This ontology describes these characteristics as the following two items: (1) Parts: information on what parts and components of the body can be focused on by this image, and (2) Resolution: information on what size can be analyzed.

3.3 Event Ontology

This knowledge describes two kinds of temporal knowledge on diseases. One is knowledge on genetics, or family history, and the other is a clinical course of a patient, or present history.

The former part is represented as a family tree, that is, tree structure as shown in Fig. 3. Each node is implemented as an object, which is linked to the ancestor or successor of this node, and to the *case-database* which describes the case of this node. For example, the arrowed black circle is linked to a typical case of this syndrome shown in Fig. 2.

The latter part is linked to each case-database. Since most of the patients treat their malformations by surgery operations, it is important to follow the clinical course after the operation. In order to realize temporal relations, each case-database has a time-stamp and has descriptions on the links to the past and the future case-database. Therefore we can retrieve the past and the future courses from given databases.

3.4 Case-Databases

These databases consist of 66 clinical cases on congenital malformations, whose patients came to the outpatient clinic in Tokyo Medical and Dental University. Each case is composed of the family history, description of symptoms, photographs of this patient, results of laboratory examinations, and medical images, all of which are stored as sub-databases.

These knowledge-databases in COBRA are implemented in the object-oriented scheme, which suggests that these clinical databases should be implemented as object-oriented databases.

4. Integration of Knowledge-Bases

The present version of COBRA supports the following four kinds of main procedures: information retrieval, expert system, case-based reasoning, and case-follow-up module, all of which COBRA uses the four aforementioned knowledge-bases.

4.1 Information Retrieval Module

Basically, COBRA provides *event-driven* interfaces. That is, users can refer to all the information related to each item in the databases. For example, when users are retrieving a case shown in Fig. 2, they can refer to any items in this case-record, such as the characteristics of the syndrome and those of symptoms.

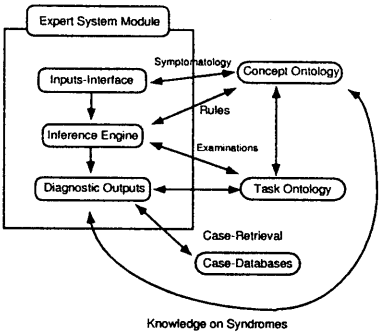

Figure 4: Integration in an Expert-system Module

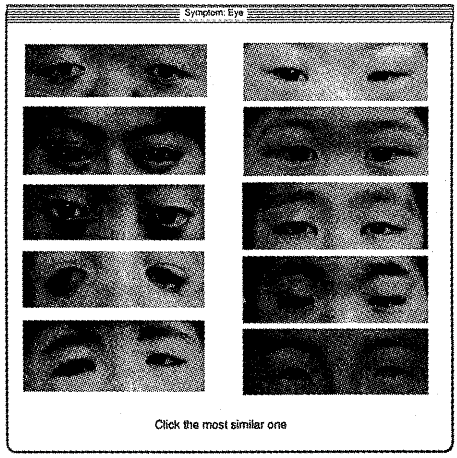

Figure 5: An Example of Input-Interface

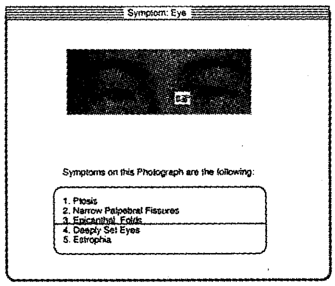

Figure 6: A Help Window

4.2 Expert-System Module

This module is developed in order to diagnose future clinical cases, and also used as an intelligent tutoring system for medical residents, as discussed in Section 1. It consists of three submodules: Input-interface, Inference engine, and Diagnostic outputs, all of which connect with concept ontology, task ontology, and case-databases. Fig. 4 shows these connections and how diagnostic procedures work. In the subsequent paragraphs, we discuss these diagnostic processes in detail.

First, a user inputs observations from menus given by Input-interface submodule. COBRA provides two kinds of interfaces, one of which is a list of descriptions on symptoms, and the other of which is a list of photographs. For our purpose shown in Section 1, COBRA mainly supports the latter interface. For example, Fig. 5 shows a list of photographs which describes typical patterns of symptoms of eyes. A user cannot only select one of those photographs, but also see their information. For example, when a user select the right bottom picture and click the help button, then COBRA shows the help window as shown in Fig. 6, which gives information on what kind of symptoms can be observed.

Furthermore, when a user clicks one of the symptoms, then COBRA gives us where the selected symptom is observed. These symptoms are also connected with its corresponding concept ontology, where the concepts of these symptoms are described.

After users select a photograph, COBRA interprets the input and transforms it into verbal information acquired from medical experts. For example, when a user selects the right bottom picture in Fig. 6, COBRA takes the following five symptoms as inputs: ptosis, narrow palpebral fissures, epicanthal folds, deeply set eyes, and estrophia, all of which are shown in the help window (Fig. 6).

Second, COBRA applies inference rules to all the inputs, calculates total certainty factors from each statistical measure attached to each symptom in the corresponding concept ontology[4], and finally orders diagnostic candidates according to the values of total certainty factors.

When other examinations, such as X-ray, are needed to make a differential diagnosis, the inference engine searches for its knowledge from task ontology, and retrieves what kind of manifestations should be got from those examinations. The inference engine also searches for the corresponding statistical measures and other important knowledge on the above manifestations from concept concept ontology. Then it calculates certainty factors for each case when a specific manifestation is derived or not.

Finally, Diagnostic-outputs submodule outputs the final candidates and retrieves typical cases for each candidates. Furthermore, this submodule searches for the concept of syndromes from concept ontology.

[4]Certainty factors are calculated using the MYCIN formulae [2].

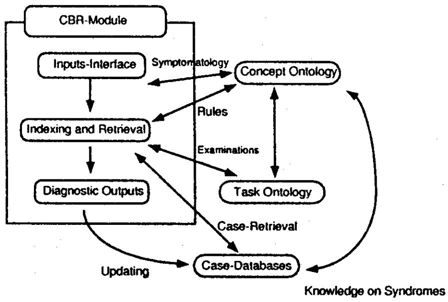

Figure 7: Integration in a CBR Module

4.4 Case-Based Reasoning Module

This module is developed in order to diagnose future clinical cases and to retrieve similar cases, based on Case-Based Reasoning(CBR) [5], and it is also used as an intelligent tutoring system for medical residents.

Although the interfaces for inputs are the same as the Expert-System module, reasoning strategy is different: when all inputs are completed, similarity measures are calculated, and the module outputs a list of best-fit cases.

A CBR module consists of three submodules: Input-interface, Indexing and Retrieval, and Diagnostic outputs, which connect with concept ontology, task ontology, and case-databases. Fig. 7 shows these connections and how case-retrieval procedures work. In the subsequent paragraphs, we discuss these diagnostic processes in detail.

First, a user inputs observations from menus given by Input-interface submodule. This module is almost the same as that in Expert-system module. That is, COBRA provides two kinds of interfaces, one of which is a list of descriptions on symptoms, and the other of which is a list of photographs. These symptoms and photographs are connected with their corresponding concept ontology where the precise knowledge on those symptoms is stored. After a user selects a photograph, COBRA interprets the input and transforms it into verbal information.

Second, COBRA calculates the following similarity measure from all the inputs. Although there are many kinds of similarities, we adopt a family of similarity measures based on a contingency table. Let us consider a contingency table for a rule of a certain disease (Table 1). The first and second column denotes the positive and negative information of a rule. The first and second row denotes the positive and negative information of a sample. Then, for example, a denotes the number of attributes in a sample which matches a rule. From these tables, several kinds of similarity measures can be defined. The best similarity measures

Table 1: Contigency Table for Similarity

		Rule		
		1	0	Total
Sample	1	a	b	a+b
	0	c	d	c+d
		a+c	b+d	a+b+c+d

Table 2: Definition of Similarity Measures

(1) Jaccard's coefficient	$a/(a+b+c)$
(2) χ^2-statistics	$N(ad-bc)^2/M$
(3) point correlation coefficint	$(ad-bc)/\sqrt{M}$

$N = a+b+c+d$, $M = (a+b)(b+c)(c+d)(d+a)$

in the statistical literature are three measures shown in Table 2. From these three measures, Jaccard's coefficient, whose computational complexity is the loweste, is used for defining similarity.

After similarity measures are calculated for all the cases, the submodule orders candidates by the values of similarity measures.

Finally, Diagnostic-outputs submodule outputs the five most similar candidates and updates case-databases with a given new case.

4.5 Case-Follow-Up Module

As discussed in Subsection 3.3, COBRA supports case-follow-up study based on the scheme of object-oriented databases as shown in Fig. 8. From the viewpoint of integration of knowledge-bases, this process can be seen as integration of case-databases, discussed in Section 2. Furthermore, this integration is classified into the following two kinds of integration. The one is linkage between case-databases and "clinical-course" database. Since case-database describes the status of a patient at one instant, as discussed in Section 2 and 3, a "clinical-courses" database, is introduced to represent the temporal relations between each case-database of the same patient.

The other one is relational description between "clinical-courses" databases and the corresponding family tree, which represents relations between patients and their families with respect to congenital malformations. For the above example in Section 3, a family tree shown in Fig. 3. is linked to the database on clinical courses. Then, this clical-courses databases are linked to each case, shown in Fig. 2. It is notable that this whole structure can be viewed as a temporal hierarchy: the temporal order of a family tree is from 20 to 40 years, whereas the temporal order of clinical courses is

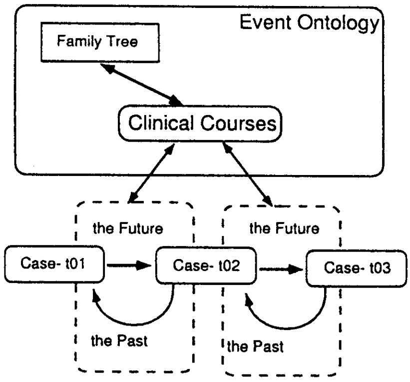

Figure 8: Case-Follow-Up Module

from 1 to 10 years, and each case describes the instant.

In this module, users can retrieve any information about the selected patient from any chronological point. For example, users can search for the clinical courses, each of which is described as case-databases, such as shown in Fig. 2.

As discussed in Section 2, since each case can be viewed as an integrated instance of concept ontology, task ontology, and event ontology, users also retrieve enough information to understand the status of the patient, such as final diagnosis, and knowledge on the final diagnostic conclusion.

This structure is very important for students or residents to learn clinical courses, and therapy dynamically, since this architecture shed light on dynamic aspects of reasoning of domain experts.

In the present version of COBRA, this architecture is only applied to the case-follow-up module, since we do not have so many follow-up data. However, we incorporate this architecture into other module in the near future, because this temporal architecture is also very important for clinical support.

5. Discussion

This system is implemented on a kind of object-oriented databases and programming language, SuperCard in Macintosh [6].

The hardest problem is that a huge space is needed to include photographs and medical images of high quality. In general, COBRA needs 1.5 to 2.0 MB to describe one clinical case-data. Therefore it spends about 560MB only to store case-databases, which makes the seeking speed very slow. However, there are more than 1000 syndromes reported in the literature, although we are now using only 260 clinical cases and 66 syndromes. This means that we need much space to extend our system.

Actually, since this size is beyond the power and capacity of personal computers, we cannot extend the PC version of COBRA into a more general version. Although one solution seems to develop our system only in Sparc station, the searching speed is too slow even in the present version: 20 to 40 sec for retriving a case, caused by loading high quality images.

Thus, there is a trade-off between the searching speed and the quality of medical images. In order to get higher speed, the quality should be lessened, whereas the speed will be low if we need much information on images. So, it seems to be two solutions in the present situation. One is to reduce as much quality of medical images as possible without loss of information. However, even a simple symptom may need high quality of images. Moreover, many symptoms should be presented in complicated cases, which are indispensable to medical education. Thus, simple reduction of images is not applicable for our purpose.

The other one is to introduce two steps for loading medical images: only small images are included in description on ontologies and case-databases, and high quality images are loaded only when we need. Compared with the above solution, this may be more applicable from the viewpoint of medical education, because precise information can be retrieved when it is needed. Thus, the latter solution seems to be better, and we are planning to incorporate the latter mechanism. It is also our future work to evaluate the proposed steps.

6. Conclusions

In this paper, a system called COBRA is introduced, which supports diagnosis and information retrieval of congenital malformation diseases and which also integrates different resources of data into multidatabases.

The results show that these knowledge-databases is easy to be implemented on the object-oriented scheme, which suggests that these clinical databases should be represented as object-oriented databases.

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