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Ontology Modelling for FDA Adverse Event Reporting System

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Abstract—Ontologies are relevant to a specific knowledge or application domain and it represents a set of concepts and their inter-relationships. Ontological design comprises of ontology development process, the ontology life cycle, the techniques and methodologies for building ontologies, and the tools and language that support them. A possible ontology model for FDA Adverse Event Reporting System(FAERS), using METHONTOLOGY is proposed in this paper.

Keywords-*Ontology, Ontology Modelling, Clinical Terminology, FAERS, METHONTOLOGY*

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I. INTRODUCTION

Ontology plays a major role in organizing and categorizing knowledge content by establishing the concepts and their inter-relationship. An ontology is domain or application dependent and it is designed for reuse and share. With the abundance of data in the medical domain, overlapping knowledge is an issue which can be taken care of by Ontology engineering[1].

The IEEE defines methodology as "a comprehensive, integrated series of techniques or methods creating a general systems theory of how a class of thought-intensive work ought to be performed".

In ontology development a new ontology concept is modeled by carrying out three categories of activities[1], namely

1) Ontology management activities
2) Ontology development oriented activities
3) Ontology support activities

FAERS[6] is a computerized database for the spontaneous reporting of adverse events and medication errors involving human drugs and therapeutic biological products. The database is maintained by the U.S. Food and Drug Administration (FDA). Data used is the Quarterly Data Extract from FAERS. Data is organized into the following files:

1) Demographic File[6] : contains patient demographic and administrative information.
2) Drug File[6] : contains drug/biologic information for as many medications as were reported for the event.
3) Reaction File[6] : contains all MDRA terms coded for the adverse event.
4) Indication File[6] : contains all MDRA terms coded for the indications for use (diagnoses) for the reported drugs.
5)Outcome File[6] : contains patient outcomes for the event.

The database uses “Medical Dictionary for Regulatory Activities" (MDRA) [5] terms to code for events of reactions and indications. MDRA[5] is a controlled vocabulary widely used as a medical coding scheme. Its subject matter comprises signs, symptoms, diseases, diagnoses, therapeutic indications, results of investigations and procedures[4]. The FAERS system does have a formal dictionary, but it is not publicly available. The primary source of the FDA dictionary is Structured Product Labeling (SPL).

II. LITERATURE SURVEY

A series of methods and methodologies have been reported for developing ontologies since 1990. Methods such as Cyc development (1990), Enterprise Ontology(1995), KACTUS(1996), METHONTOLOGY(1999), On-To-Knowledge(2001) have been used for ontology modeling either from scratch or re-engineering existing ontologies. METHONTOLOGY is among the more comprehensive ontology development methodologies[1]. It provides for building ontologies either from scratch, reusing existing ontologies as they are, or by a process of re-engineering them. The framework enables the construction of ontologies at the knowledge level or the conceptual level instead of the implementation level. Ontologies developed using METHONTOLOGY exist in various domains such as legal systems, chemistry, artificial intelligence etc.

Healthcare systems have abundant of collected medical data and thus the need for manipulating this semantically rich and highly structured clinical data in a distributed environment is very vital. The ability to share and link the wealth of collected data largely determines improvement of health care practices and the development of better bio-medical products. [7]

III. METHODOLOGY

Ontology modeling using METHONTOLOGY involves the following steps[1] :

1. Specification
2. Conceptualization
3. Formalization
4. Implementation
5. Maintenance

In METHONTOLOGY an ontology life cycle is based on evolving prototypes. For each prototype, we begin with the identification of tasks to be performed, their arrangement and the time and resources required for completion. This is followed by the ontology specification activity. The management and support activities are performed.

in parallel with the other development activities during the entire life cycle of the ontology.

To proceed further with the development process, the following components need to be identified that will help build

the ontology: Concepts, Relations, Instances, Constants, Attributes, Formal Axioms and Rules.

Concepts are taken in a broad sense. Concepts are organized in taxonomies through which inheritance mechanisms can be applied[1]. Relations represent a type of association between concepts of the domain. If the relation links two concepts, it is called binary relation. An important binary relation is Subclass-Of, used for building the class taxonomy. Each binary relation may have an inverse relation that links the concepts in the opposite direction. Instances are used to represent elements or individuals in an ontology. Constants are numeric values that do not change during much time. Attributes describe properties of instances and of concepts. Formal axioms are logical expressions that are always true and are normally used to specify constraints in the ontology. Rules are generally used to infer knowledge in the ontology, such as attribute values, relation instances, etc.[1]

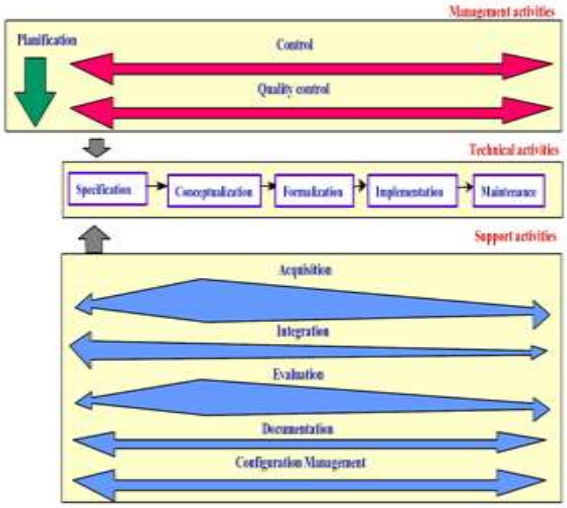


Fig 1. Development process and life cycle of METHONTOLOGY[1]

IV. IMPLEMENTATION

Conceptual modeling in METHONTOLOGY

The objective of conceptual modeling phase in METHONTOLOGY is to organize and structure the knowledge acquired during the knowledge acquisition phase. It will make use of external representations that are independent of the knowledge representation paradigms and implementation languages in which the ontology will be formalized and implemented[1]. A set of informally perceived view of the domain will be converted into a semi-formal specification with the help of intermediate representations (IRs) based on tabular and graph notations to be understood by the domain exerts and ontology developers.

The implementation details of the various tasks of conceptualization activity are in the diagram.

A. *Build glossary of terms*

The first task is to build a glossary of terms that includes all the relevant terms of the domain ,their natural language descriptions, and their synonyms and acronyms[1]. Table 1 illustrates a section of the glossary of terms of the FAERS ontology. The glossary of terms might contain several terms that refer to the same compoment. Such synonym terms should be detected.state the units for each quantity that you use in an equation.

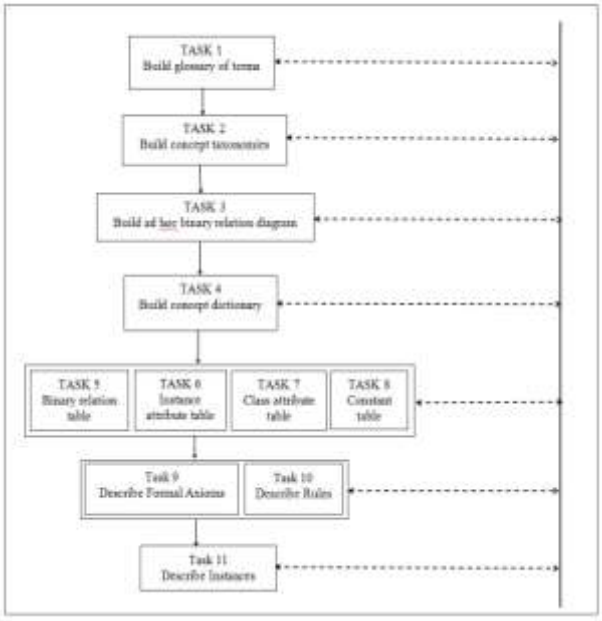


Fig 2. Tasks of the conceptualization activity according to METHONTOLOGY[1]

Table 1 Excerpt from Glossary of Terms for FAERS Ontology

NAME	DESCRIPTION	TYPE
Patient	Patient demographic information	Concept
Age	Numeric value of patient's age at event	Instance Attribute
Age_Code	Unit abbreviation of patient's age	Concept Attribute
Age_Group	Patient's Age Group code	Concept Attribute
Sex	Code for patient's sex	Concept Attribute
Weight	Numeric value of Patient's weight	Instance Attribute
Weight_Code	Unit abbreviation of patient's weight	Concept Attribute
Drug	Drug/Biologic information for the medications as reported for the event	Concept
Name	Name of medicinal product	Instance Attribute
Role_Cod	Code for drug's reported role in event	Concept Attribute
Drug_Seq	Unique number to identify a drug to a Case	Instance Attribute
Dose_Amt	Dose amount to first reaction	Instance Attribute
Dose_Unit	Cumulative dose to first reaction unit	Concept Attribute
Dose_Freq	Code for drug dosage frequency	Concept Attribute
Dose_Form	Form of dose reported	Instance Attribute
ReChallenge	Rechallenge code if reaction recurred when drug therapy was restarted	Concept Attribute
DeChallenge	Dechallenge code if reaction abted when drug therapy was stopped	Concept Attribute
Therapy	Drug therapy details	Concept
startDate	Date therapy was started for a drug	Instance Attribute
endDate	Date therapy was stopped for a drug	Instance Attribute
Duration	Numeric value of duration of therapy	Instance Attribute

B. *Build Concept Taxonomies*

The ontologist next builds concept taxonomies to define the concept hierarchy. The concept taxonomies are built by selecting terms that are concepts from the glossary of terms. METHONTOLOGY[1] uses four taxonomic relations as defined in Frame Ontology and OKBC Ontology : Subclass- Of, Disjoint-Decomposition, Exhaustive-Decomposition, and Partition[1].

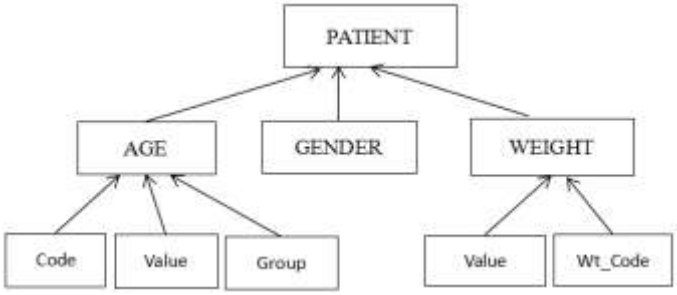
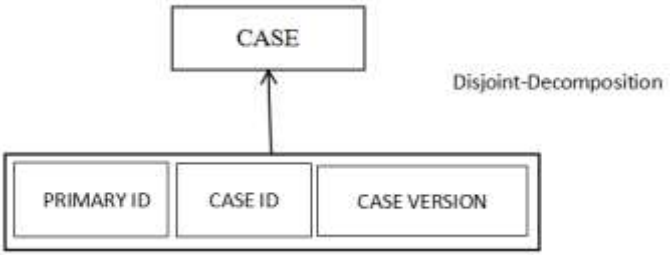


Fig. 3(a)



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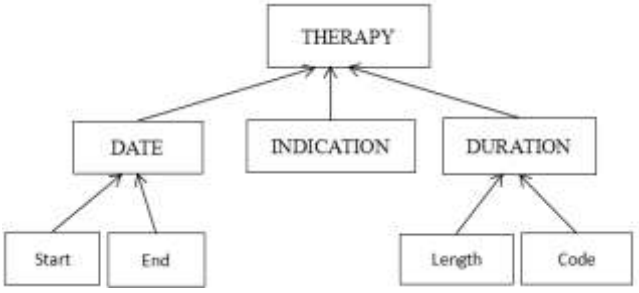

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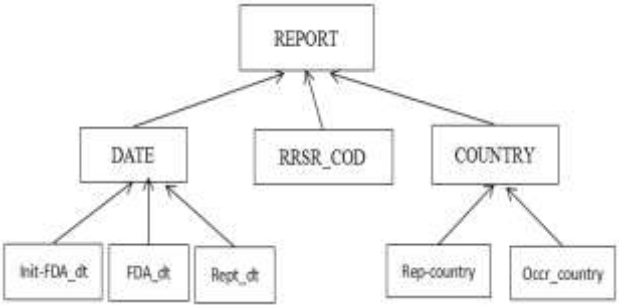


Fig. 3(d)
Fig 3. Excerpt from Concept Taxonomy for FAERS Ontology

C. *Build adhoc binary relation diagrams*

The aim of binary relation diagrams is to establish ad hoc relationships between concepts of the same or different concept taxonomy[1]. It is mandatory that before proceeding further, the ad hoc binary binary diagrams contain no errors. The domains and ranges of each argument of each relation should delimit exactly and precisely the appropriate classes for the relation. If domains and ranges are imprecise or over-specified, the relations will contain errors.

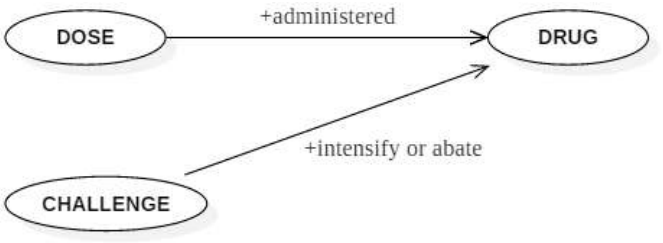
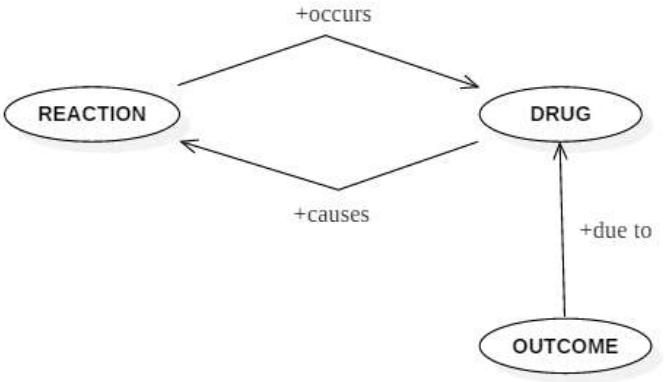


Fig. 4(a)



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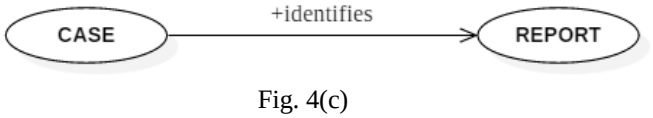

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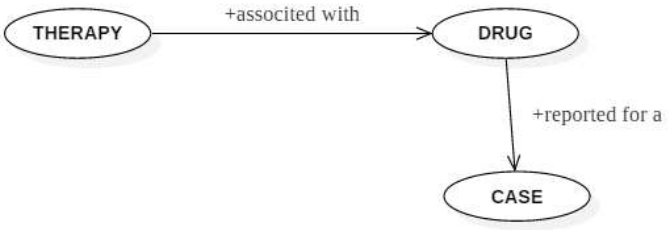

Fig. 4(d)

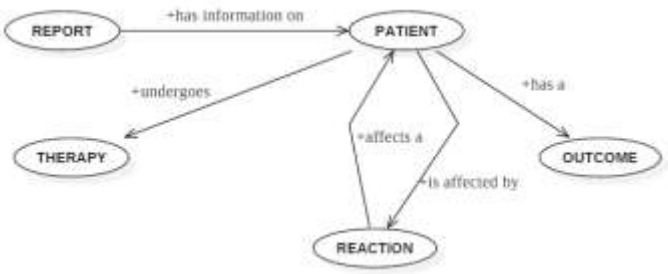

Fig. 4(d)

Fig. 4 Excerpt from Binary Relations for FAERS Ontology

D. Build concept dictionary

To build the concept dictionary, the ontologist needs to specify the properties and relations that describe each concept of the taxonomy. The concept dictionary will contain the following fields : the domain concepts, their relations, their instances and their class and instance attributes[2].

Table 2. Excerpt from Concept Dictionary for FAERS Ontology

CONCEPT NAME	INSTANCE ATTRIBUTES	RELATIONS
Case	CaseID	identifies a
	CaseVersion	
Report	PrimaryID	is identified by
Patient	Age	is reported on
	Sex	is affected by
	Weight	has a
Therapy	startDate	is associated with
	endDate	is given to
	Duration	
	Indication	
Drug	Name	is reported in
	Drug_Seq	causes
	Dose	
	Dose_Form	
Reaction	Reaction_Event	occurs due to
	Drug_Rec_Act	affects a
Outcome	Outc_Cod	due to
		occurs

E. To define ad hoc binary relations in detail

In this step all the ad hoc binary relations from the concept dictionary are described in detail. The output of this step is the ad hoc binary table. The table will contain the following fields : name of the relation, name of the source, target concept, its cardinality, inverse relation along with mathematical properties[2].

Table 3. Excerpt from Binary Relation Table for FAERS Ontology

RELATION NAME	SOURCE CONCEPT	SOURCE CARDINALITY	TARGET CONCEPT	INVERSE RELATION
identifies a	Case	1	Report	is identified by
is identified by	Report	1	Case	identifies a
is reported on	Report	1	Patient	****
is affected by	Patient	N	Reaction	affects a
has a	Patient	N	Outcome	occurs
is associated with	Therapy	N	Drug	is given for
is given to	Therapy	N	Patient	****
is reported in	Drug	N	Case	****
causes	Drug	N	Reaction	occurs due to
occurs due to	Reaction	N	Drug	causes
affects a	Reaction	N	Patient	is affected by
due to	Outcome	1	Drug	****
occurs	Outcome	1	Patient	has a

F. To define instance attributes in detail

Instance attributes are those attributes that describe the instances of the concept and whose value(s) may be different for each instance of the concept. In this step an instance attribute table is created that contains detailed description of each instance attribute. The table will contain the following fields : its name; the concept it belongs to ; its value type; and range of values; minimum and maximum cardinality; instance attributes, class attributes and constants used to infer values of the attribute; attributes that can be inferred using values of this attribute; formulae or rules that allow inferring values of the attribute; and references used to define the attribute[2].

Table 4. Excerpt from Instance Attribute Table for FAERS Ontology

INSTANCE/CLASS ATTRIBUTE NAME	CONCEPT NAME	VALUE TYPE	MAX LENGTH
Age	Patient	N(numeric)	12(upto 2 decimal places)
Weight	Patient	N(numeric)	14(upto 5 decimal places)
Name	Drug	AN(alphanumeric)	500
Drug_Seq	Drug	N(numeric)	22
Dose_Amt	Drug	N(numeric)	15
Dose_Form	Drug	AN(alphanumeric)	50
startDate	Therapy	D(date) or N(numeric)	8
endDate	Therapy	D(date) or N(numeric)	8
Duration	Therapy	N(numeric)	150
Indication	Therapy	AN(alphanumeric)	1000
PrimaryID	Report	N(numeric)	1000
CaseID	Case	N(numeric)	500
CaseVersion	Case	N(numeric)	22
Reaction_Event	Outcome	AN(alphanumeric)	500
Drug_Rec_Act	Outcome	AN(alphanumeric)	500

G. To define class attributes in detail

A class attribute table is created to describe in detail the class attributes of the concept dictionary. For each class attribute, the ontologist should fill the following information: name; the name of the concept where the attribute is defined; value type; value(s); cardinality; the instance attributes whose values can be inferred with the value of this class attribute. No such class attributes were identified.

H. To define constants in detail.

Each of the constants defined in the glossary of terms are described in detail in this step. For each constant: its name, its value type, value, the measurement unit for numerical constants, and the attributes that can be inferred using the constant are defined in the table. For the FAERS[6] ontology no constant terms were identified. Hence no constant table is generated.

I. Describe formal axioms

From the formal axioms identified at the beginning, a precise description of each is included in the Formal Axiom Table. For
each formal axiom definition, METHONTOLOGY specifies the following information: name, description, the logical expression that formally describes the axiom using first order logic, the concepts, attributes and ad hoc relations to which the axiom refers, and the variables used.

J. To define rules

At the end of this step, a rule table is formed from the rules that are needed in the ontology. The rule table will include the following attributes : name, description, the expression that

formally describes the rule, the concepts, attributes and relations to which the rule refers, and the variables used in the expression.

METHONTOLOGY proposes to specify rule expressions using the template

If <conditions> then <consequent>.

The left-hand side of the rule consists of conjunctions of atoms, while the right-hand side of the rule is a single atom.

Table 5. Excerpt from Formal Axioms for FAERS Ontology

AXIOM NAME	Unique PrimaryID
DESCRIPTION	Every primaryID associated with a FAERS report must be unique
EXPRESSION	forall(?X,?Y) ([Report]PrimaryID(?X) != [Report]PrimaryID(?Y))
CONCEPTS	Report
REFERRED ATTRIBUTES	PrimaryID
ADHOC BINARY RELATIONS	***
VARIABLES	?X ?Y

Table 6. Excerpt from Rules for FAERS Ontology

RULE NAME	Combination of PrimaryID and Drug_Seq
DESCRIPTION	If a case with a unique PrimaryID has more than one drugs reported , then the PrimaryID appears as many times as the number of drugs reported , with a unique Drug_Seq for each drug.
EXPRESSION	If [DrugName](?X)=n in [Drug] forall n>1 then [PrimaryID](?Y)=n in [Drug](PrimaryID)
CONCEPTS	Drug, Report
REFERRED ATTRIBUTES	PrimaryID, Drug_Seq, Name
ADHOC BINARY RELATIONS	is identified by, is reported in
VARIABLES	?X ?Y

V. Result and Conclusion

A possible ontology for the U.S. FDA Adverse Event Reporting System has been developed using step by step methodology lined out by METHONTOLOGY. The method of METHONTOLGY has been adopted because it is the most popular ontology development methodology. This methodology has been successfully used to develop ontologies in diverse domains. A very advantageous feature of METHONTOLOGY is that it allows modeling of ontologies using graphical and tabular intermediate representations that can be understood by experts in one domain who are not deeply involved in the ontology field.

Possible further work in developing this ontology lies in using a ontology development software tool such as WebODE that supports METHONTOLOGY.

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