Desiderata for domain reference ontologies in biomedicine

Anita Burgun

EA 3888, Faculté de Médecine, IFR 140, Université de Rennes I, France

Abstract

Domain reference ontologies represent knowledge about a particular part of the world in a way that is independent from specific objectives, through a theory of the domain. An example of reference ontology in biomedical informatics is the Foundational Model of Anatomy (FMA), an ontology of anatomy that covers the entire range of macroscopic, microscopic, and subcellular anatomy. The purpose of this paper is to explore how two domain reference ontologies—the FMA and the Chemical Entities of Biological Interest (ChEBI) ontology, can be used (i) to align existing terminologies, (ii) to infer new knowledge in ontologies of more complex entities, and (iii) to manage and help reasoning about individual data. We analyze those kinds of usages of these two domain reference ontologies and suggest desiderata for reference ontologies in biomedicine. While a number of groups and communities have investigated general requirements for ontology design and desiderata for controlled medical vocabularies, we are focusing on application purposes. We suggest five desirable characteristics for reference ontologies: good lexical coverage, good coverage in terms of relations, compatibility with standards, modularity, and ability to represent variation in reality.
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1. Introduction

Biomedical ontologies represent classes of entities in reality which are of biomedical significance and their organization. They focus on the principled definition of classes and the relations among them. Ontologies are generally created to represent knowledge in a formal, principled way that goes beyond what is typically done in terminologies. Therefore, in theory, most desiderata for controlled medical vocabularies that were listed by Cimino [1] are addressed by ontology. For example, ontologies should meet the needs for concept orientation, consistent representation and formal definitions. In practice, ontologies range in abstraction from very general concepts that form the foundation for knowledge representation for all domains to concepts that are restricted to specific domains. *Domain ontologies* represent knowledge about a particular part of the world, such as medicine whereas *upper level ontologies* are domain independent (e.g., space, time, and matter).

For both upper level ontologies and domain ontologies, we additionally distinguish between reference ontologies and application ontologies. While application ontologies are designed for specific tasks, *reference ontologies* are developed independently of any particular purpose and should reflect the underlying reality [2]. Domain reference ontologies represent knowledge about a particular part of the world in a way that is independent from specific objectives, through a theory of the domain represented. An example of reference ontology in biomedical informatics is the Foundational Model of Anatomy (FMA), an ontology of anatomy that has been in development for a decade at the University of Washington and covers the entire range of macroscopic, microscopic, and subcellular anatomy [3]. Although domain reference ontologies do not target particular user groups, several attempts have been made to use these ontologies in diverse applications that require domain knowledge.

The purpose of this paper is to explore some general use cases of domain reference ontologies in biomedicine. Specifically, we consider three kinds of applications:

E-mail address: Anita.Burgun@univ-rennes1.fr

- Managing heterogeneity of information. Domain reference ontologies should provide domain knowledge that can be used as a common framework for semantically driven integration of information from different sources that use different terminologies.
- Reasoning about complex entities. Modeling of complex biomedical classes requires knowledge in basic science such as anatomy. For example, the characterization of diseases is based on several relations, including *location*, which relates disorders to anatomical entities. Reference ontology in anatomy should provide knowledge in anatomy necessary to perform complex high level reasoning about diseases.
- Reasoning about individual data. Although not designed for specific applications, reference ontologies must provide generic knowledge for reasoning about individual data in various systems.

We analyze those kinds of applications and suggest desiderata for reference ontologies in medicine. This study focuses on the FMA and on ChEBI, the ontology of Chemical Entities of Biological Interest developed by the EBI. Our rationale for choosing the FMA and ChEBI is based on the fact that both represent entities from basic sciences.

2. Materials

2.1. The Foundational Model of Anatomy

The objective of the FMA is to provide a conceptualization of the material objects and spaces that constitute the human body; FMA components include an anatomy taxonomy (AT), which specifies the subsumption relationships of anatomical entities, and an anatomical structural abstraction (ASA), which specifies the meronomic and spatial relationships of the anatomical entities. The anatomical transformation abstraction (ATA) describes the time-dependent transformations of anatomical entities during the human life cycle, and metaknowledge (Mk) comprises the rules for representing relationships in the other three components of the model. The authors of the FMA hypothesize that this abstraction captures the information that is sufficient and necessary for describing the anatomy of any physical entity that constitutes the body, as well as that of the body itself [4]. Originally focusing on gross anatomy, the Foundational Model has been extended to the cellular and subcellular levels [5]. It is now being extended to physiology. The Foundational Model of Physiology (FMP) will serve as a symbolic representation of biological functions initially pertaining to human physiology and ultimately extensible to other species. The FMP is intended to support symbolic lookup, logical inference, and mathematical analysis by integrating descriptive, qualitative, and quantitative functional knowledge [6]. The architecture of the FMP is based on the FMA. Its authors propose the FMA as a reference ontology in biomedical informatics [7].

2.2. ChEBI

The Chemical Entities of Biological Interest (ChEBI) is "a freely available dictionary of 'small molecular entities' (i.e., atom, molecule, ion, ion pair, radical, radical ion, complex, conformer, etc.)" developed at the European Bioinformatics Institute (EBI).[1] ChEBI entities are either products of nature or synthetic products used to intervene in the processes of living organisms. Five thousand two hundred twenty four curated compounds.entities are represented in the ChEBI database dated May 25, 2005. ChEBI entities are organized in a subsumption hierarchy. ChEBI uses nomenclature, symbolism and terminology endorsed by the International Union of Pure and Applied Chemistry (IUPAC) and the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB). Although not a formal ontology, ChEBI assumes the role of a reference for chemicals [8].

3. Applications of reference ontologies

3.1. Managing heterogeneity

The existence of different vocabularies and local ontologies that are independently created and used by different groups for different purposes is the main source of difficulties for effective and efficient communication among systems. Local ontologies are conceptualizations of the world that may be partial (cover only a portion of the domain) and perspectival (correspond to a viewpoint and a goal). Several authors have explored the possibility of having either many local ontologies directly and point to point mapped one into another, or multiple local ontologies along with a reference ontology. The latter solution relies on three components: (1) a domain reference ontology, (2) local ontologies, and (3) mappings that connect local ontologies to the domain reference ontology. Direct mapping of ontologies to a domain reference ontology can be used to provide indirect mapping between every two local ontologies or terminologies.

Gennari et al. [9] propose an anatomy-based platform for integrating data sources in genomics to link the mouse disease models to human pathological conditions. Although a given mouse model may be developed with a specific pathological condition in mind, the genetic manipulation affects biological processes distributed across the entire organism and may have different manifestations across different tissues. For anatomic concepts, Gennari uses the FMA to represent the structure of the cell and its subcomponents. The FMA ontology of cellular anatomy is connected with the hierarchy of cellular components in Gene Ontology (GO) [10]. GO is organized in three separate hierarchies for molecular functions (6972 terms), biological processes (9371 terms), and cellular components

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(1524 terms). It is broadly used to annotate gene products and has become a standard ontology in the biological domain [11]. Since the entire GO cell component hierarchy consists of only 1500 terms, Gennari et al. did not choose to develop an automated approach for aligning the FMA and GO. They hand-built a database that connects about 150 terms in the FMA's ontology of cellular components to the corresponding terms in GO. As with the FMA-GO mappings, they have also connected the FMA with the Mouse Genome Database (MGD). Given this connection between FMA cellular components and GO cellular components and this connection between FMA and MGD, the FMA ontology can be used to browse GO annotation databases and MGD gene expression database. Their success in mapping parts of the GO cellular component hierarchy and the Adult Mouse Anatomical Dictionary onto the FMA suggests that commonly used biological structure ontologies can be viewed within a reference ontology of anatomy.

The indirect alignment of two anatomical ontologies through the FMA has been investigated by Zhang and Bodenreider [12]. The two anatomical ontologies under investigation were the Adult Mouse Anatomical Dictionary and the NCI Thesaurus. The direct alignment employs a combination of lexical and structural similarity. The indirect alignment derives mappings from direct alignment to the FMA (Fig. 1). Zhang showed that 91% of the direct matches between the Adult Mouse Anatomical Dictionary and NCI Thesaurus were discovered by the indirect alignment. Moreover, the indirect alignment was able to identify new matches not discovered by direct alignment.

3.2. Reasoning about complex entities

Knowledge domains such as anatomy and chemistry are relevant to a number of other biomedical fields. We borrow the term 'actor' from Rosse [7]: anatomical concepts assume the role of 'actors' in disease ontologies. The objective is to align domain reference ontologies representing anatomical entities (respectively, chemical entities) with ontologies representing more complex entities such as diseases (respectively, biological processes). The knowledge
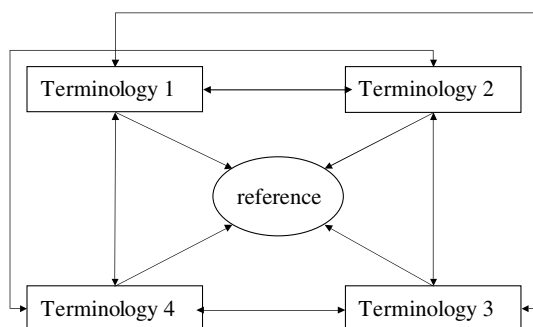

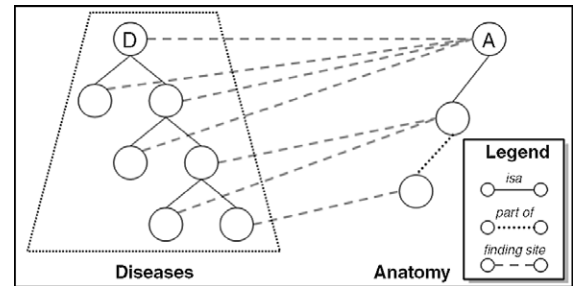Fig. 1. Aligning terminologies through a reference ontology vs pairwise alignment.

Fig. 2. A reference ontology of anatomy may help identify subsumption relations between diseases.

represented in reference ontologies, including the relations between classes in reference ontologies, may be reused to identify new relations among complex entities. Relations may be hierarchical or not (not hierarchical relations are called associative relations). Hierarchies include taxonomies, in which the relation between a node and its descendants is is-a,[2] and meronomies, in which the relation between a node and its children is part-of. Taxonomic relations among diseases parallel hierarchical (is-a and part-of) relations among anatomical entities (e.g. [13–15]). For example, tumors of the brain are tumors of the nervous system because the brain is a part of the nervous system. Analogously, tumors of the mandible are bone tumors because the mandible is a kind of bone. Applying this parallel between diseases and anatomical entities to classifying diseases in any disease ontology, one can assume the following: for a given anatomical entity A and the disease D having A as its location, the anatomical entities that are descendants of A (we will use 'descendant' for children through is-a relations) or parts-of A are expected to be locations for the descendants of D. More precisely, all diseases having A as their location are expected to be descendants of D, and all descendants of D are expected to have A, a descendant of A or a part of A as their location. We applied this approach to SNOMED CT (released on Jan 31, 2004) [16]. We evaluated the degree to which, in SNOMED CT, the classification of diseases supported by the role 'finding site' was compatible with the classification of diseases provided by subsumption relations among diseases (Fig. 2). Starting from the initial 3540 anatomical entities, the processing of the hierarchical relations between anatomical entities generated a total of 1,025,904 subsumption relations between disease entities in SNOMED CT. Among these, 40% were new relations, i.e., they were not present in the actual taxonomy of diseases in SNOMED CT. For example, the subsumption relation between *neoplasm of mandible* and *neoplasm of bone* exists in SNOMED CT. In contrast, *Fracture of base of fifth metatarsal* is not a descendant of any of the six diseases associated with *Fifth metatarsal structure*. In fact, because there is no such class

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[2] Although several authors, such as Brachman, have described several meanings of the is-a relation (e.g., conceptual containment), we will use is-a relation, subsumption, and taxonomic relation as synonyms.

as *Disorder of the fifth metatarsal* in SNOMED CT, *Fracture of base of fifth metatarsal* is a direct descendant of *Metatarsal bone fracture*. The discrepancies observed in SNOMED CT between the taxonomy of diseases and the classification of diseases with respect to anatomy can be attributed to missing classes: a class of diseases is not systematically defined for each anatomical structure. We are not necessarily suggesting that such classes be defined in SNOMED CT. However, this approach helps identify missing classes and taxonomic relations in existing ontologies of diseases. This study illustrates the role that a reference ontology of anatomy may play in developing ontologies of diseases.

This approach may be applied to other ontologies as well. For example, the entities described in GO often make reference to other entities, either from GO or from other ontologies, such as ontologies of chemical entities, cell types and organisms. We have shown that 55% of the 17,250 GO terms include in their names the name of some chemical entity (ChEBI). Of the 10,156 entities in ChEBI, 2700 (26%) were identified in the names of 9431 GO terms. For example, the entity potassium is present in 43 GO terms including potassium-uptake-ATPase activity and regulation of potassium transport. Therefore, an ontology of chemical entities may be used to classify molecular functions with respect to the substrates involved in the corresponding reactions. This approach may not be limited to hierarchical relations. We have used ChEBI, to identify associative relations within GO [17]. As already mentioned in the previous subsection, GO is organized in three independent hierarchies: molecular functions, biological processes, and cellular components. Our objective was to identify relations between GO terms especially relations across hierarchies. For example, there is an implicit relation between potassium ion transporter activity (molecular function) and potassium ion transport (biological process) but this relation is not represented in GO. Our method is based on the identification of the names of ChEBI entities in GO terms. Two GO terms whose names include the name of a given chemical entity are related, for example: potassium ion transporter activity, and potassium ion transport. There are cases in which two GO terms include the names of chemical entities that are not identical, but rather stand in a hierarchical relation, for example: cation channel activity and potassium ion transport. We distinguish between first-order relations between GO terms that share a common chemical name (Fig. 3), and second-order relations between GO entities whose names include two chemicals that are hierarchically related (Fig. 4). The use of a domain reference ontology of chemicals such as ChEBI takes advantage of the subsumption relations between chemicals, and therefore helps identify second-order relations. This approach can be generalized to other ontologies of chemicals as well as other kinds of ontologies [18].
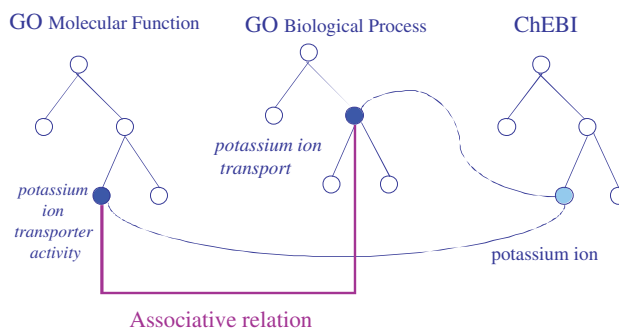

Fig. 3. An ontology of chemicals may help identify first-order relations across GO hierarchies.
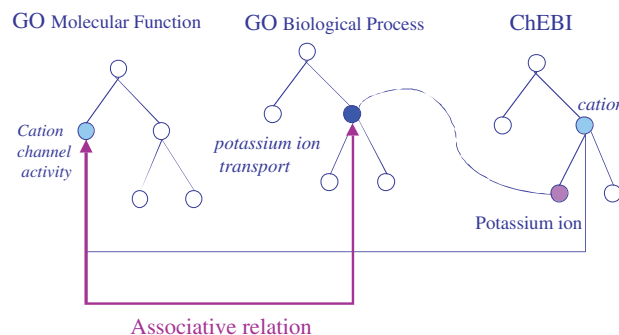

Fig. 4. An ontology of chemicals may help identify second-order relations across GO hierarchies.

3.3. Reasoning about individual data

Ultimately, ontologies should be useful to manage individual data and support reasoning about them. The distinction between normal and pathological features is central to medicine. To our knowledge, no systematic evaluation of the FMA in the context of clinical decision systems has been performed yet. Systems combining FMA and rule-based knowledge are still under development. The Virtual Soldier project is a large effort on part of the US Defense Advanced Research Projects Agency (DARPA) to explore the feasibility of using both general anatomical knowledge and specific computed tomographic images of individual soldiers to aid the rapid diagnosis and treatment of penetrating injuries.[3] To achieve that goal, it is necessary to combine geometric data with anatomic knowledge and reasoning services [19,20]. The organ–tissue system will represent a complex human visualization/simulation. The anatomical simulator will be queried for structural information and will also display certain anatomical and physiological features important for the visualization of penetrating wounds. The FMA is used as the ontology providing a framework for the structural elements of the body. A geometric model of patient anatomy is constructed and each geometric structure is linked to the corresponding anatomic class in the FMA. In its current stage, the Virtual

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[3] www.virtualsoldier.net.

Soldier project aims at supporting the diagnosis of wound injuries to the thorax. Reasoning services have been developed to predict the damage to organs injured by a projectile, either directly or indirectly. Anatomical knowledge is necessary to infer secondary injuries such as ischemic regions of the heart when a coronary artery is severed, or hemopericardium when the wall of the heart is perforated. The current approach has not incorporated uncertainty related to injuries yet. A limitation mentioned by Rubin is that the FMA knowledge sources are 'canonical, while particular patient anatomy can be variable. [….] This limitation can be overcome by extending our ontologies to model anatomic variation' [21].

4. Desiderata for biomedical reference ontologies

A number of groups and communities have investigated general requirements for ontology design (e.g. [22]). Some of the common well admitted themes that have been described include: precision and clarity (formal, unambiguous), consistency (control, quality), explicitness, flexibility (expressivity, evolution). Many of the above requirements can be seen to resonate with the desiderata put forward by Cimino.

Some authors have advocated that ontologies must be designed for applications, for example Noy and McGuinness wrote "there is no correct way to model a domain [..] The best solution almost always depends on the application that you have in mind and the extensions that you anticipate" [23]. The decisions in ontology design are mainly guided by the potential applications of the ontology. Conversely, the FMA has not been designed for any specific purpose. Its authors have employed a 'disciplined approach for the de novo creation of a new knowledge base. The elements [...] consist of **a set of declared foundational principles**, **a high level scheme** for representing the referents of concepts and relationships [..] **aristotelian definitions** and a **knowledge modeling environment** that assures implementation of principles and the inheritance of definitional and non-definitional attributes'. Recently, Rosse has summarized this approach as follows: declare a theory about a particular domain of reality, and make use of methods of top-level ontologies [24]. This approach should be valid for any domain reference ontology. We have assumed that, although not designed for any specific application, reference ontologies must serve various *applications*. The three kinds of applications that we have explored in this study enable us to suggest five additional desirable characteristics for domain reference ontologies. Those desiderata focus on application purposes. As such, they complement the characteristics previously highlighted by C. Rosse that were focusing on design purposes.

4.1. Good lexical coverage

The indirect alignment of two ontologies through a reference ontology (e.g., the method investigated by Zhang

and Bodenreider for anatomy) is cost-effective: n ontologies require $n-1$ mappings to a reference ontology vs $n(n-1)/2$ pairwise mappings. Most existing aligning methods, such as the aligning approach developed by Zhang, rely heavily on the lexical similarity. Similarly, methods exploiting the terminological component of ChEBI (i.e., the names of chemical entities) have been used to link the Gene Ontology to ChEBI. Therefore, the lexicon is a fundamental component of the ontology. Each concept in the reference ontology must be associated with the corresponding preferred terms and synonyms. With the objective of terminology alignment, following Zhang, we propose two characteristics for reference ontologies: (i) broad coverage on terms of lexical entities, (ii) inclusion of many synonyms. These characteristics have already been stressed for controlled vocabularies by Cimino. The paradox resulting from the extension of this position to ontologies is only apparent. The primary purpose of domain reference ontologies is somewhat different from that of controlled vocabularies. For example, the objective of the FMA is to represent declarative knowledge about the organization of the human body. Therefore, from this point of view, it is possible to rely primarily on formal definitions to align reference ontologies with other terminologies, rather than on lexical information. However, ontologies are also used to enhance interoperability. In this context, the need for good lexical content remains for interfacing purposes. This occurs because (i) not all existing terminologies provide formal definitions of their terms, (ii) no mapping techniques that rely purely on formal constraints are usable yet, and therefore mapping methods generally exploit lexical similarity.

4.2. Good coverage in terms of relations

Reference ontologies may be viewed as a means to organize partitions of a more complex domain (e.g. [25]). As shown previously, an ontology of anatomical entities may be used to classify diseases with respect to their locations, as well as an ontology of chemical entities may be used to classify molecular functions with respect to the chemicals involved. Linking reference ontologies to ontologies that describe adjacent domains relies on exploiting their structures in addition to mapping their terms. By exploiting the hierarchical relations among chemical entities in ChEBI, our method identified second-order associative relations between GO terms (pairs of GO terms whose names include chemical entities standing in a hierarchical relation) in addition to the first-order associations (pairs of GO terms whose names share a chemical entity). Formally clarified relationships (e.g. [26]), as well as good coverage in terms of relations in reference ontologies are necessary to infer new relations within or across other ontologies [27].

Although mainly unformal, cross-references to other repositories are a means to enrich representation. For example, by exploiting cross references between ChEBI

entities and other chemical entity repositories (e.g., CAS registry number), additional information (e.g., synonyms) can be extracted from external resources (e.g., PubChem) also referencing these identifiers.

4.3. Compatibility with standards

In this study, we have focused on knowledge processing. Reference ontologies have been proven to be useful to structure domain knowledge and to organize knowledge related to other ontologies. As domain reference ontologies are to be linked with other ontologies, that represent either the same domain or adjacent domains where reference classes play the role of actors, compatibility with knowledge representation standards is needed. While Gennari et al. did not develop an automated approach for mapping the FMA and GO, the other applications of reference ontologies presented in this paper rely on computerized knowledge processing. Therefore, this study confirms the necessity of releasing reference ontologies in standard formats.

4.4. Modularity

There are many reasons for thinking about ontology modularization. Those reasons include cooperative modelling of ontologies [28], reusability [29], and efficient reasoning [30]. Modularity helps to manage knowledge in very large domains such as biomedicine. It will help to maintain and reuse parts of this knowledge as smaller modules are easier to handle than large ontologies [31]. Once such modular domain reference ontologies are publicly available, future ontologies become more likely to be built upon existing ontology modules. A specific problem that occurs in the case of large domains is the problem of efficient reasoning. Modularization will help develop efficient reasoning methods. We have given examples in which the concepts of the reference ontology assume the role of basic components or actors in more complex entities. Reference ontologies must be modular to act as backbones for partitioning the domain, and provide basic knowledge for reasoning in adjacent or broader domains.

Assuming that reference ontologies must be modular, there are a couple of requirements that domain reference ontologies have to fulfill to improve reasoning in a modular ontology architecture. The requirements suggested in the WonderWeb project[4] comprise loose coupling of existing ontologies, self-containment, and integrity. Loose coupling describes links between pre-existing ontologies that share topics but may be implemented in different languages. Self-containment recognizes that reasoning can proceed independently in any of the pre-existing ontologies, but can benefit by importing additional information. Integrity is associated with correct reasoning in the presence of

autonomous modules. Moreover, as already mentioned by Jim Cimino for medical terminologies, versioning issues must be addressed.

4.5. Ability to represent variation in reality

Reference ontologies are expected to be helpful in managing individual data. This aspect, however, may not be always applicable to biomedicine. Specific to life science is the number of variants in almost every class of entities while reference ontologies rely on a theory of particular domains of reality [24]. Therefore, an ontology that complies with all the current recommendations may yet be too limited to represent reality. Life sciences are characterized by variations in reality. A significant property of a biomedical reference ontology, therefore, must be its ability to represent variations in reality, to represent individuals and to connect with data and real facts. Biomedical ontologies must not be limited to canonical models and must be extended to model variation in domain entities and relations.

5. Conclusion

Reference ontologies may be analyzed from multiple points of view, including semantic aspects (e.g., the level of granularity) and formalism (e.g., description logics). In our analysis, we have focused on knowledge processing. Reference ontologies have been proven to be useful to organize knowledge related to other ontologies. Some methods that use reference ontologies to correlate information from different sources and align existing terminologies, as well as methods that use modular ontologies to infer new knowledge in ontologies of more complex entities, have already been evaluated. The applications that we present in this paper rely on the FMA and ChEBI but can be generalized to other ontologies. Reference ontologies are also expected to fit reality. Therefore, as life sciences are characterized by variations in reality, reference ontologies representing canonical knowledge must be extended to model and represent those variations.

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