

Grounding a Hyper-Ontology on mCODE Conceptual Model and Foundational Ontologies for Semantic Interoperability in Oncology

Mirna El Ghosh^{1,*}, Christel Daniel¹, Catherine Duclos², Varvara Kalokyri³, Jean Charlet¹, Melanie Sambres¹, Gianna Tsakou⁴, Manolis Tsiknakis³ and Ferdinand Dhombres¹

¹Sorbonne Université, Inserm, Université Sorbonne Paris-Nord, LIMICS, Paris, France

²Université Sorbonne Paris-Nord, Inserm, Sorbonne Université, LIMICS, Paris, France

³Institute of Computer Science, Foundation of Research and Technology Hellas, Heraklion, Greece

⁴MAGGIOLI S.P.A., Research and Development Lab, Marousi, Greece

Abstract

Grounding biomedical ontologies in core ontological conceptual models considering foundational ontologies is a prominent top-down approach neglected in domain-specific ontologies but is required to support semantic interoperability. This study discusses developing a core ontological model for mCODE (minimal Common Oncology Data Elements), which captures and reflects the main oncology's ontological semantics on which a FAIR-compliant hyper-ontology for the oncology domain is grounded. To conduct the ontological analysis, Ontology-Driven Conceptual Modeling (ODCM) is applied using OntoUML, an ontologically well-founded language whose meta-model complies with the Unified Foundational Ontology (UFO). The top-down approach has helped overcome conflicting or heterogeneous descriptions of oncology concepts, maintaining coherent ontological content and semantic interoperability.

Keywords

Ontological Analysis, Conceptual Modeling, OntoUML, Foundational Ontologies, mCODE, Semantic Interoperability, Oncology

1. Introduction and Motivation


Tumor (or *Neoplasm*), *Tumor Morphology*, and *Cancer* (or *Malignant Tumor*) are core concepts in the oncology domain used to describe different medical contexts. However, conflicting or heterogeneous representations of these concepts in commonly known biomedical ontologies or terminologies, such as SNOMEDCT¹ and NCIT², make interoperability challenging (see Figure 1). SNOMEDCT is an ontology-based medical terminology standard that has been largely used to develop ontologies in the biomedical domain. NCIT is a reference terminology in the oncology

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*Corresponding author.

✉ mirna.el-ghosh@inserm.fr (M. E. Ghosh)

ORCID 0000-0002-0877-7063 (M. E. Ghosh)

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¹<https://www.snomed.org/>, Accessed April 23, 2024

²<https://ncithesaurus.nci.nih.gov>, Accessed April 23, 2024

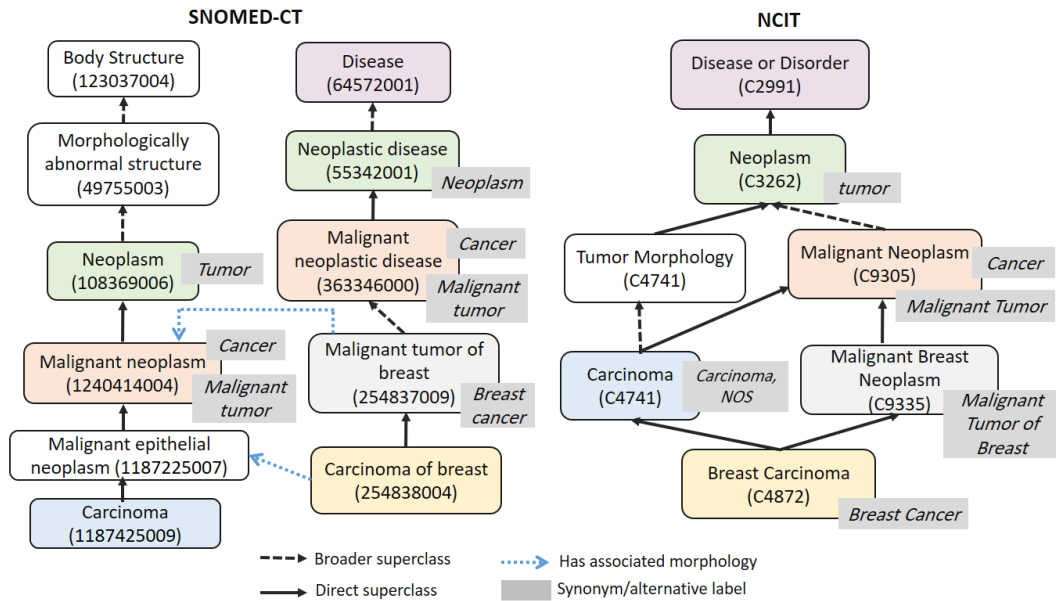


Figure 1: An example of a conflicting description of oncology concepts in SNOMEDCT/NCIT (colored shapes are potential mappings between SNOMEDCT and NCIT)

domain developed and maintained by the National Cancer Institute. SNOMEDCT differentiates between *Neoplasm*, or *Tumor*, (108369006) and *Malignant neoplastic disease* (363346000), having as synonyms *Malignant tumor* and *Cancer*, where the former is a “morphologic abnormality” that belongs to *Body structure* (123037004) and the latter is a *Disease*, or *Disorder*, (64572001). However, in NCIT, *Neoplasm* (C3262) is a *Disease or Disorder* (C2991) having *Tumor Morphology* (or *Neoplasm by Morphology*) (C4741) and *Malignant neoplasm*, or *Cancer*, (C9305) as specific categories. In this context, mapping *Carcinoma of breast* (SNOMEDCT:254838004) with *Breast Carcinoma* (NCIT:C4872) is challenging due to the heterogeneity of their ascendants. Facing this heterogeneity and to clarify these concepts’ specifications and medical aspects, we refer to the minimal Common Oncology Data Elements (mCODE)³ [1] largely adopted within healthcare establishments which are increasingly implementing FHIR⁴. mCODE is a “Domain of Knowledge” implementation guide intended to show how to represent clinical concepts generally, aiming to increase interoperability in the oncology domain. Among various profiles and extensions, *Tumor*, *Tumor Morphology*, *Histology/Morphology*, and *Primary Cancer Condition* are defined in mCODE STU4 model. In this context, inspired by [2], there is a need for an ontological analysis that reveals the *ontological conceptual model* of mCODE, helping to achieve semantic clarity on oncology’s main concepts.

In the EUCAIM project⁵, we employ an ontological approach toward semantic interoperability among heterogeneous cancer image data models and distributed big cancer data repositories [3]. We propose developing a FAIR-compliant hyper-ontology to integrate and federate large volumes

³<https://build.fhir.org/ig/HL7/fhir-mCODE-ig/>, Accessed April 11, 2024

⁴<https://www.hl7.org/fhir/>

⁵<https://cancerimage.eu/>

of cancer image and clinical data, including many types of cancer (e.g., Breast cancer, Cancer of prostate, Lung cancer, etc.), aiming to establish semantic interoperability among the diverse data sources. The hyper-ontology goal is to define domain-specific concepts and ground them on core oncology concepts in a coherent semantic context. Additionally, semantic mappings are applied with various controlled vocabularies and ontologies in the biomedical domain (e.g., SNOMEDCT, NCIT, ICD-O-3, etc.). To tackle the heterogeneity of oncology concepts and ensure a well-founded representation of the oncology domain, we propose grounding the hyper-ontology on validated foundational ontologies (e.g., UFO [4, 5], BFO [6, 7]), which help to improve interoperability by being “translators of intended meaning” [8]. The grounding process considers developing the mCODE *core ontological model* that reflects the main ontological semantics of the oncology domain. To conduct the ontological analysis, there is a need for a language that supports making explicit the ontological nature of real-world entities and the relations between them [9]. In this regard, Ontology-Driven Conceptual Modeling (ODCM) is applied using OntoUML⁶ [10], an ontologically well-founded language whose meta-model complies with the ontological distinctions and axiomatization of UFO. In the remainder of the paper, section 2 overviews this study’s background, section 3 discusses the grounding approach, the formal results are given in section 4, and section 5 concludes the paper.

2. Background

2.1. EUCAIM’s Hyper-Ontology

Hyper-ontology is a common semantic meta-model required to explore heterogeneous data collections⁷, federated querying, and image annotation/segmentation. Its main challenge is facilitating integration and interoperability among data stored and modeled using diverse clinical and imaging data models and associated terminologies. Two main data models are considered in EUCAIM: OHDSI-OMOP⁸ and HL7-FHIR⁹. In OMOP, domains are defined to which the concepts of the standardized vocabularies can belong, such as *Person*, *Condition*, *Measurement*, *Drug*, and *Procedure*. Meanwhile, FHIR is built upon a set of resources, including *Patient*, *Observation*, *Medication*, *Procedure*, and *Condition*. In EUCAIM, the data heterogeneity is exposed in two aspects: *semantic*, such as the example discussed in the introduction (Section 1) and *syntactic*, such as in OMOP/FHIR. For instance, the *PSA* lab test is defined in OMOP as a SNOMED concept (*Prostate specific antigen measurement (63476009)*) from the *Measurement* domain and as a LOINC concept (*Prostate specific Ag [Mass/volume] in Serum or Plasma (LP18192-2)*) from the *Observation* resource in FHIR. Also, the *Lesion* concept (SNOMEDCT:52988006), which is a morphologic abnormality, is defined as *Observation* in OMOP and *Condition* in FHIR. To tackle the heterogeneity challenges, maintain semantic interoperability, and simplify the hyper-ontology development, an iterative hybrid approach is proposed, composed of *bottom-up* and *top-down* strategies and supported by ontology layering and modularization. The bottom-up strategy relies on the clinical and imaging data, associated terminologies, and their mappings to

⁶<https://ontouml.org/>

⁷<https://catalogue.eucaim.cancerimage.eu/>

⁸<https://www.ohdsi.org/data-standardization/>

⁹<https://www.hl7.org/fhir/>

build the content of the *domain-specific* layer. The *domain* layer is constructed based on the *is-a* mappings applied considering the *domain-specific* layer. The *core* and *upper* layers, the focus of this study, are developed using a top-down strategy, which aims to ground the hyper-ontology in core conceptual models and foundational ontologies, supporting semantic interoperability. Integrating these strategies will maintain the ontology's structure and semantic content.

2.2. OntoUML

As stated by Guizzardi [9], “Semantic interoperability cannot be achieved without the support of *ontologies* and *ontology*”. While *ontologies* aim to capture domain conceptualization (e.g., domain ontologies), *ontology* represents the discipline through formal methods and theories clarifying conceptualizations (e.g., foundational ontologies). Lightweight ontology languages, such as OWL¹⁰, are insufficient to explicitly represent the ontological nature of a given domain, i.e., conceptualization. There is a need for a “*language truly ontological by nature*”, such as OntoUML [9]. OntoUML is an Ontology-Driven Conceptual Modeling (ODCM) language whose meta-model complies with UFO, where the modeling primitives of OntoUML reflect the ontological distinctions and axiomatization of UFO [11, 5]. Two main entities are defined in UFO: *endurants*, which are the most dominant, and *perdurants* (or *occurents*). Objects are *endurants* that have specific properties and are classified by «kind» in UFO. Examples of objects *kinds* are *Person*, *Medication*, and *Body structure*. *Subkinds* are subtypes of *kinds*, such as *Breast* and *Prostate*. Other types of entities are defined in UFO, such as *roles* and *phases*, which represent “contingent or accidental properties of objects” [2]. For instance, *Cancer Patient* is classified as «role» and *Alive Person* is classified as «phase». Objects can also be classified as *modes*, such as *Disease/Disorder*, which are existentially dependent on their bearers (e.g., *Patient*). Besides, *Qualities* (e.g., *size*) are objects that existentially depend on the entities they characterize (e.g., *tumor*). Finally, *Events*, *perdurants* that *exist only in the past* [2], can be represented using the stereotype «event». Relationships between *Endurants* and *perdurants* are reciprocal, where *kinds*, *subkinds*, *phases*, and *roles* can participate in *events*. Also, *events* can create *endurants*. In this section, we briefly introduced selected modeling primitives from OntoUML; for more details, refer to [10, 11].

3. Ontology-Oriented Grounding Approach

The hyper-ontology grounding approach aims to build the core and upper layers, considering the mCODE ontological conceptual model and foundational ontologies. Using OntoUML, we develop the mCODE ontological model as a *reference model* [12], independent from any computational language, which captures and reflects the basics of the oncology domain. *Ontological unpacking* process, which refers to a *process of ontological analysis that reveals the ontological conceptual model*, is applied as a prominent top-down approach that can effectively ensure semantic interoperability according to FAIR principles [2]. The intended model aims to capture and explicitly and unambiguously represent the basic concepts of the oncology domain and their connections. For this purpose, we refer to the mCODE guide that consists of various profiles and extensions organized into different thematic groups, including:

¹⁰<https://www.w3.org/OWL/>

- *Disease Characterization*: includes data elements specific to the diagnosis (e.g., date, location), cancer staging, and tumor characteristics (histological classification, grade, morphology, and behavior of the tumor cell);
- *Health Assessment*: contains information about the patient's general health before and during treatment, such as comorbidities, performance assessment, laboratory tests, and history of metastatic cancer;
- *Cancer Treatments*: includes reporting of procedures (surgery and radiotherapy) and medications used to treat a cancer patient or relevant to that treatment;
- *Outcomes*: includes disease status, tumor, and tumor size.

Based on the hyper-ontology requirements (stated as Competency Questions (CQs) in the Ontology Requirements and Specifications Document (ORSD) [13]), we selected basic elements from different thematics to build the mCODE core conceptual model, such as *Cancer Patient*, *Histology/Morphology*, *Tumor Morphology*, *Cancer-Related Surgical Procedure*, *Cancer-Related Medication Administration*, *Primary Cancer Condition*, and *Cancer Stage*. These elements will be analyzed and represented using the stereotypes of OntoUML to build the core layer, and their anchoring with generic concepts will be conducted in the upper layer.

3.1. Core Layer

The core layer comprises different modules according to the mCODE thematic groups: *Disease Characterization*, *Health Assessment*, *Cancer Treatment*, and *Outcomes*. The modeling of each module is guided by a set of competency questions (CQs), which fulfill the main requirements of modeling the general aspects of oncology. *Cancer Patient* is a concept from *Patient Information* group¹¹ used in the different modules and defined as *a patient diagnosed with or receiving medical treatment for a malignant growth or tumor*.

Disease Characterization The main CQs for the disease characterization module are: CQ1) How are cancer conditions classified? CQ2) Who has been diagnosed with primary cancer? CQ3) In what body location is the cancer condition identified? CQ4) Is there any histology/morphology associated with the cancer condition? CQ5) How is the cancer stage/grade specified? CQ6) Is the cancer condition classified by a certain stage/grade? CQ7) Are there any tumor marker tests for the cancer condition? CQ8) Are there any results generated by lab tests? In this module, the following elements are considered from mCODE:

- *Primary Cancer Condition*: captures the cancer diagnosis (original or first neoplasm in the body) and is associated with *Malignant neoplastic disease* (SNOMEDCT:363346000);
- *Secondary Cancer Condition*: captures secondary malignant neoplasms related to primary condition and is associated with *Secondary malignant neoplastic disease* (SNOMEDCT:128462008);
- *Histology/Morphology*: describes the morphologic and behavioral characteristics of cancer and conforms with, among others, *Malignant neoplasm (morphologic abnormality)* (SNOMEDCT:1240414004);

¹¹<https://build.fhir.org/ig/HL7/fhir-mCODE-ig/group-patient.html>, Accessed May 2, 2023

- *Tumor Morphology*: represents ICD-O-3 morphology determined from examination of tumor sample and is associated with *Tumor morphology panel Cancer* (LOINC:77753-2);
- *Cancer Stage*: is a parent profile for *observations* regarding cancer stage, grade, or classification. The stage is an assessment of the extent of cancer in the body, according to a given cancer staging classification system (e.g., TNM stage group);
- *TNM Stage Group*: is a specialization of *Cancer Stage* dedicated to AJCC TNM staging;
- *Tumor Marker Test*: is an observation that relates to the result of a tumor marker test (e.g., *Prostate specific Ag [Mass/volume] in Serum or Plasma* (LOINC:2857-1)). We differentiate between the lab tests and the values generated by these tests (e.g., *Negative*, *Positive*, or numeric values). Figure 2 depicts an example of using this profile.

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Resource Observation "tumor-marker-test-egf"
Profile: Tumor Marker Test Profile

status: final

category: Laboratory (Observation Category Codes#laboratory)

code: Epidermal growth factor receptor Ag [Presence] in Tissue (LOINC#39004-7)

subject: Patient/cancer-patient-john-anyperson " ANYPERSON"

effective: 2019-04-01

performer: Practitioner/us-core-practitioner-kyle-anydoc " ANYDOC"

value: Positive (qualifier value) (SNOMED CT#10828004)

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Figure 2: An example of using *Tumor Marker Test* profile from mCODE.

Considering the definitions and specifications in mCODE, we propose the reference model of the *Disease Characterization* module depicted in Figure 3. *Primary Cancer Condition* and *Secondary Cancer Condition* are cancer disease phases (original/secondary) generalized by *Neoplastic Disease*, an *intrinsic mode* inherent in the *Patient* and located in a certain *Body Location*. *Cancer Patient*, diagnosed with a *Primary Cancer Condition*, is a *Patient* defined as role specializing *Person (kind)* (see Figure 8). *Cancer Stage*, a *quality* that classifies/characterizes a malignant neoplastic disease (*Primary Cancer Condition*), is specialized using different *subkinds*, *TNM Stage Group*, *Cancer Grade*, and their subtypes. *Histology/Morphology* (e.g., *Malignant neoplasm*), that “characterizes” cancer regarding the morphologic and behavioral aspects is an *intrinsic mode* dependent on its bearer(s) (e.g., *Malignant tumor of breast*, *Tumor* (see *Outcomes*)). Thus, the morphology specification deviates from SNOMEDCT and NCIT but aligns with ICD-O-3 (International Classification of Diseases for Oncology), which separates the topographical and histological nature of neoplasms. ICD-O-3 is the official classification for coding cancer diseases in cancer registries. However, neoplasms are classified as *Body Structure* in SNOMEDCT (see Figure 1), which is a material independent entity (see Figure 8) contradicting the dependent nature of morphology, and *Disease or Disorder* in NCIT, which is a vague representation, confusing the distinction between cancer condition and morphology. Finally, classifying *Tumor Marker Test* (e.g., PSA, ER, HER2) as *Laboratory Test* that generates *Lab Test Result* as qualities

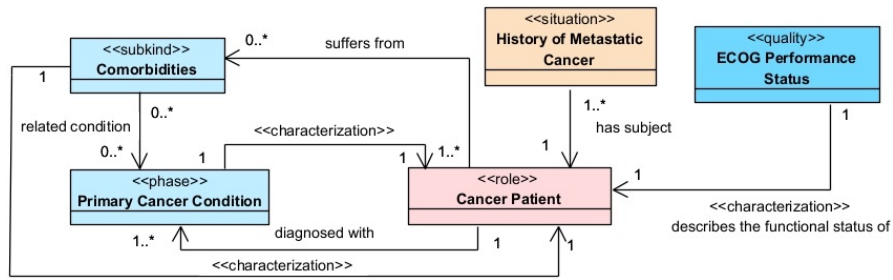


Figure 4: Health Assessment module represented using OntoUML.

- *Cancer-Related Surgical Procedure*: designates a surgical action addressing a cancer condition and is associated with *Surgical Procedure* (SNOMEDCT:387713003).
- *Cancer-Related Medication Administration*: is an episode of medication administration for a patient diagnosed with a primary or secondary cancer condition.

Figure 5 depicts the modeling of *Cancer Treatment* using OntoUML. We note that radiotherapy treatment is out of this study’s scope. A *Cancer Patient* diagnosed with *Primary Cancer Condition* has undergone some *Cancer-Related Surgical Procedure*, which surgically treats the condition located in a specific body site. *Cancer-Related Medication Administration* is a procedure that prescribes a *Medication* (substance) to treat the cancer.

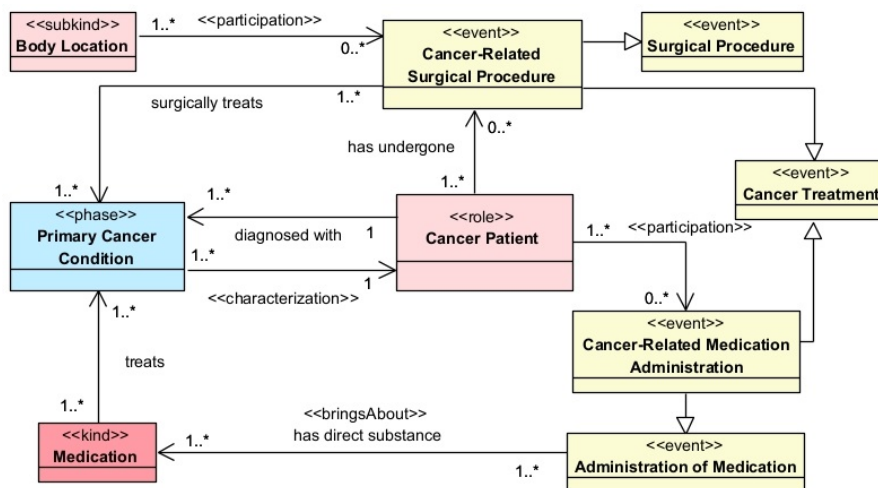


Figure 5: Cancer Treatment module represented using OntoUML.

Outcomes The main CQs for the cancer treatment module are: CQ1) Who suffers from the tumor? CQ2) In which body location is the tumor identified? CQ3) Is there any cancer condition related to this tumor? CQ4) Is there any morphology associated with the tumor? CQ5) How is the size of an identified tumor recorded? In this module, three main elements are considered from mCODE:

- *Tumor*: identifies a tumor (body structure) that has not been removed from the body (see Figure 6 for an example);
- *Tumor morphology*: defines the morphology (normal and abnormal) associated with the tumor;
- *Tumor size*: records the dimensions of a tumor.

```

Resource BodyStructure "tumor-lobular-carcinoma-left-breast"
Profile: Tumor Profile

Related Condition Extension: Condition/primary-cancer-condition-breast

identifier: BodyStructure/Tumor 1234 (use: usual)

location: Left breast structure (body structure) (SNOMED CT#80248007)

patient: Patient/cancer-patient-eve-anyperson " ANYPERSON"

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Figure 6: An example of using *Tumor* profile from mCODE.

Figure 7 depicts the modeling of *Outcomes* module using OntoUML. *Tumor*, identified as a rigid entity located in a specific body site and characterized by a *Tumor Morphology*, has a related condition with which a *Cancer Patient* is diagnosed. A *Tumor* is characterized by a *Tumor Size* (*quality*), which is recorded using a specific *Laboratory Procedure*.

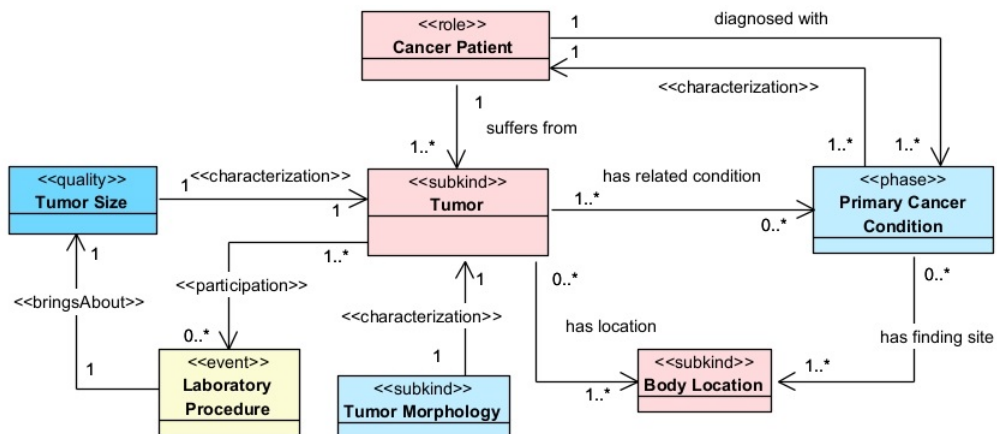


Figure 7: *Outcomes* module represented using OntoUML.

3.2. Upper Layer

The upper layer aims to define generic categories, such as *Disease*, *Morphology*, *Treatment*, *Procedure*, *Body Structure*, etc.), which generalize the core layer content. Anchoring the core concepts with upper-level categories is performed using OntoUML, which considers the ontological distinctions of UFO [11, 5]. For instance, *Comorbidities* and *Neoplastic Disease* are specifications

(*subkinds*) of *Disease*, which is an *intrinsic mode* existentially dependent on its bearer (*Cancer Patient*); *Tumor Morphology* is a specific type of *Histology/Morphology*, which is an *intrinsic mode* inherent in cancer conditions; *Surgical Procedure* and *Administration of Medication* are specific types of *Treatment* procedure (perdurant); *Body Location* and *Tumor* are specific types (*subkinds*) of *Body Structure* (rigid type of endurants). Compared to BFO [6, 7], the intrinsic modes (*Histology/Morphology* and *Disease*) could be specified as *Generically dependent continuant* (BFO:0000031) and the endurants (*Patient* and *Body Structure*) as *Independent continuant* (BFO:0000004). However, using UFO and the modeling primitives of OntoUML has permitted us to ontologically analyze, clarify, and unambiguously represent concepts such as *Morphology* and *Disease* and connect them with appropriate semantic relations.

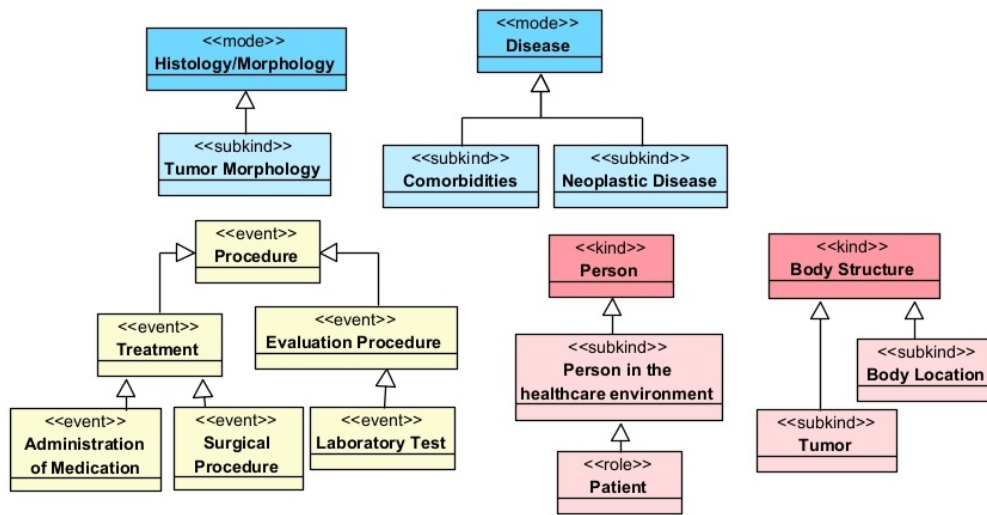


Figure 8: Excerpt of the Upper Layer represented using OntoUML.

4. Results

The operational version of the mCODE ontological model is generated as an OWL file [13]. The semantic integration experiment with the bottom-up version of the hyper-ontology [13] is conducted as follows. Under the supervision of experts, the elements defined in the mCODE ontological model are analyzed to find/match a correspondent concept/entity (i.e., addressing a similar semantic/medical context) described in the hyper-ontology. Also, we consider the associated standard concepts recommended in mCODE (e.g., *Primary Cancer Condition* is associated with *Malignant neoplastic disease* (SNOMEDCT:363346000)). Figure 9 depicts an Excerpt of the integration results in the core layer around *Disease* and *Morphology*, which are defined as separate categories but semantically connected using *Has associated morphology* semantic relation. Maintaining the core layer has positively affected the domain layer (Figure 10), where cancer conditions (e.g., *Carcinoma of breast*) and morphology types (e.g., *Malignant epithelial neoplasm*) are classified in a coherent semantic content in contrast to SNOMEDCT and NCIT (see Figure 1).

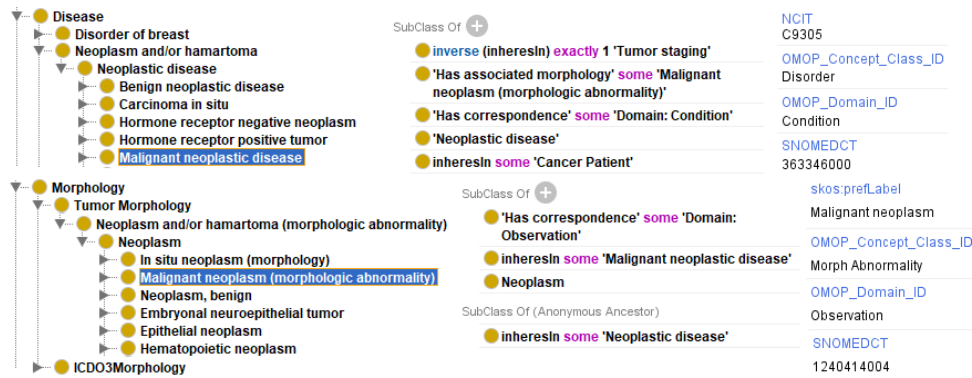


Figure 9: An excerpt of the hyper-ontology *Core Layer* around *Disease/Morphology* (Protégé).

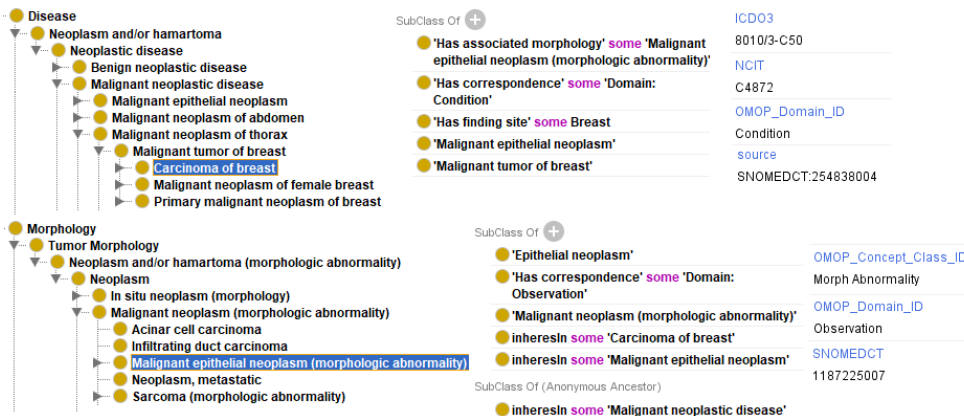


Figure 10: An excerpt of the hyper-ontology *Domain Layer* around *Disease/Morphology* (Protégé).

5. Conclusion

Considering foundational ontologies for biomedical ontologies development is a growing interest in biomedical research [8, 2]. Various domain and domain-specific ontologies have been developed and shared in the biomedical domain to support interoperability, complying with the FAIR principles. However, conflicting/heterogeneous definitions of biomedical concepts (e.g., morphology/disease in SNOMEDCT/NCIT) make semantic interoperability challenging. Achieving semantic interoperability requires the use of *ontologies* as domain conceptualization (e.g., domain ontologies) and *ontology* as a discipline (e.g., foundational ontologies) [9]. In this study, we relied on the Unified Foundational Ontology (UFO) [11, 5] and the Ontologically-Driven Conceptual Modeling language OntoUML, which is based on the ontological distinctions of UFO, to build a core ontological model for the oncology domain considering the mCODE model [1]. The ontological distinctions of UFO have permitted, using OntoUML, to uncover and clarify the nature of real-world entities from the oncology domain (e.g., morphology/disease) and explicitly represent the ontological nature of these entities. Besides, the nature of relations between entities in the oncology domain has been identified and characterized using a variety

of semantic associations. This study's main related work is the ontological unpacking process applied in genomics and virology to address conceptual uncertainty within the domain of SARS-CoV-2 data and knowledge [2]. In further work, we will analyze and represent, in the light of UFO, the genomic aspects specified in mCODE to enrich the hyper-ontology biological content. Also, domain experts will help maintain the hyper-ontology's upper layer. Finally, the bottom-up results will be integrated to create a complete version of the hyper-ontology. This project is co-funded by the European Union under Grant Agreement №101100633.

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