Modeling CIViC Interpretations using SEPIO

CIViC Curation Jamboree and Hackathon

SEPIO Overview

SEPIO is an Ontology and Data Modeling Framework

- Developed to provide rich, computable representations of the **evidence** and **provenance** behind scientific **assertions**
- The core ontology defines a **generic model** that can be applied in any domain and **extended with domain-specific** features.
- This model is the foundation of the **larger framework** that supports the creation of **custom ontology-based schema** for specific applications called **SEPIO Profiles**.
- The SEPIO Framework consists of four components:
  1. The SEPIO Core Ontology
  2. SEPIO Core Information Model
  3. SEPIO Profiles
  4. SEPIO Value Sets

SEPIO Value Proposition

Human Understanding and Discourse: as a simple and domain-agnostic conceptual model and vocabulary, it supports shared understanding communication about varied and abstract concepts and terms.

Data Interoperability: as a standard for data representation, its adoption can support data integration and exchange, enabling access to rich and more comprehensive data for research and clinical applications.

Knowledge Creation: as a modeling framework, it facilitates creation or re-use of schema tailored for specific domains. Access to rich models and data this supports can enable deeper curation, performed in context of relevant existing knowledge.

Computability: as a data model, it is designed to structure key features of evidence and provenance in a way that allows automated evaluation of assertions and their evidence.

Semantic Data: rooting of SEPIO models in ontologies enables generation of 'semantically-enhanced' data, where knowledge encoded in these supporting ontologies can add value by making the data better interpretable by humans and machines.

The SEPIO Modeling Framework

Four core components work together to facilitate the creation and re-use of customized ontology-based schema, that are supported by a common ontological model and semantic infrastructure.

1. **The SEPIO Core Ontology**
2. The SEPIO Information Model
3. SEPIO Profiles
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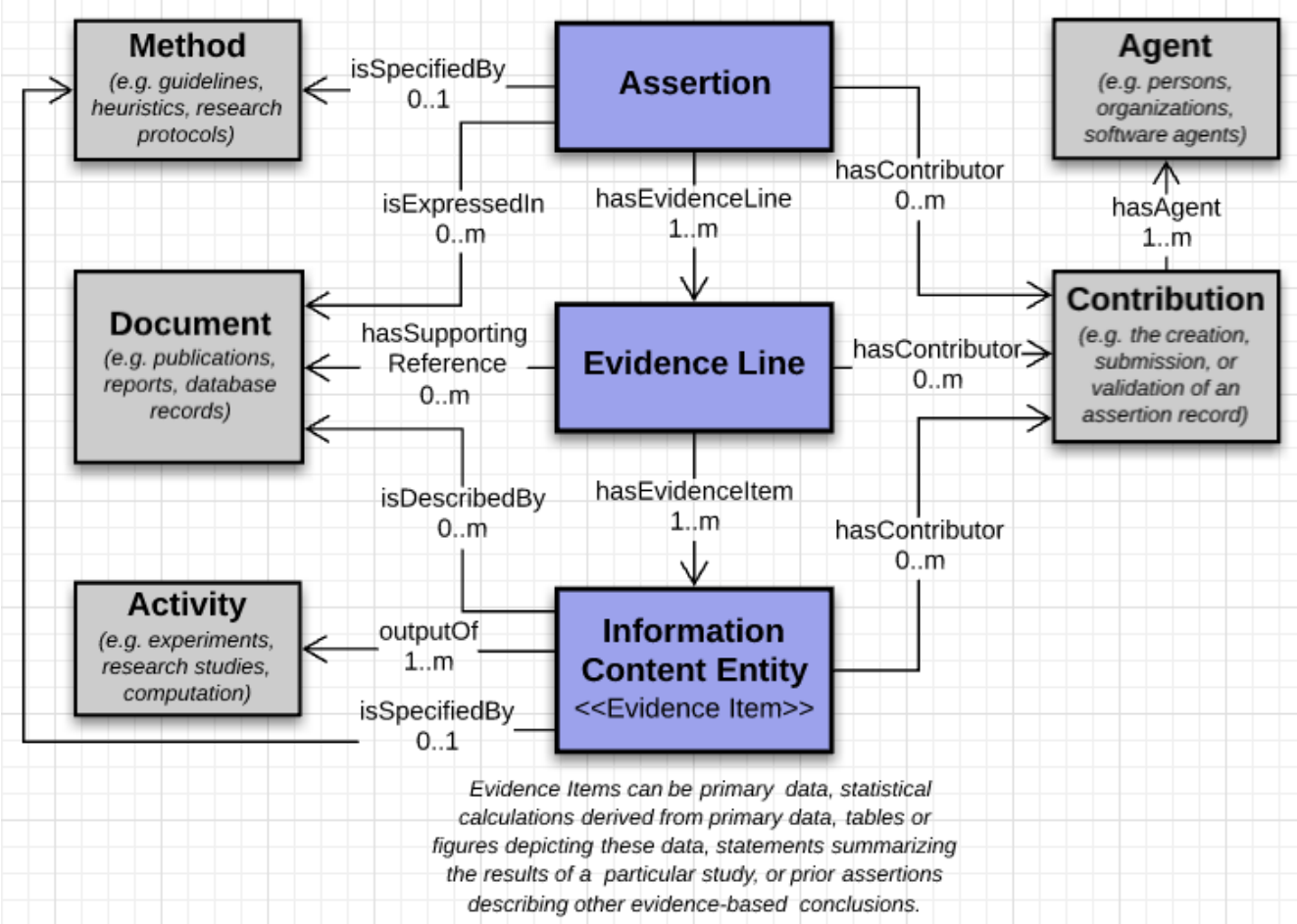
1. The SEPIO Core Ontology

- Provides foundational definition of the core domain-agnostic model, implemented in OWL2 DL language
- Re-uses when possible from existing ontologies and evidence frameworks (BFO, IAO, OBI, ECO, …)
- Built around a set of simple and generic high-level concepts and relationships



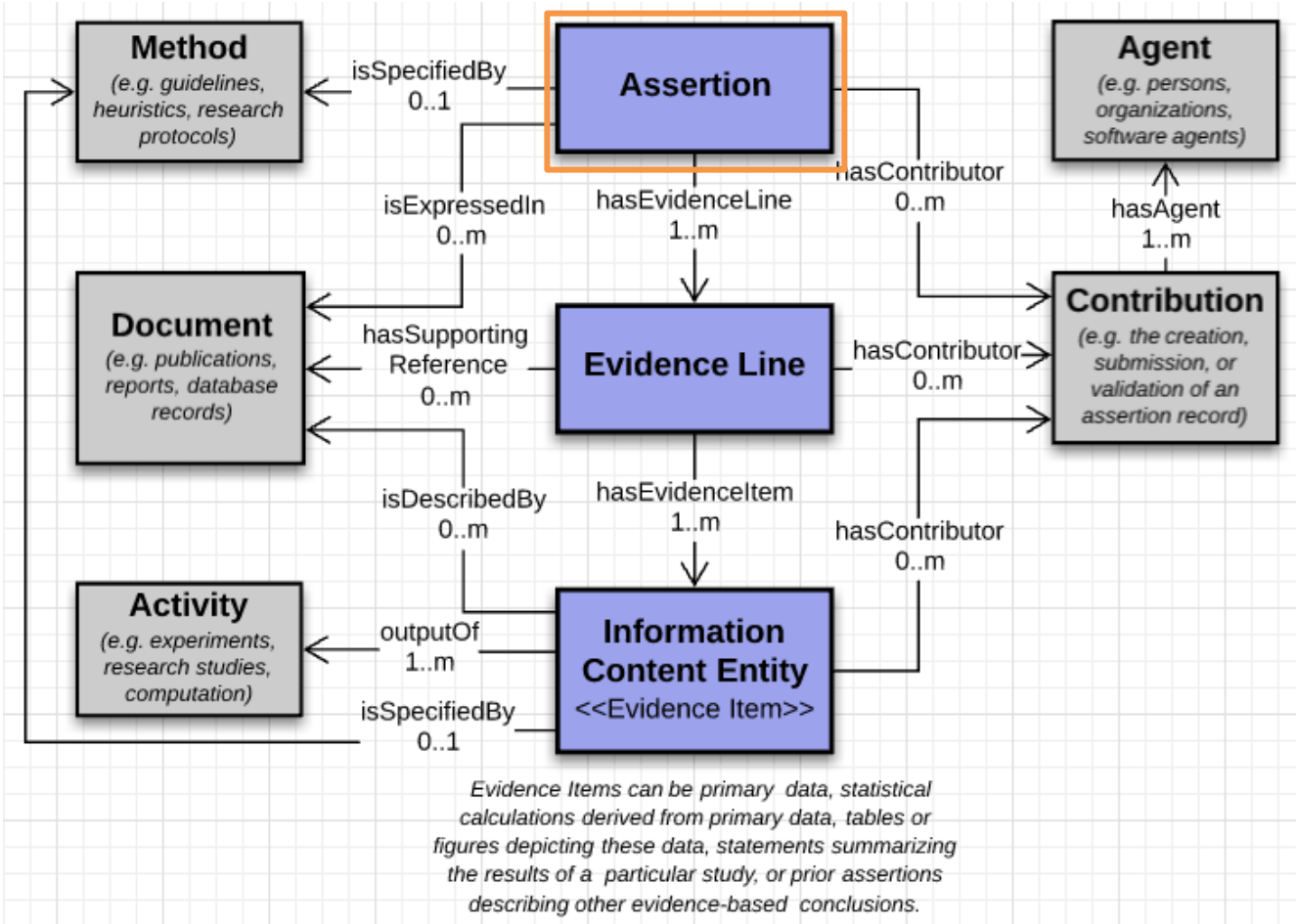
1. The SEPIO Core Ontology

Assertion

Definition: an evidence-based statement of purported truth, as made by a particular agent on particular occasion.

Example: Counsyl Genetics' 2015 Assertion that the BRCA2 variant c.8023A>G is pathogenic for Breast Cancer.

Comments: Assertions put forth a particular 'Proposition' as true. More than one Assertion, made by different agents on different occasions, can put forth the same Proposition.



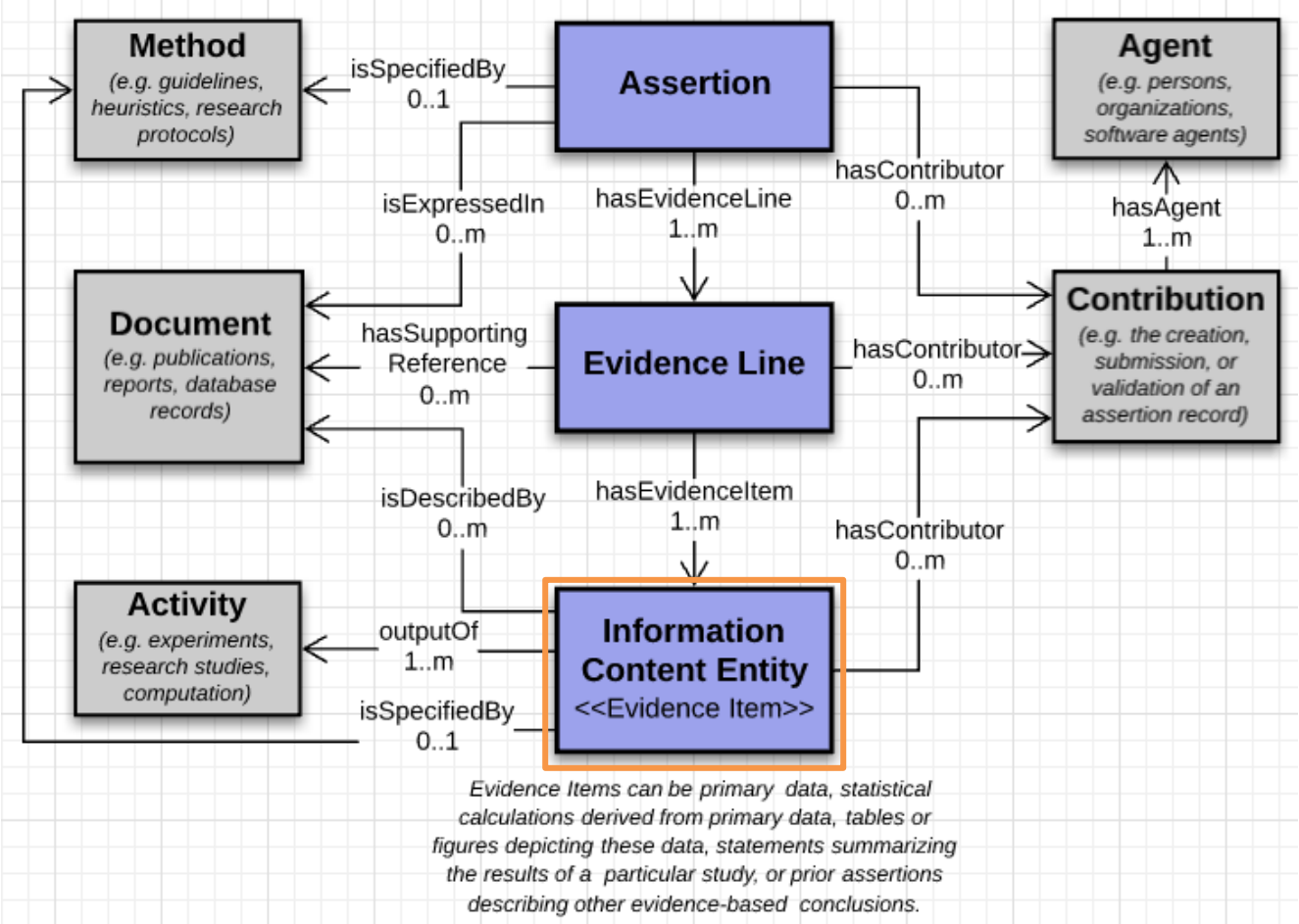
1. The SEPIO Core Ontology

Evidence Item

Definition: an individual piece of information that is interpreted to build an argument for or against an Assertion

Example: the 0.0021% population frequency of the BRCA2 variant c.8023A>G in healthy NFE individuals in ExAC.

Comments: Evidence Items can be primary data, derived statistical calculations, tables/figures depicting these data, statements summarizing the results of a particular study, or prior assertions based on their own lines of evidence.



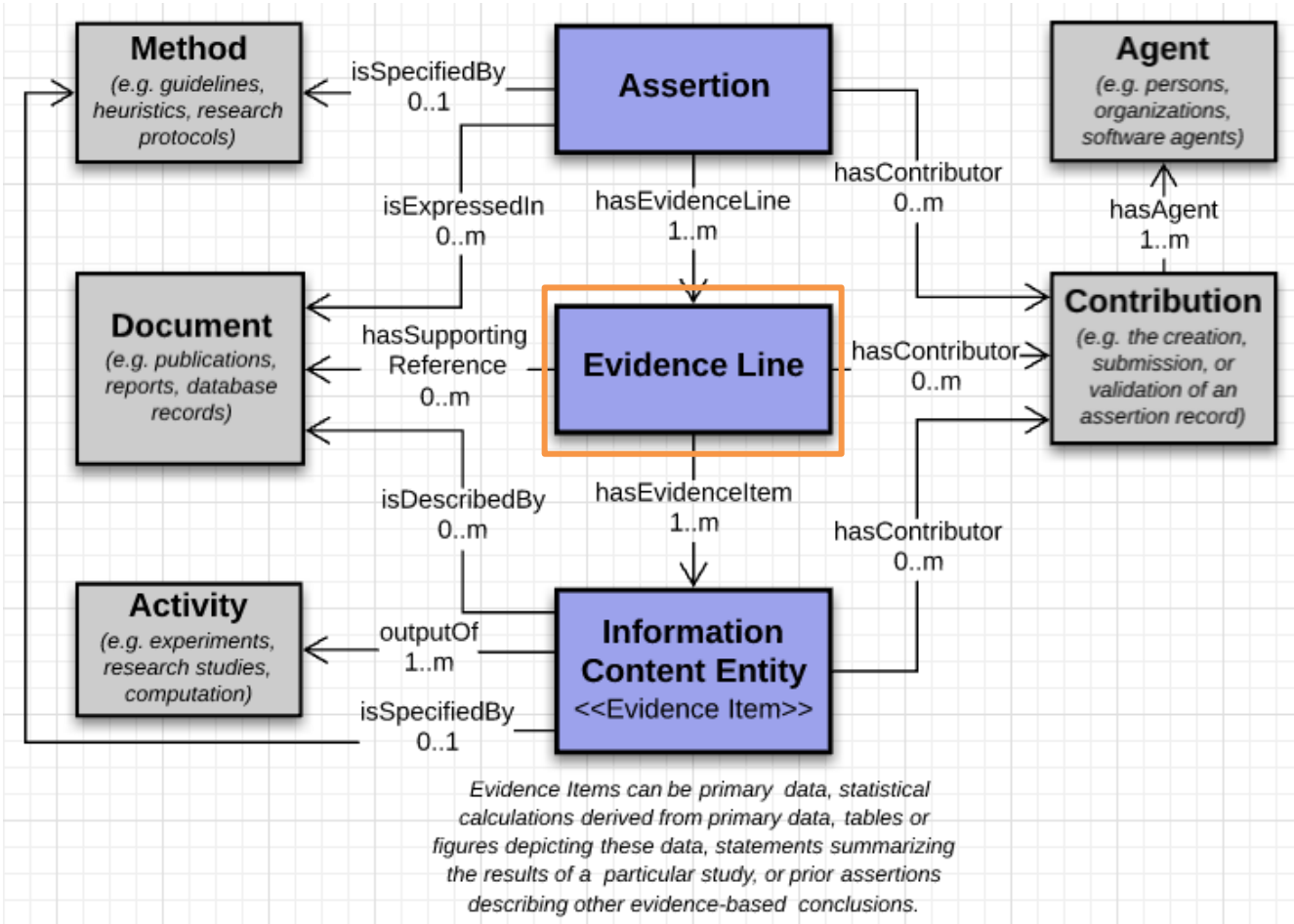
1. The SEPIO Core Ontology

Evidence Line

Definition: independent, meaningful arguments relevant to the validity of an Assertion, that are supported by one or more Evidence Items

Example: the argument made for the BRCA2 variant's pathogenicity based on its observed absence in healthy populations.

Comments: Representing Evidence Items separately from the 'arguments' they make is an important feature that lets us describe properties of information emerging only through its interpretation as evidence.

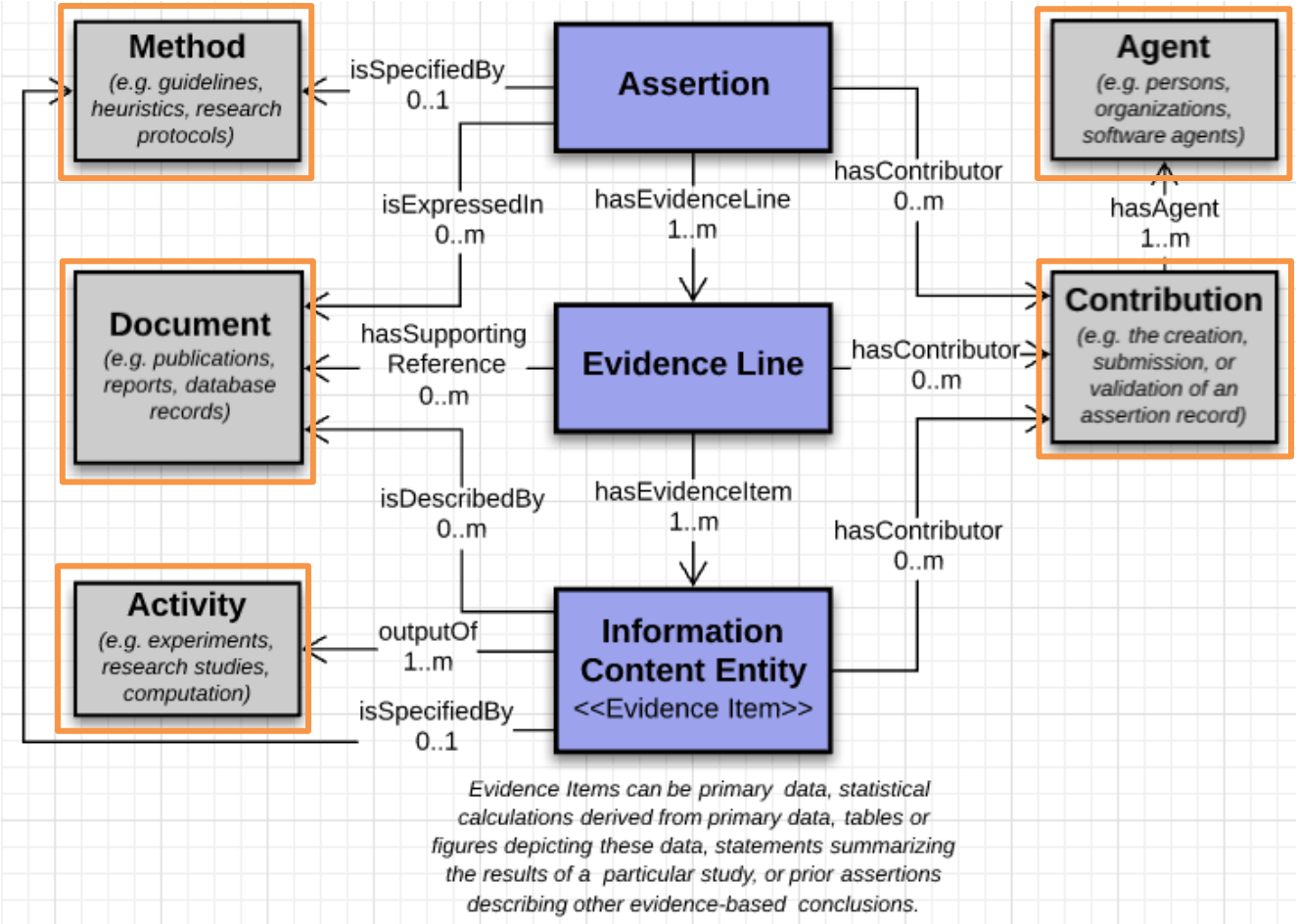


1. The SEPIO Core Ontology

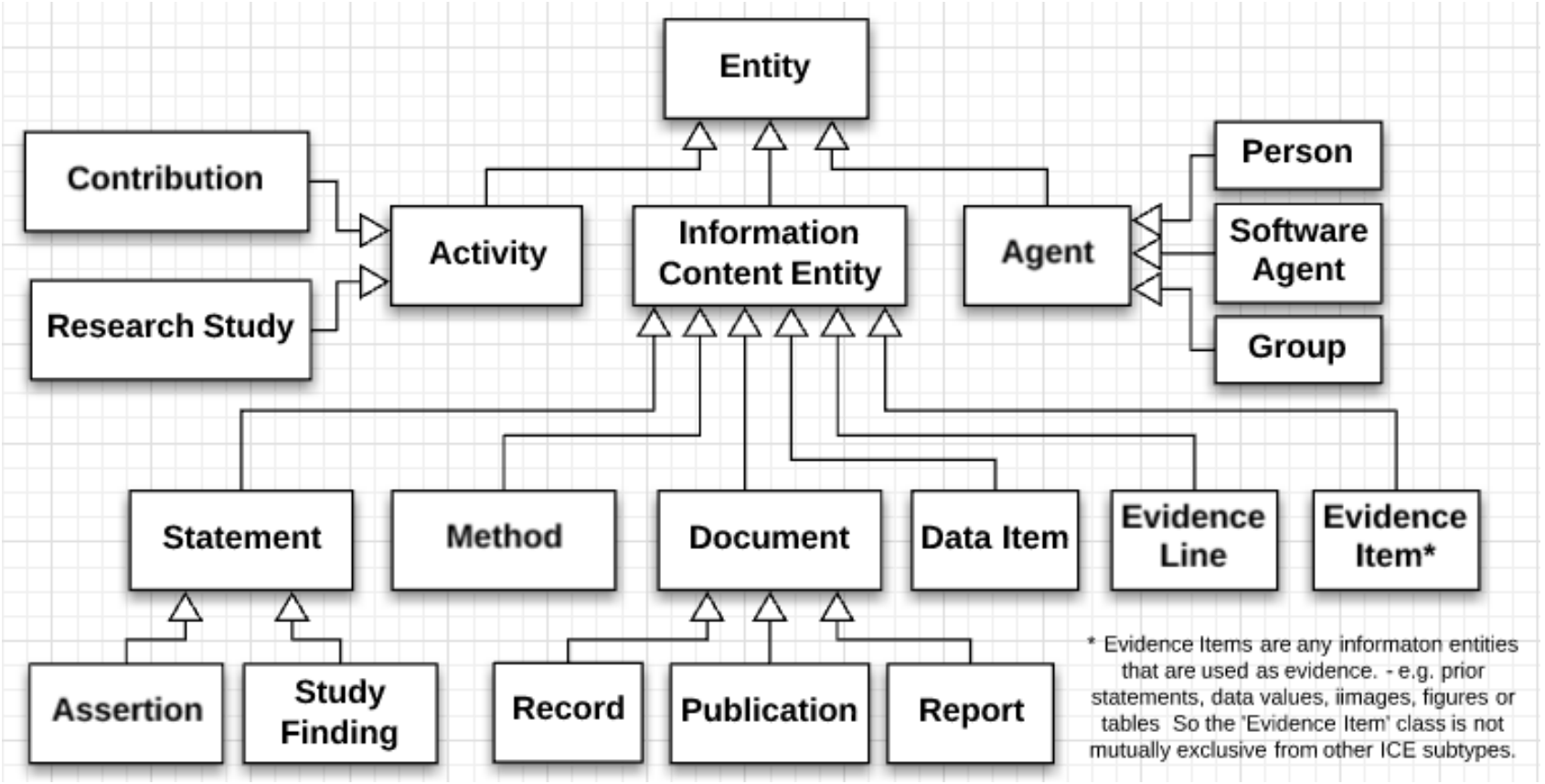
Provenance

Surrounding the core axis are familiar concepts that let us describe in rich detail who, how, and when these core informational objects were created:

- **Contributions** made to them by **Agents**
- **Activities** they perform to do so
- **Methods** that specify these activities
- **Documents** created to describe them.



SEPIO Class Hierarchy



Hierarchical relationships between the high-level classes/types in the SEPIO core ontology and model

SEPIO Mapping to A 'Universal Reality'

SEPIO's domain-agnostic model is based on what we see as a universally true view of three tasks involved in making evidence-based assertions:

1. The **identification** and **curation** of information that might be useful as evidence for a particular proposition/hypothesis being evaluated . . . Evidence Items
2. The **grouping** and **interpretation** of this information as discrete/independent, meaningful arguments that provide support for or against this proposition . . . Evidence Lines
3. The combined **assessment** of all relevant arguments to **assert** a final conclusion about the truth of the proposition . . . Assertions

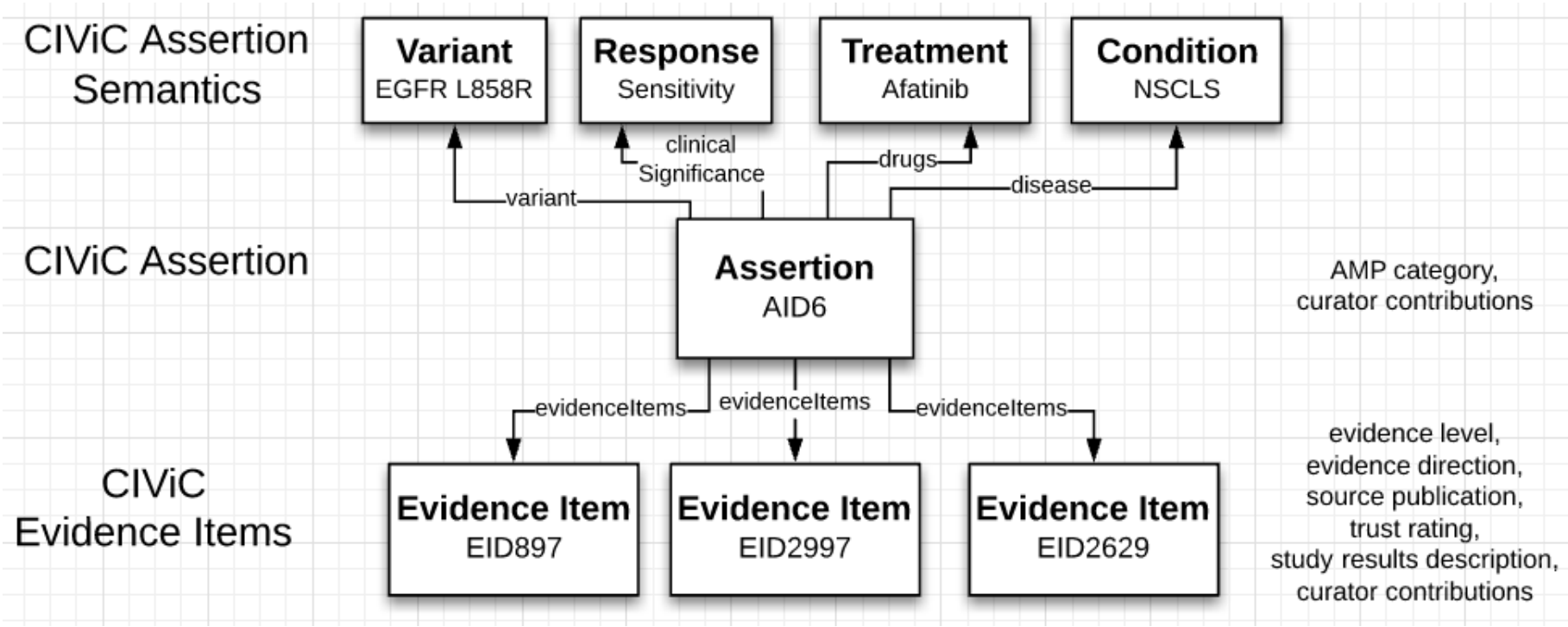
The outputs of these tasks map onto the entities comprising the core axis of the model (Evidence Items, Evidence Lines, Assertions)

The benefit here is that no matter how complex the information used as evidence, how nuanced the reasoning and interpretation of this evidence, or how idiosyncratic an existing schema may be, we should always be able to map to core SEPIO model because of its basis in a universal reality.

This is key to its ability to be applied in diverse domains, and to accommodate representation and integration of data from diverse systems and applications.

Shape of a CIViC Predictive Assertion

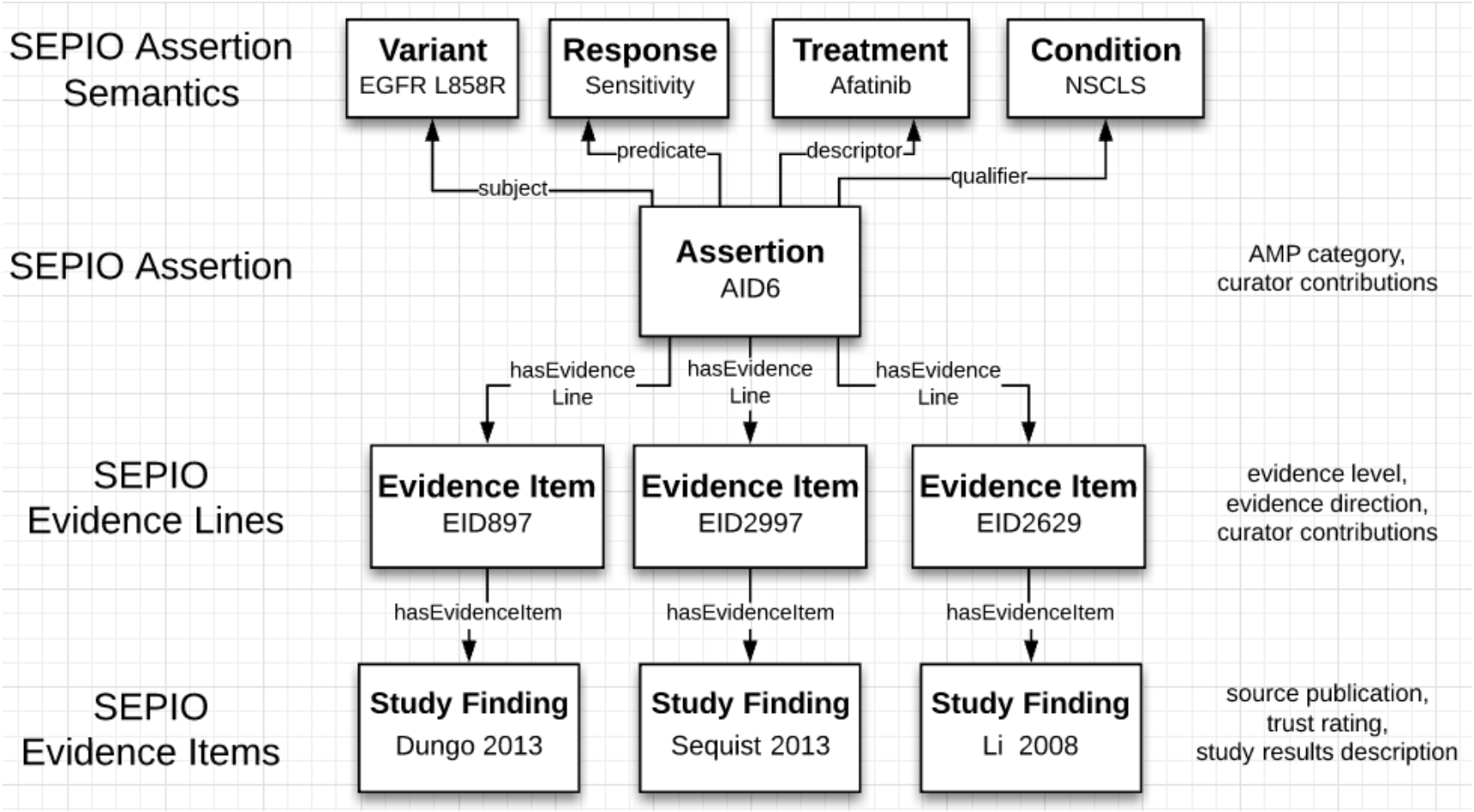
Assertion: *"EGFR L858R positive NSCLC is sensitive to afatinib"* (link)



High-level structure of CIViC data model

Shape of a SEPIO Predictive Assertion

Assertion: *"EGFR L858R positive NSCLC is sensitive to afatinib"* (link)



More granular modeling diagrams here.

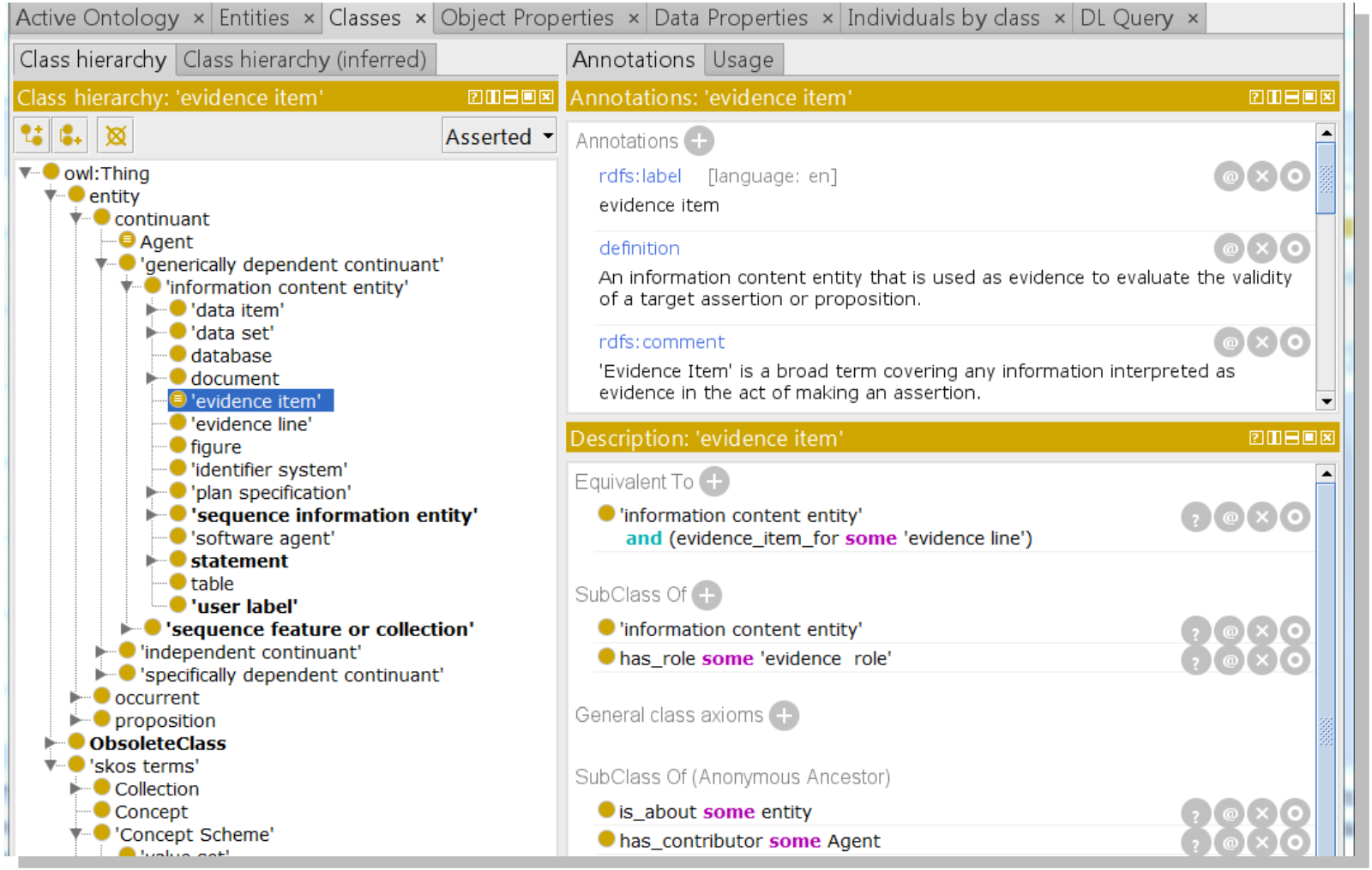
The SEPIO Modeling Framework

Four core components work together to facilitate the creation and re-use of customized ontology-based schema supported by a common ontological model and semantic infrastructure.

1. The SEPIO Core Ontology
2. **The SEPIO Information Model**
3. SEPIO Profiles
4. SEPIO Value Sets

2. The SEPIO Core Information Model

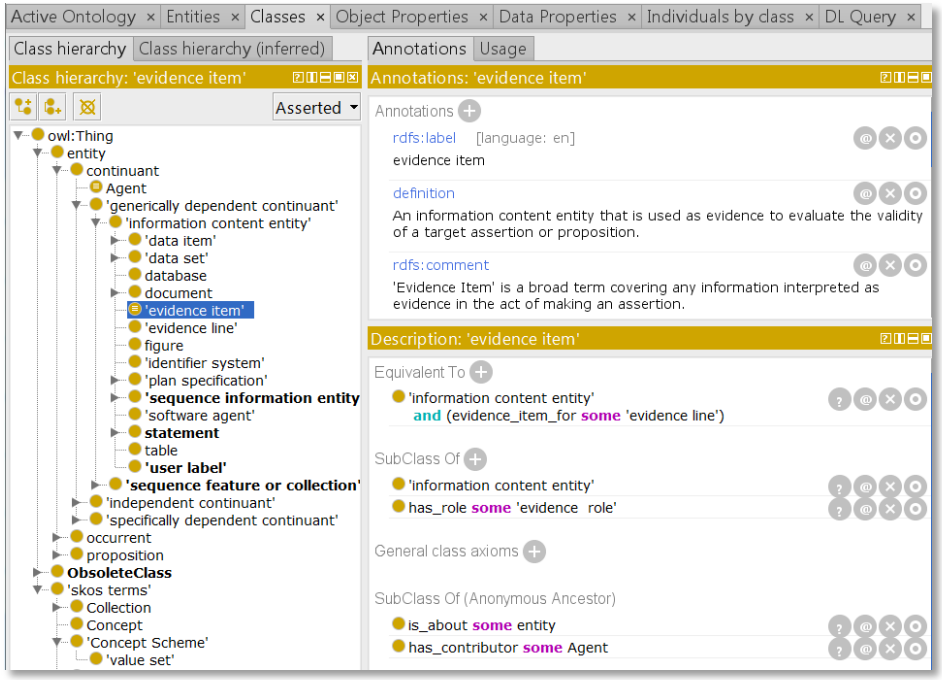
Ontologies define necessary and sufficient conditions for class membership, but typically don't encode you closed-world constraints necessary for schema specifications.

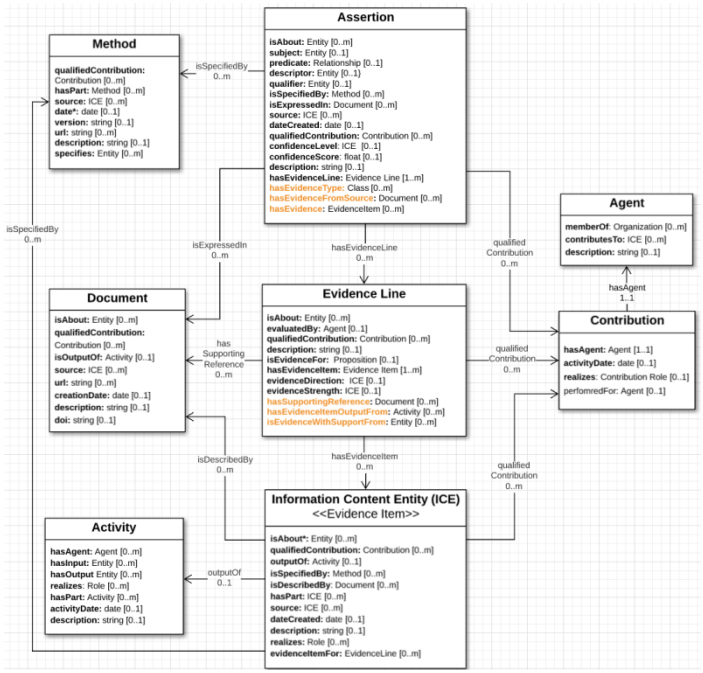


The Evidence Line class as defined in the SEPIO Ontology, viewed using the Protégé ontology editor.

2. The SEPIO Core Information Model

Provides a *UML-like view* of the 'maximal' model supported by the core ontology, that specifies how terms and design patterns defined in SEPIO can be used to structure data.





Presents the model in a form familiar to data modelers, to guide them in creating custom SEPIO-based schema to support specific use cases and applications.

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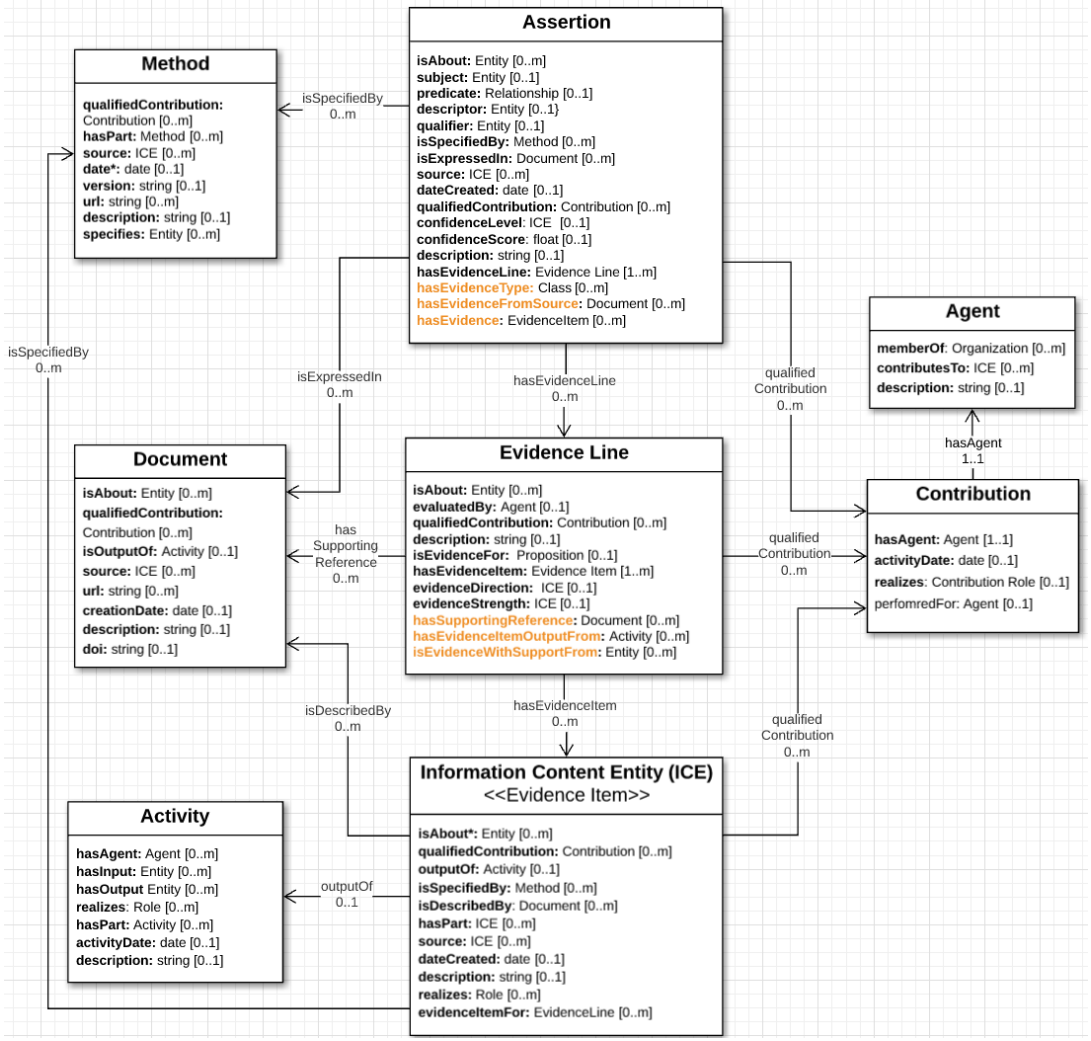

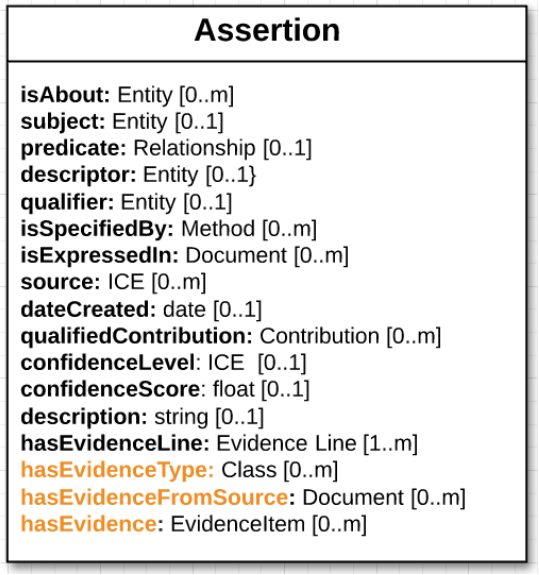

The complete, maximal SEPIO Information Model. Orange attributes are 'shortcut relations that can be used to directly related types not connected by a primary attribute.

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4. SEPIO Value Sets

3. SEPIO Profiles

Domain- or application-specific data models that *refine* the maximal information model, and can *extend* it with terms to support custom schema for a particular use case.

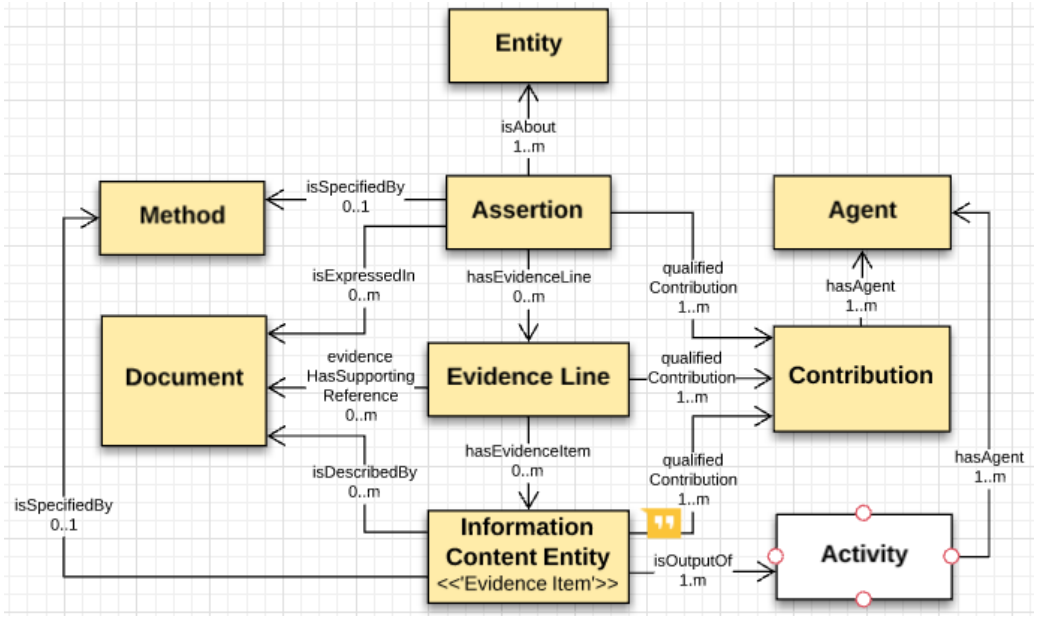
Creating a SEPIO Profile:

1. Select the relevant elements of the maximal information model
2. Use these to define the basic structure of an application-specific data model
3. Extend the model with required domain-specific specializations of core data types
4. Update core structure to use domain-specific specializations.
5. Flesh out profile by defining specific attributes and design patterns required to model the target data
6. Define cardinalities and data type constraints to meet application requirements.

The resulting model can be implemented as a formal schema that contains a subset of 'maximal' SEPIO types and attributes, extended with domain-specific concepts, and structured to support a particular application use case.

3. SEPIO Profiles

Domain-specific data models that refine the maximal information model, and can extended it with terms to support custom schema for a particular application.



Concepts from the core SEPIO model required to model ClinGen ACMG Variant Interpretation data are in light orange.

Creating the ClinGen ACMG Profile:

1. Select the relevant elements of the maximal information model
2. Use these to define the basic structure of an application-specific data model
3. Extend the model with required domain-specific specializations of core data types
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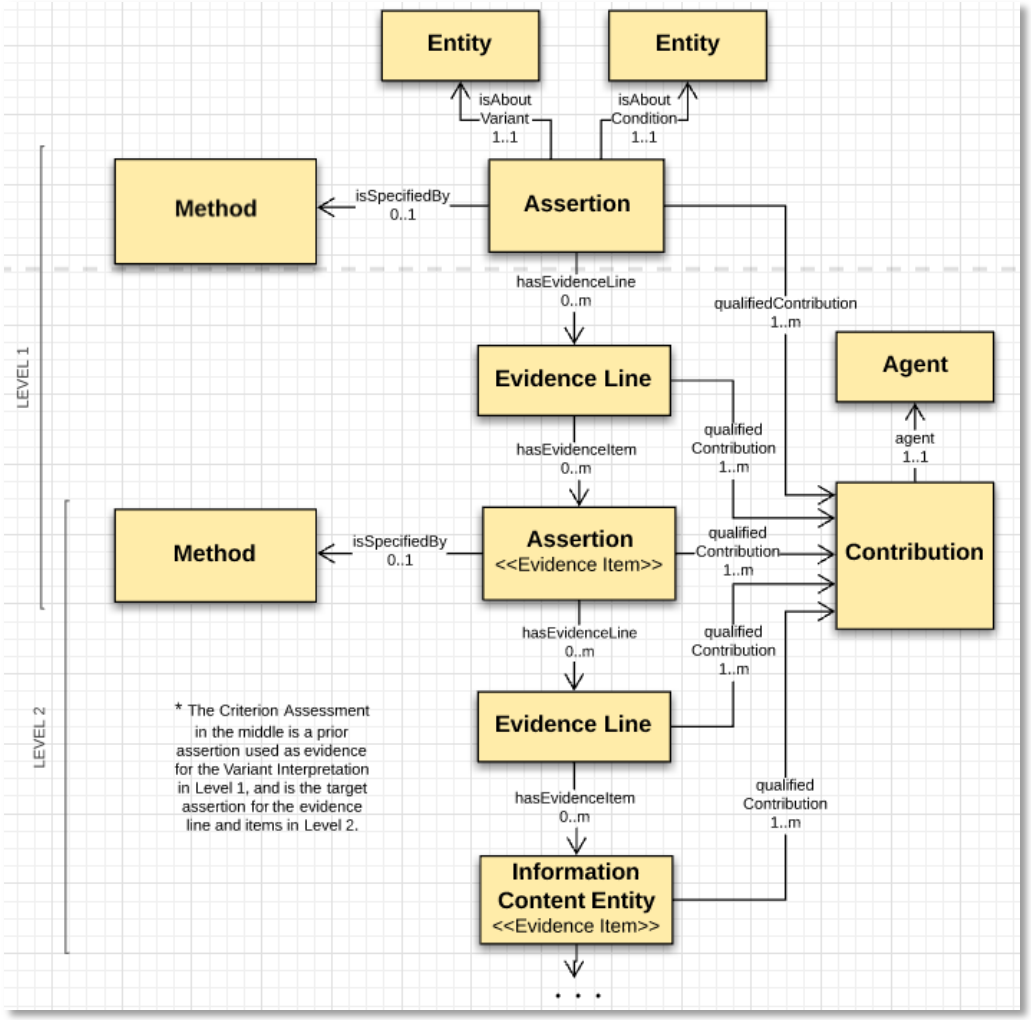
3. SEPIO Profiles

Domain-specific data models that refine the maximal information model, and can extended it with terms to support custom schema for a particular application.



High-level structure of the model defined for the ClinGen ACMG Variant Interpretation SEPIO Profile

Creating the ClinGen ACMG Profile:

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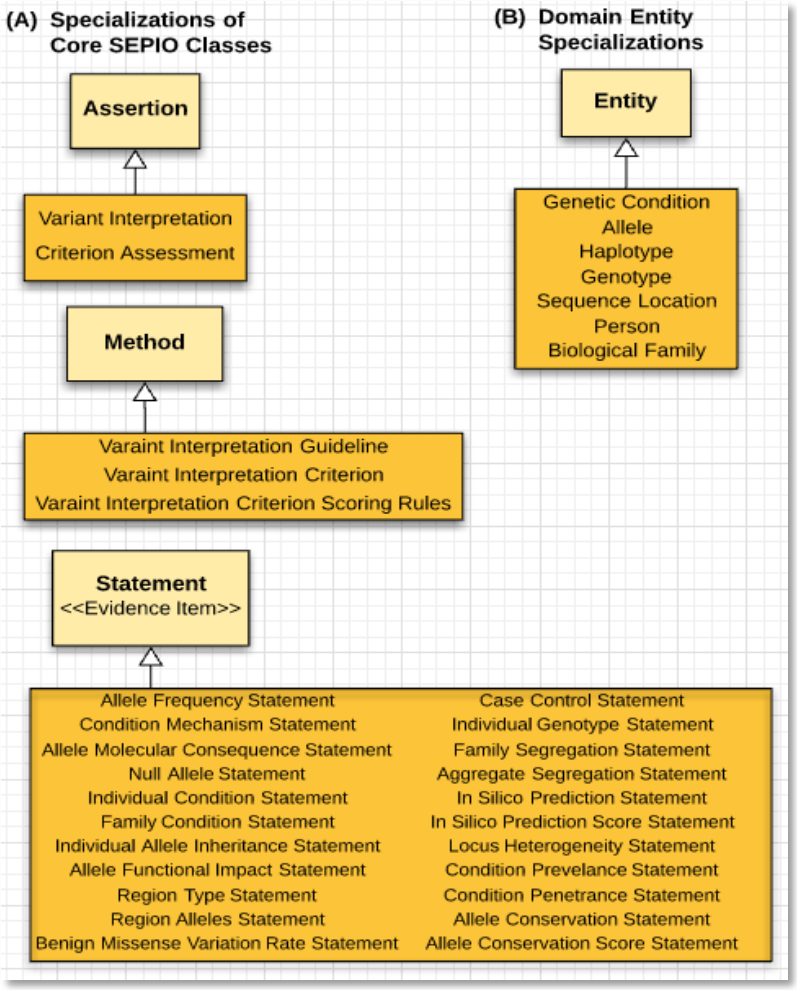

Specializations implemented to support the ClinGen ACMG Variant Interpretation SEPIO Profile

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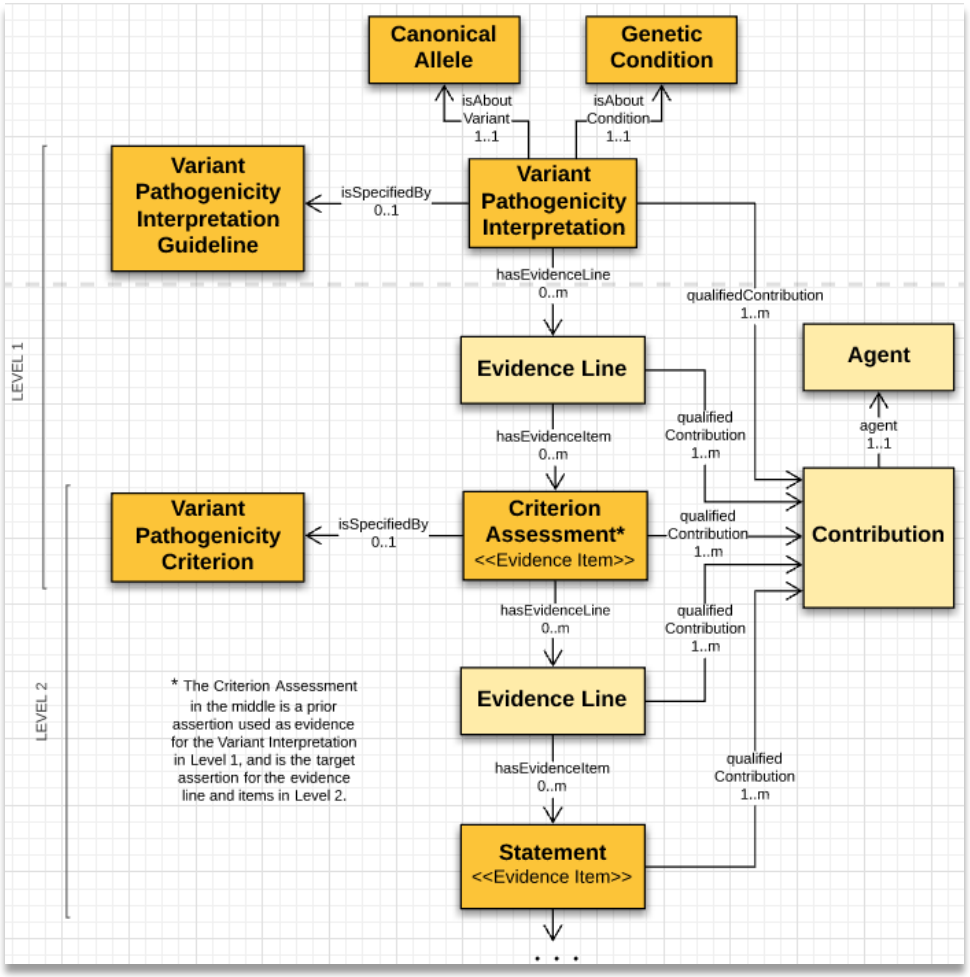

High-level structure of the ClinGen ACMG Variant Interpretation SEPIO Profile, with specializations of core SEPIO classes in dark orange

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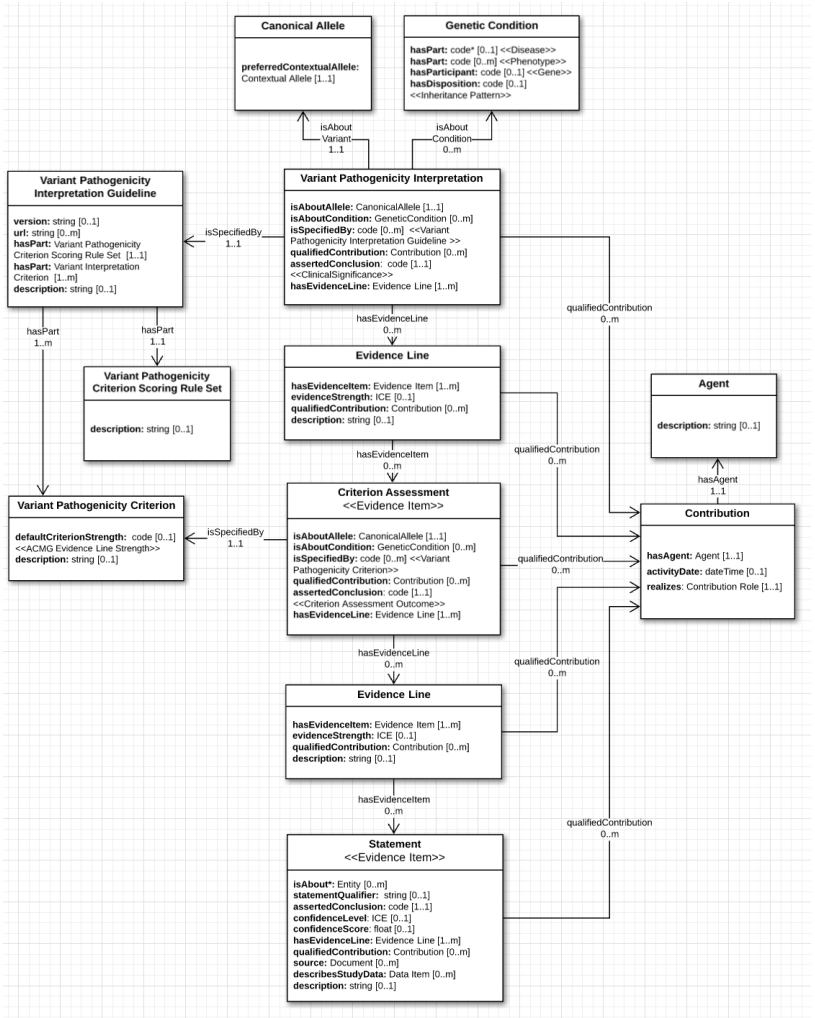
3. SEPIO Profiles

Domain-specific data models that refine the maximal information model, and can extended it with terms to support custom schema for a particular application.



Low-level view of the attributes and relationships defined for the of the ClinGen ACMG Variant Interpretation SEPIO Profile

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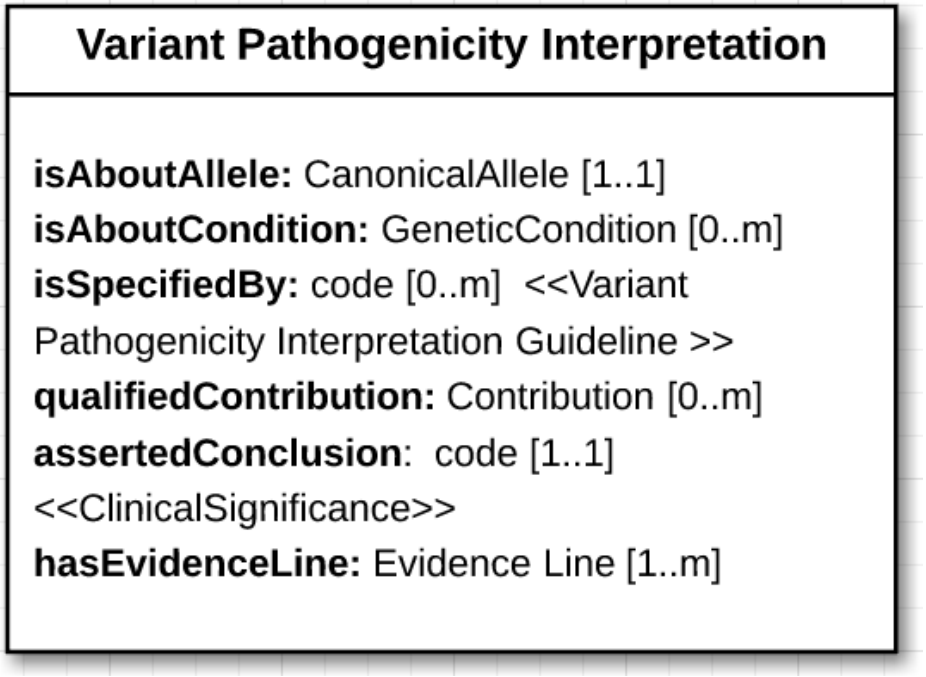

Application-specific cardinality and data type constraints defined for the Variant Pathogenicity Interpretation specialization of the core SPEIO Assertion Class

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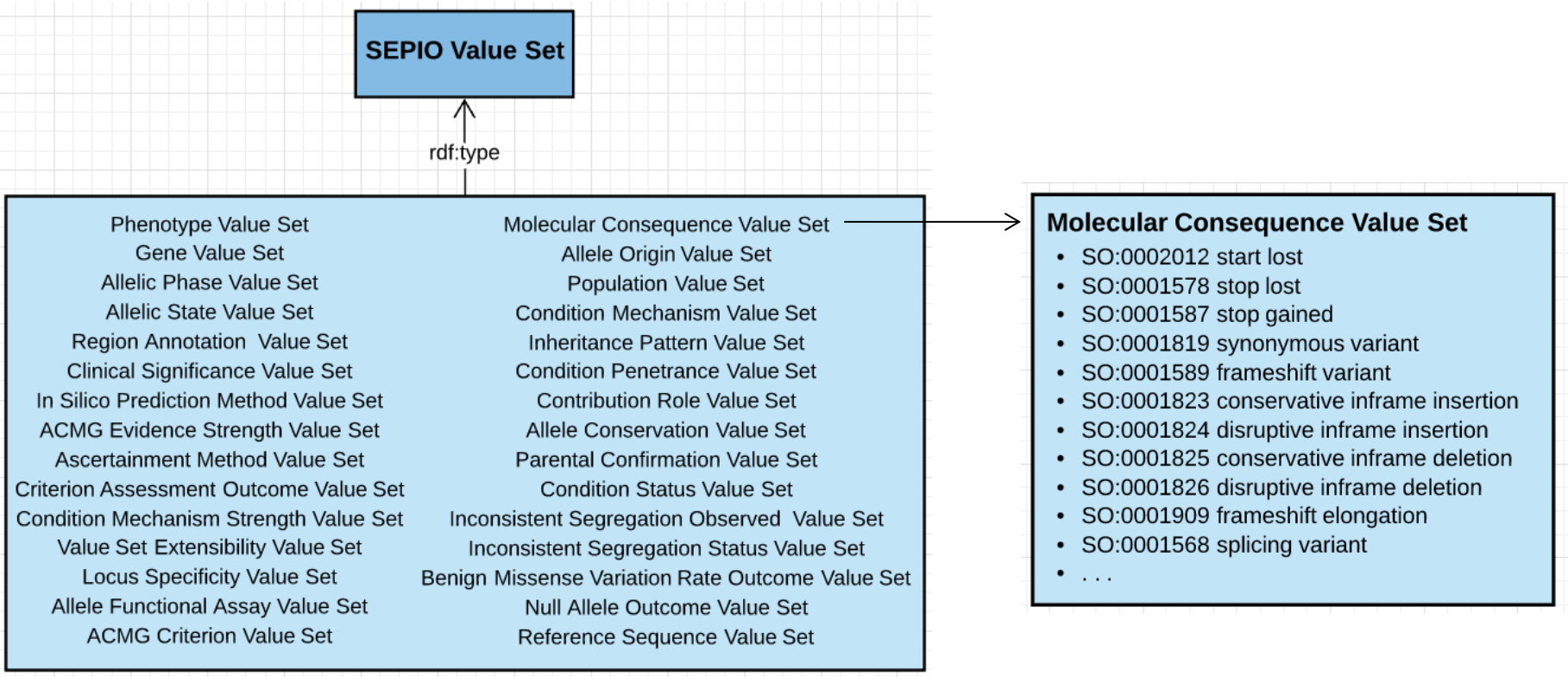
4. SEPIO Value Sets

Re-usable collections of terms that can be bound to attributes in a particular schema to constrain and standardize data entry.

SEPIO provides a Value Set Model based on the SKOS framework to support the implementation of value sets as part of the profile's ontology extension.



Value sets implemented for the ClinGen ACMG Variant Interpretation Profile, and an example of the values for the Molecular Consequence Value Set, which use IRIs from the Sequence Ontology

Example Variant Pathogenicity Interpretation Record Based on the ClinGen ACMG Profile

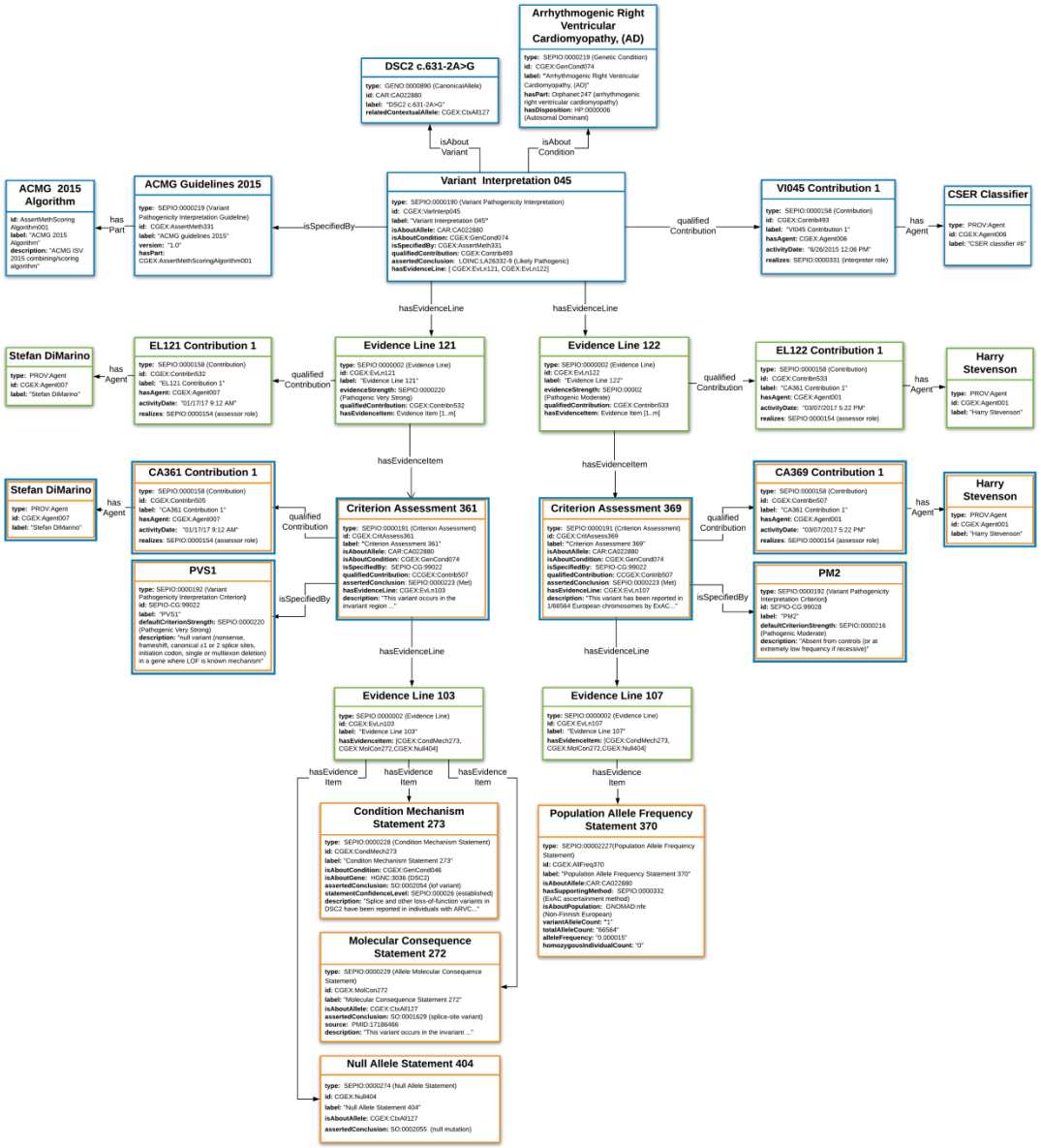
A ‘likely pathogenic’ interpretation of the DSC2 c.631 2A>G variant based on two ACMG criteria evaluated as ‘met’:

1. The **PVS1** criteria, as supported by previous assertions that the variant is a splice-site mutation that causes loss of gene product function, and that LOF of the affected gene is a known mechanism of disease

2. The **PM2** criteria, as supported by population frequency data demonstrating the variant to be absent in a Gnomad population of healthy Non-Finnish Europeans.

Source ClinGen data can be found here.

Larger original image can be found here.



Data Model Alignment

Example 1: Assertion Curation Paradigm
SEPIO-Model of CIViC Assertion6 Record

Assertion: EGFR L858R positive NSCLC is sensitive to afatinib (link)

Evidence Lines (three of the six evidences provided in the CIViC assertion record are included):

1. **EID2997** – based on official FDA treatment guidelines (link)
2. **EID879** – based on the results of a formal clinical trial (link)
3. **EID2629** – based on preclinical data from cell line studies (link)

See diagrams of modeling proposals here.

Modeling Proposal 1 (Basic): Structures CIViC data at existing level of curation - with most details about evidence reported in free-text summary rather than formally structured

Modeling Proposal 2 (Enhanced): Illustrates how SEPIO could accommodate a deeper level of curation where evidence and provenance information are more richly are structured.

Example 1: Assertion Curation Paradigm
SEPIO-Model of CIViC Assertion6 Record

Take Homes:

- Overall the structure and semantics of the SEPIO representation is very similar to the native CIViC model.
- A key difference is that SEPIO creates separate representations of the study finding (Evidence Item) and its interpretation as evidence (Evidence Line)
- Representation of the study finding as its own object provides an opportunity to describe its provenance, re-use it across different interpretation records, and unpack the data it describes into a richer structured form.
- The SEPIO model also aims to apply developing GA4GH standards to structure statement semantics and model key domain entities.
- The proposed 'enhancements' would require a moderately deeper level of curation, but would be enabled by a simple SEPIO-based data model that includes value sets to support structured capture of evidence and provenance metadata

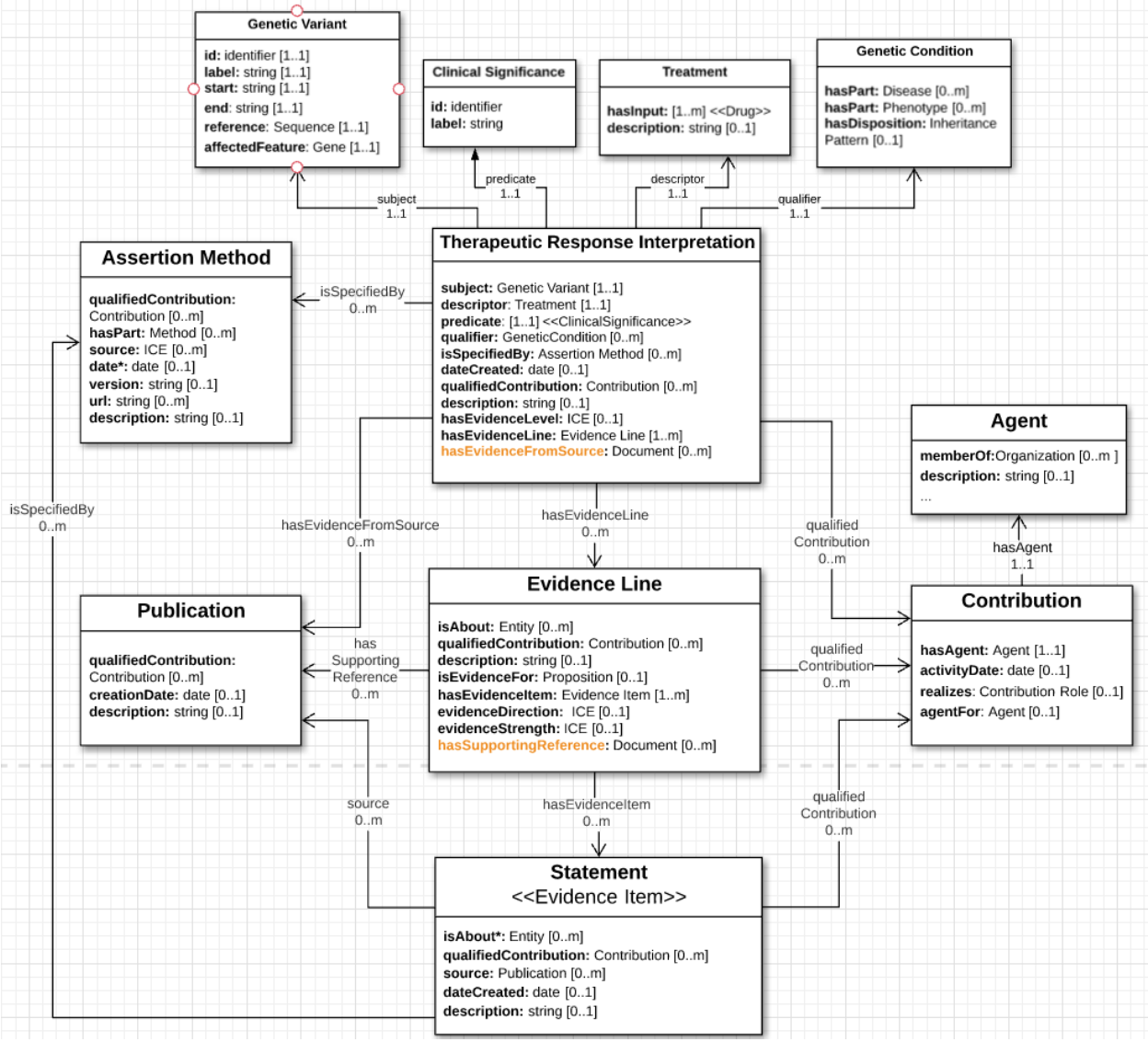
Towards SEPIO Profiles for CIViC Data

1. Assess alignment of SEPIO and CIViC models
    a. Evaluate examples of SEPIO-based CIViC Assertion and Evidence Items
    b. Do proposed models accurately reflect CIViC data?

2. Define and assess changes to CIViC model and architecture required for SEPIO adoption
    a. Feasibility?
    b. Implications for CIViC curation workflow and tools?

3. Explore areas to expand structured curation of evidence
    a. define scope of extensions
    b. implications for curation workflow and tooling
    c. define extended model using SEPIO framework
    d. consider possible terminologies/ontologies

Straw Man Profile for Predictive Interpretations



See complete set of profile diagrams here.

Example 2: Evidence Line Curation Paradigm
SEPIO-Model of CIViC Evidence Item 879 Record

Evidence Line: The argument provided by the results of a formal clinical trial (link) for the proposition that "EGFR L858R positive NSCLC is sensitive to afatinib".

Separates the representation of the Study Finding as an **Evidence Item**, from the interpretation of this finding as evidence which is captured in an **Evidence Line**.

The **Evidence Line** includes an assessment of direction and strength of support provided by this evidence.

The variant, treatment, and condition that the evidence is about is wrapped into a **Proposition** object, which captures the semantics of the statement the evidence is curated toward

See diagrams of modeling proposals here.

Curation Paradigms Supported by SEPIO

1. **Assertion Curation:** An assertion is made by some agent, and evidence supporting the assertion is captured
   a. *e.g. CIViC assertion (AID) records*
   b. *e.g. ClinVar variant pathogenicity (SCV) records*

2. **Evidence Item Curation:** Information that could be used as evidence for assertions in some domain are captured independently of their use as evidence.
   a. *e.g. MACE2K automated extraction of literature findings*

3. **Evidence Line Curation:** Curated evidence items are evaluated to determine the direction and/or strength of evidence they provide for a particular proposition.
   a. *e.g. CIViC Evidence Statement (EID) records*

4. **Evidence Level Curation:** Evidence items or lines are curated, and assertion is made about the total support the collectively provide for a particular proposition.
   a. *e.g. ClinGen gene dosage and gene validity records*

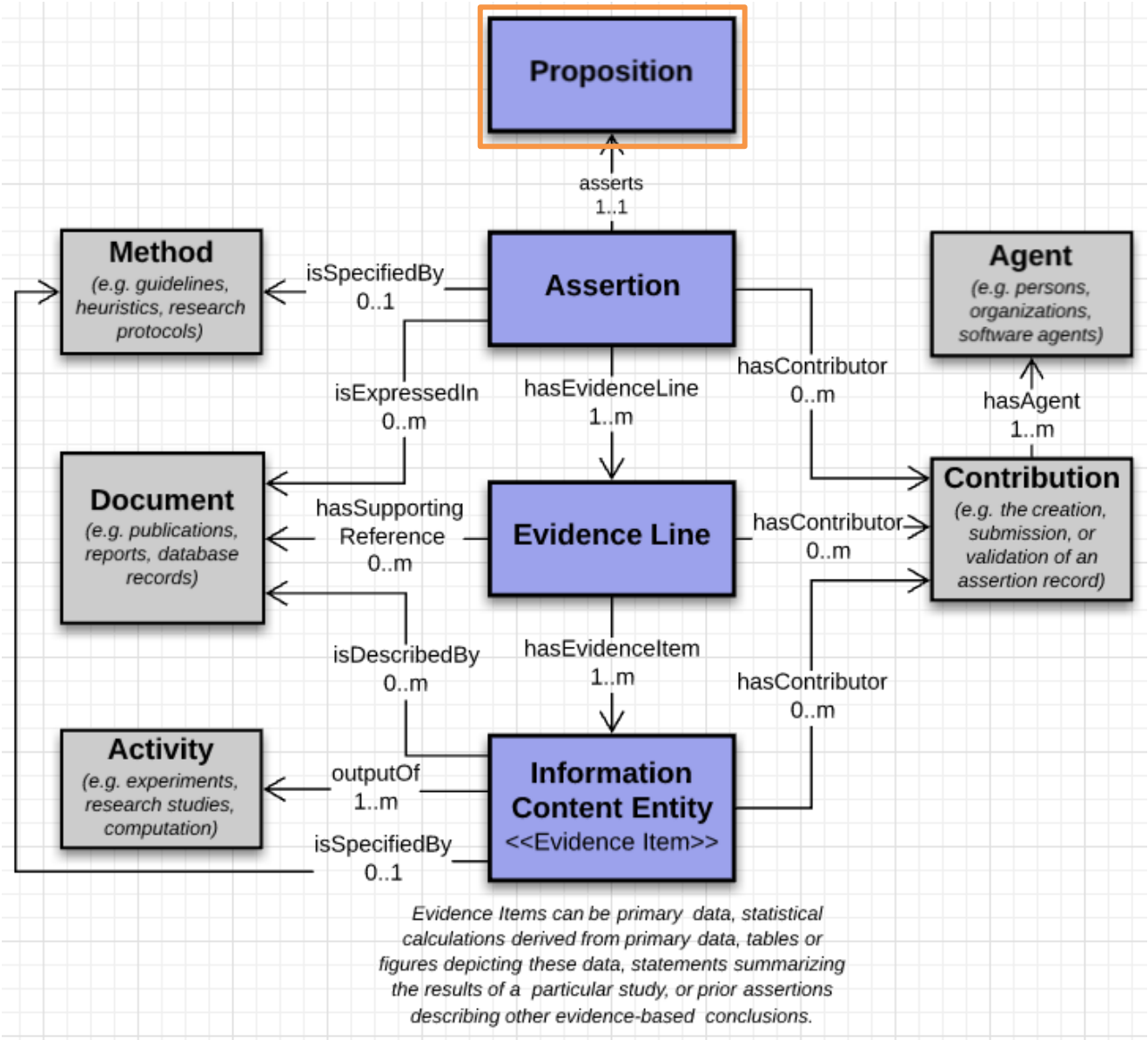
Propositions in the SEPIO Core Model

Propositions

Definition: an abstract concept representing the meaning of a statement that may or may not ever be asserted as being true

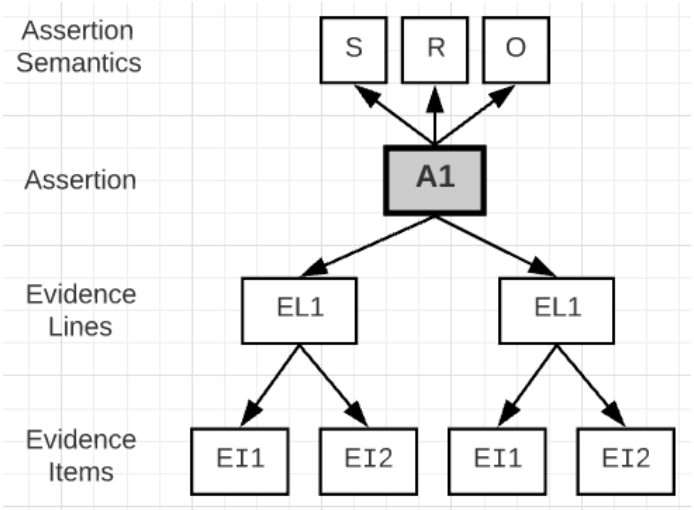
Example: the abstract notion of the BRCA2 c.8023A>G variant being pathogenic for Breast Cancer (as opposed to a particular agents Assertion that this fact is true)

Comments: Propositions are an important concept to understand, but are not commonly used in practice in SEPIO models.



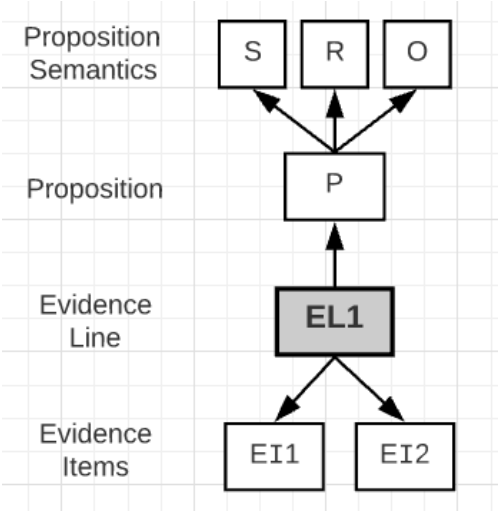
Curation Paradigms Supported by SEPIO

Assertion Paradigm

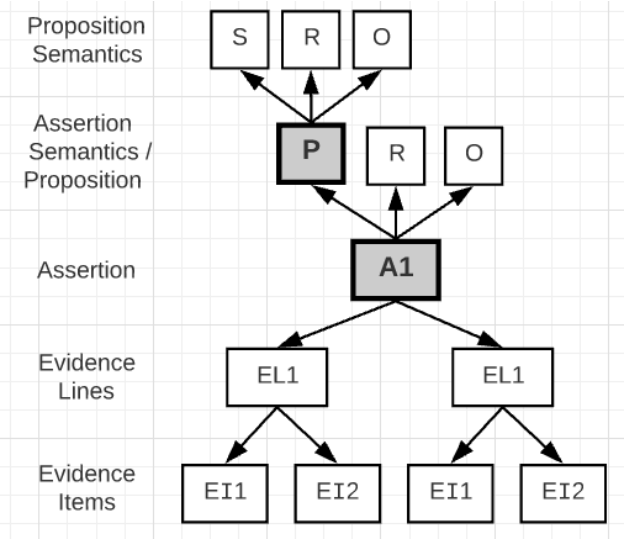


Evidence Item Paradigm

Evidence Line Paradigm



Evidence Level Paradigm

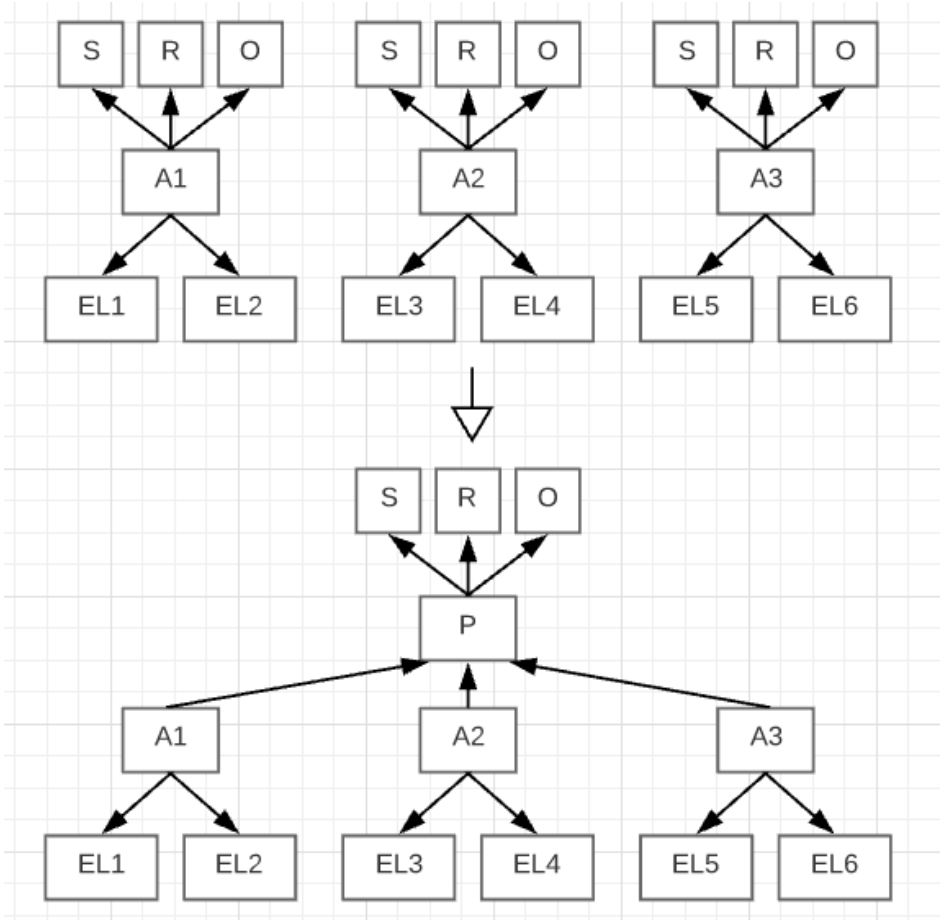


S = subject, R = relationship, O = object

Utility of Propositions

Use Case: Consolidating Assertion Semantics

Achieve more efficient modeling by eliminating redundant representation of semantics of assertions expressing same fact



Example: ClinVar can have multiple SCV assertion records that all put forth the same proposition as true.

A = assertion

EL = evidence line

EI = Evidence Item

P = proposition

S = subject

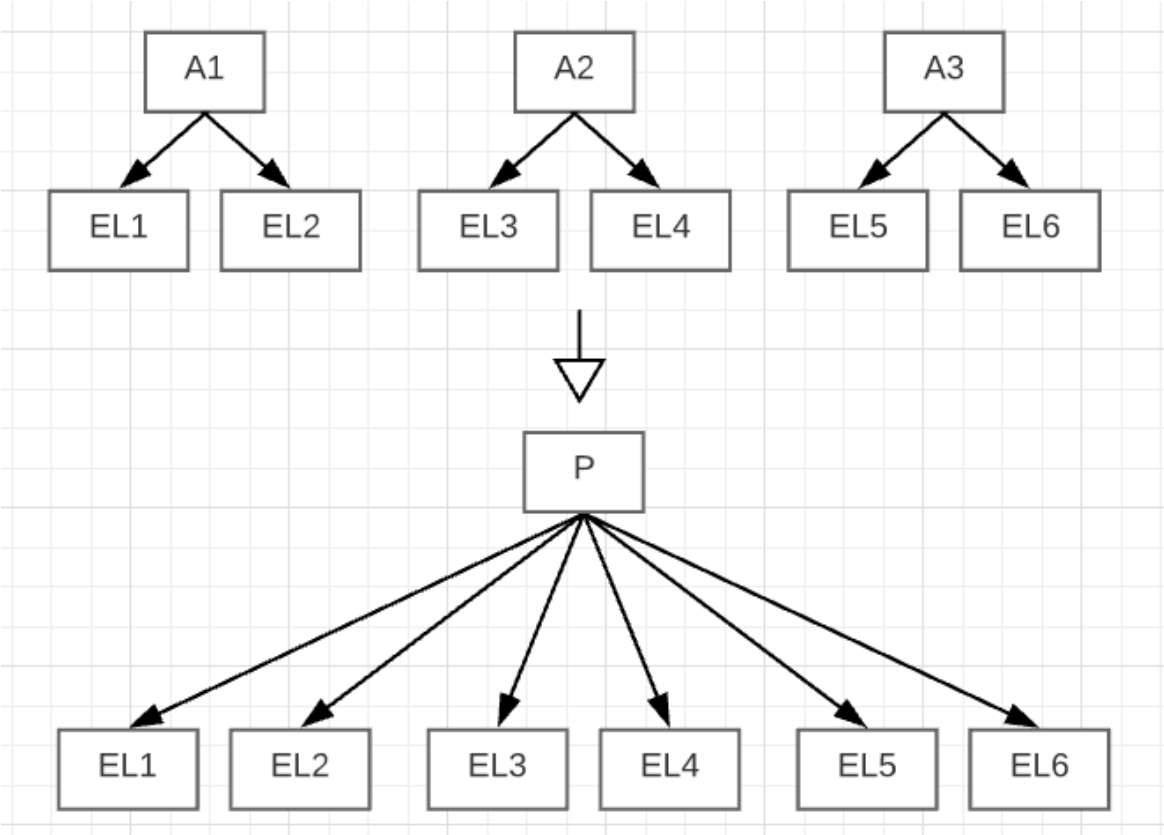
R = relationship

O = object

Utility of Propositions

Use Case: Aggregating Evidence

Capture all evidence that supports an abstract fact, as opposed to each separate assertion of this fact



A = assertion, EL = evidence line, P = proposition

Extra Slides . . .

Highlights and Misconceptions

- Core ontology provides a domain agnostic model as the foundation of a larger framework that supports extensions for custom domain specific schema (SEPIO Profiles).
  - So SEPIO does not provide complete schema ready to use off the shelf - but rather a foundation on which to create custom, ontology-based schema for specific applications, that are rooted in common modeling framework.
  - Creation of these Profiles requires work/effort on part of implementers/adopters. But framework provides support needed to do so in an efficient and systematic manner (tools and documentation are provided to guide adopters in implementing Profiles for their domain or application).
  - Rooting of SEPIO data models in ontologies enables generation of 'semantically-enhanced' data, where knowledge encoded in supporting ontologies can add value by making the data better interpretable by humans and machines.

Highlights and Misconceptions

- The remit of SEPIO is capturing what knowledge has been asserted as true a domain of discourse, what information supports or refutes such assertions, how this information was is interpreted as evidence, and the agents and methods involved in these processes.
  - Its remit is not modeling real-world phenomena in a particular domain of discourse that these assertions are about, nor is it providing detailed accounts of experimental workflows used to generate scientific data used as evidence.
  - For example, SEPIO provides patterns for representing the reasoning that led to an assertion that variant X confers sensitivity to Treatment Y for Condition Z, but it does not support modeling of the mechanistic relationships between these entities in the biomedical domain of discourse.
- Provides a built-in flexibility in a variety of forms. Does not try to define a single model to suit all use cases, but provide a flexible framework with consistent in interoperable options for modeling using the same building blocks, to different levels of complexity and precision.
  - Incremental Expressivity . . .
- It is at the level of specific Profiles that actual constraints required for structuring data for a working application are defined. The generic SEPIO model is not sufficient for this. Profiles build on this core model and define constraints based on requirements of a domain-specific application.

Computational Evaluation of Assertions

SEPIO captures aspects of evidence and provenance required for rigorous computational evaluation of assertions.

Evidence:

1. **Quantity**: How many distinct, meaningful arguments support the assertion.
2. **Quality**: How meaningful & reliable is a particular type or line of evidence.
3. **Diversity**: Are the supporting lines of evidence based on diverse experimental systems and approaches.
4. **Concordance** : How many lines of evidence support vs dispute the assertion.

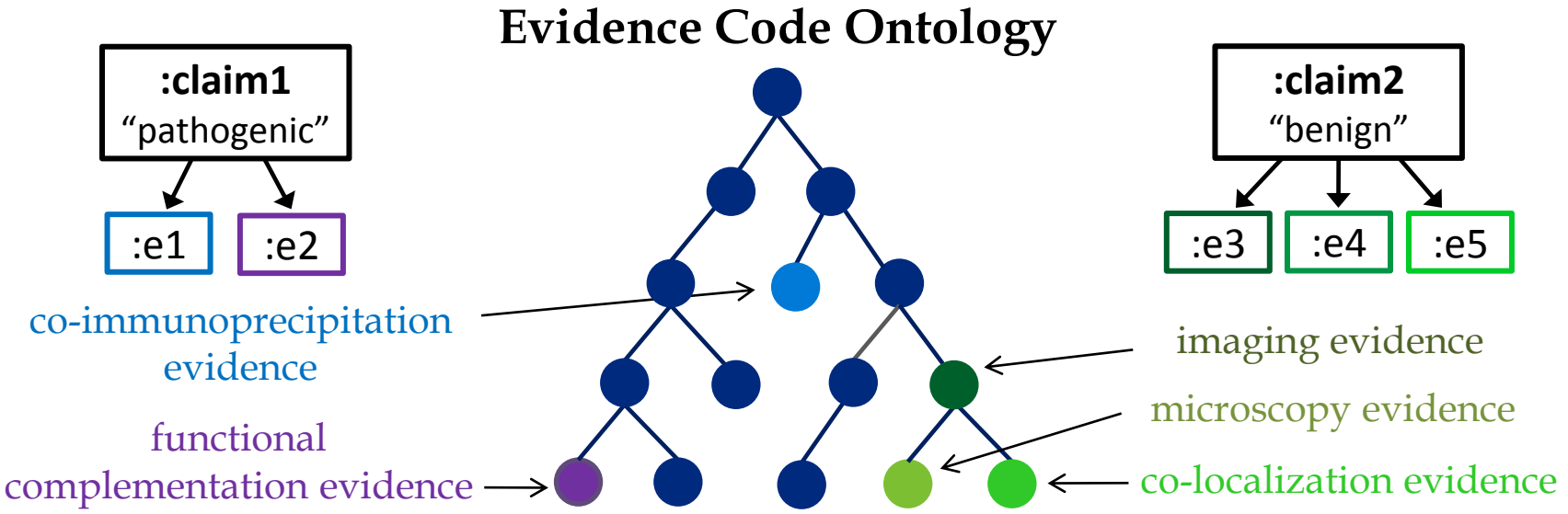
Provenance:

1. Who made assertion, interpreted evidence, and generated supporting data
2. When and how were these activities performed.

Computational Evaluation of Assertions

Algorithms can leverage semantics of SEPIO models to compute quantitative metrics of evidence **quality**, **quantity**, **diversity**, and **concordance** – supporting automated evaluation of claims.

A **diversity-based metric** can leverage the structure of supporting ontologies such as **ECO** or **OBI**, to calculate the semantic similarity of evidence lines for a given claim



Competency Questions

1. Find all variants associated with disease X, based on functional evidence from mouse model systems.
2. Show me what types of data and experiments support the validity of this claim?
3. Show me all lines of evidence that refute this claim, along with their supporting data and provenance information
4. Find variants of uncertain significance where additional population data may be useful in making a definitive classification.
5. Are there certain factors (data or method types, asserting agents or guidelines) that are common for claims that are controversial, i.e. conflict with other claims?
6. What researchers are most widely attributed for method or data used as evidence supporting variant classifications for Alzheimer's-related disorders.

SEPIO Model Recap

1. SEPIO Concepts and relationships are generic and apply universally in any domain – based in realism that mirrors the cognitive processes involved in making an evidence-based assertion
2. Organizes evidence data at different levels to support different use cases (Study, Evidence Line, Assertion, Proposition)
3. Explicitly represents provenance of assertions, and separately tracks the provenance of all evidence supporting or refuting it (typically by describing studies that generate data or findings used as evidence)
4. Evidence lines are key organizing nodes that let us capture how info interpreted and applied as evidence to support or refute a claim
5. Evidence lines also essential for assess the quantity, quality, diversity, and concordance of evidence for a claim – four key dimensions that are essential for computational evaluation use cases
6. SEPIO allows us to organize evidence date at different levels and represent many perspectives on evidence, to support different types of questions and use cases

```
{
  id: 6,
  type: "assertion",
  name: "AID6",
  summary: "EGFR L858R positive NSCLC is sensitive to
  afatinib.",
  description: "L858R is among the most common
  sensitizing EGFR mutations in NSCLC, and is assessed
  via DNA mutational analysis, including Sanger
  sequencing and next generation sequencing methods.
  Tyrosine kinase inhibitor afatinib is FDA approved,
  and is recommended (category 1) by NCCN guidelines
  along with erlotinib, gefitinib and osimertinib as
  first line systemic therapy in NSCLC with sensitizing
  EGFR mutation.",
▸ gene: {…},
▸ variant: {…},
▸ disease: {…},
▸ drugs: […],
  evidence_type: "Predictive",
  evidence_direction: "Supports",
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  open_change_count: 0,
  pending_evidence_count: 0,
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    ▸ {…},
    ▸ {…},
    ▸ {…},
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    ▾ {
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        name: "EID879",
        description: "A phase III clinical trial
        (NCT00949650) found that median progression fr
        survival among patients with exon 19 deletions
        or L858R EGFR mutations (n = 308) was 13.6
        months for afatinib and 6.9 months for
        chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; p
        = 0.001).",
      ▸ disease: {…},
      ▸ drugs: […],
        rating: 4,
        evidence_level: "B",
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        evidence_direction: "Supports",
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          ▸ last_modified: {…},
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          ▾ variant: {
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          ▾ gene: {
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              name: "EGFR"
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  phenotypes: [ ],
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    ▸ accepted: {…}
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  provisional_values: { },
  errors: { }
```


Assertion object
(identifier, description)

Assertion semantics -domain entities it is about, and outcome (confers sensitivity)

Assertion Method (NCCN)

Assertion Evidence Level (AMP)

Evidence Lines (6)

Evidence Line
identifier, description

'Proposition' evaluated toward
Study Finding quality
Evidence Line Strength
Evidence Line Direction

Evidence Line Contributions/Provenance