Efforts toward a More Consistent and Interoperable Sequence Ontology

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The Sequence Ontology (SO)

- Member of the OBO library and candidate for the OBO Foundry
- Developed with goals of standardizing vocabulary and semantics of biological sequence annotation and increasing interoperability among software developers and users
- Represents types of biomacromolecular sequences, qualities & sequence variation

Use of the SO

- Has a sizable user base in the model-organism database community
- Genome Model Organism Database (GMOD) schemas, formats & tools rely on the SO
- Other uses of the SO have sprouted, including those in natural-language processing & reasoning with multiple ontologies

Motivation

- The SO is mature in ways, but issues remain:
  - Abstract vs. physical nature of sequences remain muddled
  - The SO is not well-integrated with other OBOs
  - Representation and use of corresponding DNA, RNA & peptide sequence is inconsistent

Current Efforts

- We are seeking to address these issues by:
  - Representing both abstract and physical sequences & linking them appropriately
  - Integrating (or setting up for integration) with ChEBI, PRO, RNAO, GO, CHEMINF & IAO
  - Consistently representing corresponding DNA, RNA & peptide sequences & harmonizing their use in annotations

The Nature of Sequences

- Hoehndorf *et al.* (*BMC* Bioinformatics, 2011) have posited 3 types of sequences:
  - *Abstract sequences*: abstract entities that are "independent of space and time: either [they] … are not located in space and time, or they are located everywhere and at all times"; only one instance of the abstract sequence ACA
  - *Syntactic sequences*: sequence representations as those in biomedical databases & text representations
  - *Molecular sequences*: Physical chains of nucleotides or amino acides

The Nature of Sequences

- In previous attempts to integrate with the BFO, SO developers have elaborated that SO sequences are *generically dependent continuants*, defined as continuants dependent on one or more independent-continuant bearers

(Mungall *et al.*, *J Biomed Inform*, 2011)

The Nature of Sequences

- However, this conceptualization is problematic:
  - SO developers have acknowledged a discordance in sequence attributes, *e.g.*, `wild_type_rescue_gene` is a `rescue_gene` that `has_quality wild_type`
  - More straightforwardly, biologists fundamentally regard sequences as molecular entities
  - This molecular view is reflected in the natural-language definitions in the SO

The Nature of Sequences

- Since molecular sequences are the more fundamental concepts, we argue that they should be explicitly represented
- However, there are at least a small number of SO classes whose conceptualizations as molecular entities do not seem sensible, *e.g.*, `match`
- Thus, some abstract sequences will be needed
- Our proposed solution is to represent sequences in two parallel ontologies

Parallel Sequence Ontologies

- One will be an evolution of the Sequence Ontology:Molecules (SOM) effort, with an enlarged domain of all SO molecular-sequence concepts
- This will be renamed the Molecular Sequence Ontology (MSO), since most SO concepts refer to parts of molecules
- The many formal definitions of SO concepts will be transferred to the MSO
- MSO concepts will be bridges to GO, PRO, RNAO & ChEBI

Parallel Sequence Ontologies

- The corresponding abstract sequences will remain in SO, which should minimize disruption to SO annotation efforts
- Corresponding abstract & molecular sequences will be identically named but use their respective namespaces
- SO concepts will be formally defined in terms of corresponding MSO concepts

Parallel Sequence Ontologies

- Since SO concepts will be formally defined in terms of MSO concepts, an OWL reasoner will be able to automatically generate the hierarchyof the former from the latter
- In addition to linking to the MSO, SO concepts will be connected to CHEMINF & thus indirectly to IAO

Integration with Other OBOs

- For the MSO, we seek integration with ChEBI, PRO, RNAO & GO
- MSO concepts will be subclasses of `CHEBI:molecular entity`
- A current high-level SO class is `region`, defined as a sequence feature with an extent greater than zero, which will be more precisely renamed to `monomeric sequence`

Integration of MSO with ChEBI

- "sequence" can refer to either a whole sequence or a proper subsequence, which will be encapsulated in the top-level `monomeric sequence`
- `monomeric sequence` will be fundamentally divided into `monomeric sequence molecule` and `monomeric subsequence`
- This subdivision will enable us to assert equivalency of specific existing ChEBI macromolecular classes & specific MSO subclasses of `monomeric molecule`

Integration of MSO with ChEBI

- We can further link MSO to ChEBI by defining MSO sequence types in terms of constituent ChEBI monomers, *e.g.*:

```
MSO:'peptide sequence' subclassOf
  MSO:'monomeric sequence' and
  has_proper_monomeric_part
   some CHEBI:'amino-acid residue' and
  has proepr_monomeric_part
   only CHEBI:'amino-acid residue'
```

Integration of MSO with PRO & RNAO

- The PRO could link to the MSO by making its top-level `protein` a subclass of `MSO:peptide sequence molecule`
- Likewise, the RNAO will be able to integrate with the MSO by subclassing RNA-specific sequences and structures from more general MSO concepts

Integration of MSO & GO

- GO classes representing processes operating on sequences will be able to rely on relevant MSO classes, *e.g.*, for `RNA processing`, which is "[a]ny process involved in the conversion of one or more primary RNA transcripts into one or more mature RNA molecules":

```
GO:'RNA processing' subclassOf
  GO:'biological_process' and
   part_of
     GO:'biological_process and
     results_in_derivation_from
       some MSO:'primary transcript' and
     results_in_derivation_to
       some MSO:'mature transcript'
```

Integration of MSO & GO

- These can be seen as extensions to the OBO cross-product effort (Mungall *et al.*, *J Biomed Inform*, 2011)
- Currently, there are a plethora of vetted cross-product definitions among a number of OBOs as well as among concepts within the SO, but none among SO concepts and those of external OBOs

Integration of SO, CHEMINF & IAO

- SO concepts will be subsumed by `information about a chemical entity` from CHEMINF
- SO will thus be indirectly connected to IAO, as this CHEMINF class is itself a subclass of `IAO:information content entity`, which is “an entity that is generically dependent on some artifact and stands in relation of aboutness to some entity”

Integration of SO, CHEMINF & IAO

- We will use `denotes`, a subrelation of the IAO's fundamental `is_about` relation, to formally define most SO concepts in terms of the MSO, *e.g.*,

```
SO:transcript subclssOf
   CHEMINF:'information about a
     chemical entity' and
   denotes some MSO:transcipt
```

Integration of SO, CHEMINF & IAO

- Hypothetical, improbable & even impossible abtract sequences could be created, but we consider this an orthogonal issue, and there have been recent efforts to address this
- Since SO concepts will be formally defined in terms of MSO concepts, the classification of the former will be automatically generated from the latter

DNA, RNA & Peptide Sequences

- Sequences are annotated overwhelmingly at the genomic level, even with many SO concepts at RNA & peptide levels
- There are implicit semantics in that the given RNA- or peptide-level concept annotation holds for the RNA or peptide sequence *coded by* the annotated DNA sequence

DNA, RNA & Peptide Sequences

- RNA- and peptide-level SO classes are informally defined as RNA/peptide seqeunces, but they are sometimes subsumed by DNA concepts, *e.g.*, `transcript` is a `gene_member_region`
- We are seeking to make the SO more consistent in terms of both the ontology itself and its use in sequence annotations

DNA, RNA & Peptide Sequences

- Natural-language definitions of concepts should match formal structure, so either the RNA-level definition of `transcript` should change, or it should not be subsumed by a DNA-level concept
- We argue that classes should be defined as they are canonically conceptualized, so `transcript` should be defined at the RNA level
- Its formal classification should reflect this

DNA, RNA & Peptide Sequences

- For this classification, we have created a set of sequence classes defined in terms of type of monomer
- Currently, monomer type is represented by a set of polymer attributes & sequences are attributed these qualities, *e.g.*, `DNA`, `RNA` and `peptidyl` are all qualities, and `RNA chromosome` is formally defined as:

```
'RNA chromosome' subclassOf
    chromosome and
    has_quality some RNA
```

DNA, RNA & Peptide Sequences

- For each type of monomer, we are creating a primary sequence class, *e.g.*, `DNA sequence`, `RNA sequence`, `peptide sequence`
- Rather than relying on qualities for specifying monomer type, we will use existing ChEBI monomer classes
- As many monomer types are already represented in ChEBI, this reduces effort on our end & abides by the principle of OBO orthogonality

DNA, RNA & Peptide Sequences

- Monomeric sequences are thus subdivided into two orthogonal axes:
  - Whole molecules vs. proper subsequences
  - Monomer types
- However, all these direct subclasses will be necessarily and sufficiently defined, enabling automatic classification

DNA, RNA & Peptide Sequences

- To address issue of discordance between represented concepts & annotated sequences, we propose:
  - Creating corresponding DNA, RNA & peptide sequence classes
  - Defining/linking them accordingly
  - Guiding annotators to their proper use
- To minimize confusion, name in parallel, *e.g.*, for `polypeptide domain`, also create `DNA coding for polypeptide domain` & `RNA coding for polypeptide domain`

DNA, RNA & Peptide Sequences

- To link these, one option is to state each association as the product sequence being created from the template sequence, *e.g.*,

```
'polypeptide domain' subclassOf
  'peptide sequence' and
  created_from_template
     some 'RNA coding for polypeptide domain'
```

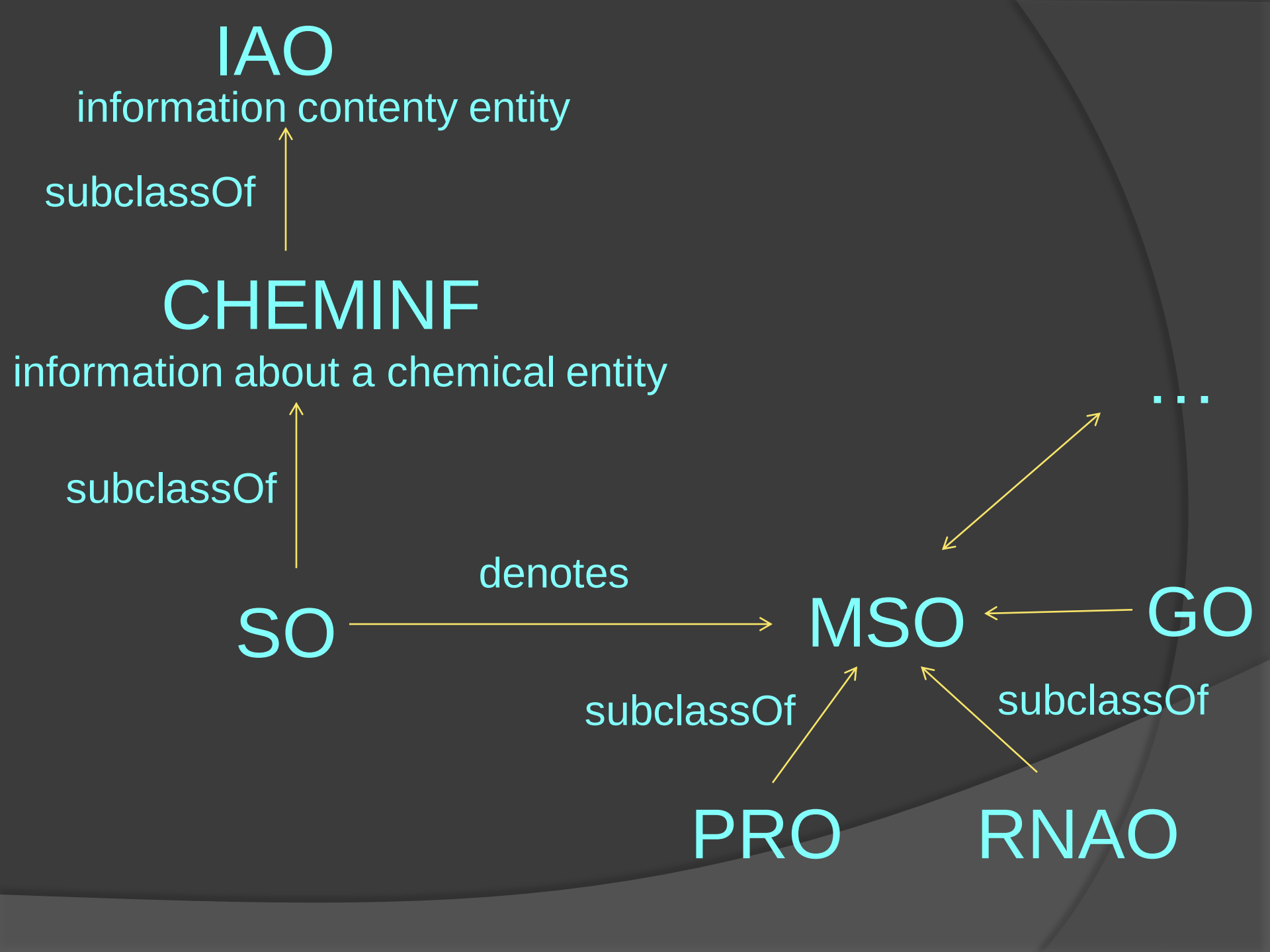
- However, this seems odd and circular

DNA, RNA & Peptide Sequences

- The other option is to state each association in the reverse direction, *e.g.*,

```
'RNA coding for polypeptide domain'
   subclassOf
      'RNA sequence' and
       template_for only 'polypeptide_domain'
```

- This seems more sensible in that it reflects the class
- A universal (only) rather than an existential (some) restriction would be needed


IAO
information contenty entity
subclassOf
CHEMINF
information about a chemical entity
subclassOf
SO
denotes
MSO
GO
...
subclassOf
subclassOf
PRO
RNAO

Conclusions

- Our recent efforts in the continuing development of the SO:
  - Representation of molecular vs. abstract sequences
  - Integration of the SO with ChEBI, PRO, RNAO, GO, CHEMINF & IAO
  - Consistent representation & use of corresponding DNA, RNA & peptide sequences
- In addition to increasing interoperability of SO with other OBOs, we anticipate that this will improve consistency both internally and with respect to external resources

Thanks!