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# The Semanticscience Integrated Ontology (SIO) for biomedical research and knowledge discovery

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## Abstract

The Semanticscience Integrated Ontology (SIO) is an ontology to facilitate biomedical knowledge discovery. SIO features a simple upper level comprised of essential types and relations for the rich description of arbitrary (real, hypothesized, virtual, fictional) objects, processes and their attributes. SIO specifies simple design patterns to describe and associate qualities, capabilities, functions, quantities, and informational entities including textual, geometrical, and mathematical entities, and provides specific extensions in the domains of chemistry, biology, biochemistry, and bioinformatics. SIO provides an ontological foundation for the Bio2RDF linked data for the life sciences project and is used for semantic integration and discovery for SADI-based semantic web services. SIO is freely available to all users under a creative commons by attribution license. See website for further information: <http://sio.semanticscience.org>.

## Background

Biomedical research is poised to enter an era of unprecedented large scale data analysis powered by hundreds of public biological databases and hundreds of millions of patient records. There is a real and urgent need to explore effective methods for biomedical data integration and knowledge management [1,2]. Semantic-based technologies, such as ontologies, offer a proven method to exploit expert-based knowledge in the analysis of large datasets through terminological reasoning such as correspondence, classification, query answering and consistency checking [3-5].

The Semantic Web effort, as pursued under the auspices of the World Wide Web Consortium (W3C), provides a set of standards to facilitate the representation, publication, linking, querying and discovery of heterogeneous knowledge using web infrastructure [6]. In particular, the Resource Description Framework (RDF) [7] enables triple-based assertions about resources using web-friendly identifiers, RDF Schema (RDFS) [8] offers vocabulary to create terminological hierarchies, and the Web Ontology

Language (OWL) [9] assists in the construction and interpretation of ontologies as sophisticated logic-based expressions to more precisely capture the meaning of types and relations between entities. With dozens of high value datasets now available in RDF and hundreds of biological ontologies expressed using OWL, there is a tantalizing opportunity to use these resources in knowledge discovery. Biomedical researchers have made use of Semantic Web technologies to uncover curation errors in systems biology models [10], find putative disease-causing genes [11], identify aberrant pathways [12], and uncover alternative drug therapies based on mechanism of action [13], among others [14]. These knowledge-based applications use automated reasoning over a coherent knowledge base often crafted from multiple and different underlying representations. Ontology-design patterns offer a simple way to guide users towards a uniform representation of knowledge [15-17].

With the goal of facilitating knowledge discovery through simple, but effective ontology-based data integration, we developed the Semanticscience Integrated Ontology (SIO). SIO offers classes and relations to describe and relate objects, processes and their attributes with specific extensions in the biomedical domain. Its relations cover aspects of spatial and temporal qualitative reasoning

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including location, containment, overlap, parthood and topology; participation and agency, linguistic and symbolic representation, as well as comparative and other information-oriented relations. Using straightforward mappings, we report on the substantial benefits afforded by SIO in the retrieval of RDF-based linked data and automatic composition of OWL-described semantic web services. Although SIO development is driven by needs in the biomedical domain, we show that SIO can be applied to a broader set of domains.

This paper is organized as follows: we first describe the current state of the SIO OWL implementation, and then we describe ontological foundations and essential relations in mereotopology, participation and reference. We then present three uses of SIO in knowledge representation and outline its use in the integration of data and web services. We finish with a brief comparison with related work. As a matter of convention, we use 'single quotes' to indicate labels, boldface to indicate **classes**, and italics to indicate *relations*.

### The semanticscience integrated ontology

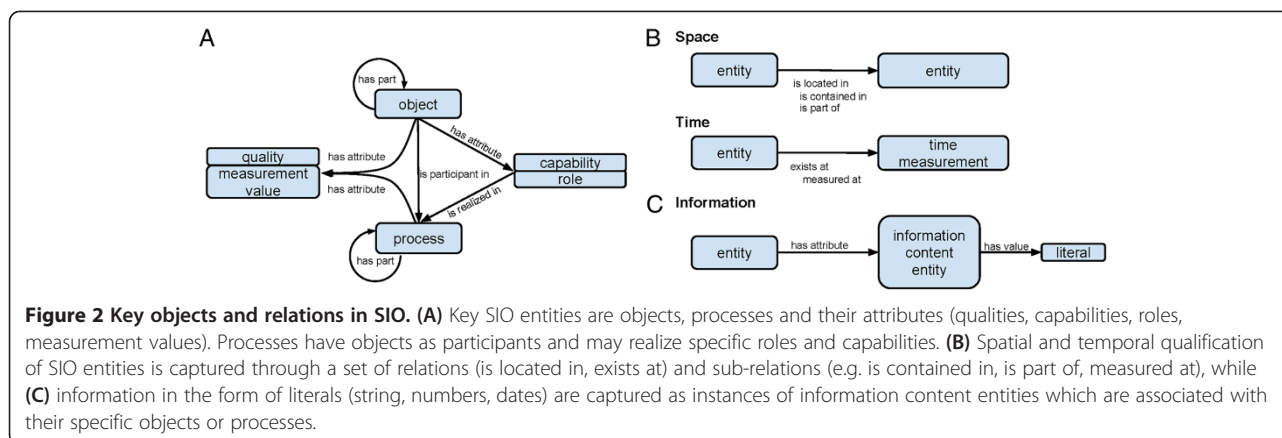
As of November 2013, SIO (v1.0) is implemented as an OWL-DL ontology (SRIQ(D) expressivity) that comprises of 1396 classes, 203 object properties, 1 datatype property,

8 annotation properties, 7272 axioms, 1747 subClassOf axioms, 43 equivalentClass axioms, and 209 subPropertyOf axioms. English labels are provided using the *rdfs:label* annotation property while human readable, English language definitions are provided using the Dublin Core (dc:) Metadata term *dc:description*. The ontology has maximum depth of 41 subclasses while the average number of children is 2. Figure 1 shows a slice of the class and object-property hierarchies where 'entity' is the top level class and 'is related to' is the top level object property.

### Ontological foundation

SIO adheres to a three-dimensional worldview that is familiar to most scientists – one that distinguishes between processes and the objects that participate in them. An **'object'** is an **'entity'** that occupies space and is fully identifiable by its characteristics at any moment in time in which it exists. A **'process'** is an **'entity'** that unfolds in time and has temporal parts. While an entity *'exists at'* and *'is located in'* some space and time (Figure 2B), these need not be real space or real time, but may instead occur in a hypothetical (propositional), virtual (electronic), or fictional (creative work) setting. A **'quality'** (intrinsic attribute), **'capability'** (action specification) or **'role'** (behavior, right and obligation) may exist at some time in the





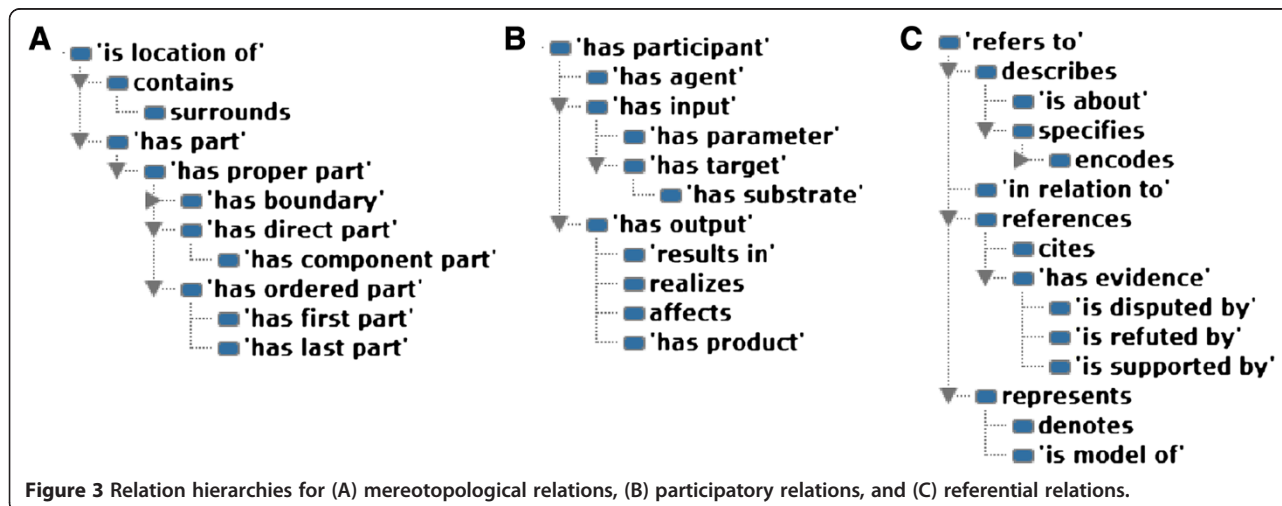
entity that bears it, but it *'is realized in'* a process in which it plays a critical role (Figure 2A). The value of an **informational entity** such as a **'measurement value'** (**'quantity'** or **'position'**) is represented as a literal - string, number (integer, float, double), boolean or date - using the *'has value'* data property (Figure 2C).

### Mereotopology

SIO offers a number of mereotopological relations that can be used to describe one or more entities in terms of their spatial organization (Figure 3A). The parent relation *'is located of'* is a transitive relation that holds true if the spatial or temporal region of one entity fully overlaps with the spatial or temporal region of another entity. *'has part'* is a relation that is reflexive in the sense that the whole is a part of itself, and is also transitive in that a component of a part is also a component of the whole. Therefore, a query on the *'has part'* relation will return the whole as an answer. *'has proper part'* is an irreflexive and asymmetric relation that ensures that the whole is different from and not one of its proper parts. *'has direct part'* enables users to quantify the number of parts (via a cardinality

restriction) at a desired type granularity, which is not otherwise possible in OWL over the transitive *'has part'* relation. *'has component part'* may be used to indicate that the part is intrinsic to the whole, and that the removal of the part changes the identity of the whole, with the caveat that there is no logic in OWL to directly infer this. *'contains'* is a transitive relation in which the 3D spatial region occupied by entity A fully overlaps with the spatial region occupied by entity B, but it is not the case that A has B as a part. *'surrounds'* is a relation that can be used to indicate that A *'contains'* B and either A *'is adjacent to'* B or A *'is directly connected to'* B.

The next set of mereotopological relations allows one to specify how the parts are positioned to one another. *'is connected to'* is a symmetric, transitive relation that specifies that components either directly share a boundary (they are directly connected to each other) or that they are indirectly connected by a path of unbroken direct connections. *'is directly connected to'* is a symmetric relation that indicates that two components share a boundary. Since this relation is non-transitive, we can use it in statements to quantify the number of connections from one part to other kinds of



parts. *'is directly before'* is a relation between entities placed on a dimensional axis in which the projection of the position of the first entity is numerically less than the projection of the position of the second entity, and the entities are adjacent to one another. This is useful for indicating the spatial positioning of residues in linear biopolymers such as proteins or nucleic acids. A domain specific relation such as *'is covalently connected to'* then enables one to describe the atomic connectivity within a molecule such as methane (Figure 4).

### Processes and participation

SIO provides a set of relations to describe processes in terms of their participants and their actions (Figure 3B). *'has participant'* indicates which entities participate in a process. *'has agent'* specifies entities that directly or actively participate in the process. *'has input'* specifies entities at the start of the process. *'has parameter'* specifies those variables (and their values) used in the process. *'has target'* specifies entities that are modified during the process, but retain their identity. *'has substrate'* specifies entities that are consumed (or are sufficiently changed that they lose their canonical identity). *'has product'* specifies new entities formed as a result of a process. Relations such as *'has substrate'*, *'has target'*, *'has product'* are examples of role-specialized relations. In SIO, more explicit role-based assertions can be formulated by stating that the role of an entity is realized in the process. For instance, Figure 5 shows a description of phosphorylation of an enzyme by ATP in which substrate and product roles are realized.

SIO includes an OWL2 property chain [realizes o is role of -> has participant] which enables an OWL2 DL reasoner to infer that entities having the realized role are also participants of the process.

### Referential relations

Referential relations in SIO are used to indicate what an object refers to or the nature of the mention of one entity by another (Figure 3C). At the top level, *'refers to'* enables this basic mention, while *'references'* is a relation where one entity mentions another, *'describes'* is a relation where one entity provides a detailed account of another, and *'represents'* is a relation where one entity is a sign, symbol or model for another. *'describes'* is further partitioned into *'is about'* where one entity provides information about another while *'specifies'* contains specific information that can be used as evaluation criteria to determine the degree of conformance. *'references'* is further subdivided into *'cites'* as a relation to refer to by way of example, authority or proof, and *'has evidence'* which is a relation between a proposition and something that demonstrates the truth of the assertion. *'has evidence'* has three sub-properties (*'is supported by'*, *'is disputed by'*, *'is refuted by'*) which can articulate the type of evidence that one entity offers another. Finally, *'represents'* is subdivided into *'denotes'* which is a relation between an entity and what it is a sign or indication of, or what it specifically means, and *'is model of'* which indicates that an artifact is a model or representation of another.

```
'methane'  
equivalentClass  
  'molecule'  
  and 'has component part' exactly 4 'methane hydrogen atom'  
  and 'has component part' exactly 1 'methane carbon atom'  
  and 'has component part' only  
    ('part of' some 'methane carbon atom' or 'part of' some 'methane hydrogenatom')  
  
'methane hydrogen atom'  
equivalentClass  
  'hydrogen atom'  
  and 'is component part of' exactly 1 'methane'  
  and 'is covalently connected to' exactly 1 'methane carbon atom'  
  
'methane carbon atom'  
equivalentClass  
  'carbon atom'  
  and 'is component part of' exactly 1 'methane'  
  and 'is covalently connected to' exactly 4 'methane hydrogen atom'
```

**Figure 4** Exact description of a molecule of methane using mereotopological relations in equivalent class axioms.

```
'substrate-enzyme phosphorylation by ATP'
equivalentClass
'biochemical reaction'
and 'realizes' some
('substrate role' and 'is role of' some 'ATP-substrate enzyme complex')
and 'realizes' some
('product role' and 'is role of' some 'ADP-substrate-phosphorylated-enzyme complex')
```

**Figure 5** Description of a process in terms of the participants and their roles.

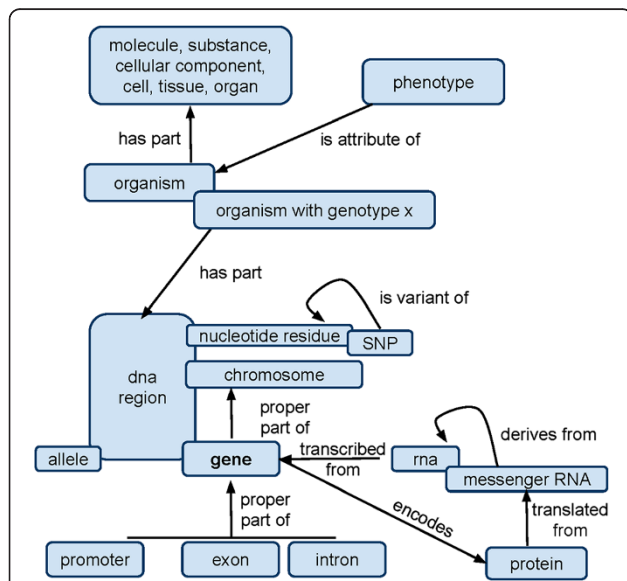
### Use cases

In this section we detail three use cases that outline how SIO can be used to represent biomedical knowledge, scientific experiments, and measurements.

### Biomedical knowledge

In addition to the foundational classes and relations described above, SIO offers additional classes and relations to describe elements of biomedical interest including proteins, lipids, nucleic acids, small molecules, genotypes, phenotypes, biochemical reactions and pathways (Figure 6).

For instance, we can describe an enzyme-encoding gene as a gene that encodes a protein whose function is to covalently modify another chemical entity in some chemical reaction (Figure 7).



**Figure 6** Conceptual map of SIO entities and the relations between them as it pertains to molecular biology. Rounded boxes indicate classes. Arrows indicate relations. Overlap of one concept on another indicates a subclass relationship (e.g. Gene is a type of DNA region).

Phenotypes arising from specific genotypes can be expressed as attributes of an organism having a gene with a certain nucleotide (Figure 8).

### Scientific experiment

In this use case, we describe the various parts and relationships within a scientific investigation. A scientific **‘experiment’** (Figure 9) is a **‘procedure’** that aims to support, dispute or refute a well formulated **‘hypothesis’** by **‘analysis’** of **‘data’** obtained through **‘observation’** and/or **‘measurement’**. Experiments *usually* involve:

- the development of a research **‘plan’** which includes, but is not limited to:
  - the formulation of a **‘hypothesis’**
  - the formulation of aims and **‘objectives’**
  - the formulation of a **‘study design’**
- the execution of the research plan which includes, but is not limited to:
  - the **‘selection, preparation or collection’** of a **‘sample’**
  - the **‘collection of data’** through **‘observation,’ ‘assay’** or **‘measurement’**
  - the **‘analysis’** of **‘data’**
  - the preparation of an investigational **‘report’**

Figure 9 illustrates a pattern to express the relationship among a research plan, study design, experiment and its parts (e.g. sample preparation, measurement, analysis). Temporal parts are linked to the whole using SIO’s *‘has proper part’* relation, while temporal ordering is achieved with SIO’s *‘precedes’* relation.

A **‘description’** provides detailed information *‘about’* some **‘entity’** (**‘object,’ ‘process’** or **‘attribute’**), a **‘hypothesis’** is a proposed explanation of some phenomena, and an **‘objective’** is a description of a desired outcome. A description that *‘specifies’* a set of actions to be executed is an **‘action specification’** and include **‘plans,’ ‘study designs,’** recipes and **‘protocols’**. A plan should clearly identify (*‘specify’*) one or more **‘objectives,’** and

```
'enzyme-encoding gene'  
  
subClassOf  
  'gene'  
  and 'encodes' some  
    ('protein' and 'has function' some 'to covalently modify'  
      and 'in relation to' some 'chemical entity'  
      and 'is realized in' some 'chemical reaction')
```

**Figure 7** Description of an enzyme-encoding gene.

optionally specify a **'hypothesis'** or **'study design'** as **'attributes'**. A plan, like any action-based specification *'is manifested as'* a **'process'**. An objective *'is realized in'* an experiment if and only if its outcomes are fully apparent. Data generated from the experiment may also serve as *'evidence for'* the hypothesis, and more specifically found to be *'in support of'*, *'in dispute of'*, or *'in refutation of'* the hypothesis. The Ontology for Biomedical Investigations (OBI) features more specific assays, material and data processing techniques [18].

#### Measurements and measurement values

Measurement values such as quantities or spatial positions are captured as information content entities (ICE), where the ICE is an attribute of the entity in question and the literal value is captured using SIO's *'has value'* data property. Units of measurements such as those defined by the Unit Ontology (UO) are indicated with SIO's *'has unit'* object property. The following RDF/N3 example (using the labels as URIs subset of SIO) shows how SIO captures Rob's mass of 74.5 kg using a measurement scale on Jan 15, 2012 at 12:03 pm EDT (Figure 10).

#### Applications

##### *Semantic data integration and question answering*

The Bio2RDF project uses Semantic Web technologies to offer the largest network of linked data for the life sciences [19]. Although the Bio2RDF approach provides minimal syntactic and referential interoperability (using RDF and a shared URI pattern), it does not address the issue of semantic interoperability across its datasets.

Recent work [20] mapped SIO types and relations to Bio2RDF's dataset-specific types and relations, thereby enabling SIO-based queries over linked data. In that work, resources such as DrugBank [21], the Pharmacogenomics Knowledgebase [22] and the FDA's National Drug Code Directory (NDC) all provide drug information, and the types [http://bio2rdf.org/drugbank\\_vocabulary:Drug](http://bio2rdf.org/drugbank_vocabulary:Drug), [http://bio2rdf.org/pharmgkb\\_vocabulary:Drug](http://bio2rdf.org/pharmgkb_vocabulary:Drug), and [http://bio2rdf.org/ndc\\_vocabulary:human-prescription-drug](http://bio2rdf.org/ndc_vocabulary:human-prescription-drug) were mapped as subclasses of the SIO class **'drug'**. Bio2RDF vocabulary mappings to SIO also make it possible to execute complex SPARQL queries over multiple Bio2RDF endpoints. For example, Figure 11 shows a SPARQL query that retrieves all the biochemical reactions in the Bio2RDF BioModels database [23] that are involved in the Gene Ontology (GO) term "protein catabolic process" or one of its subclasses.

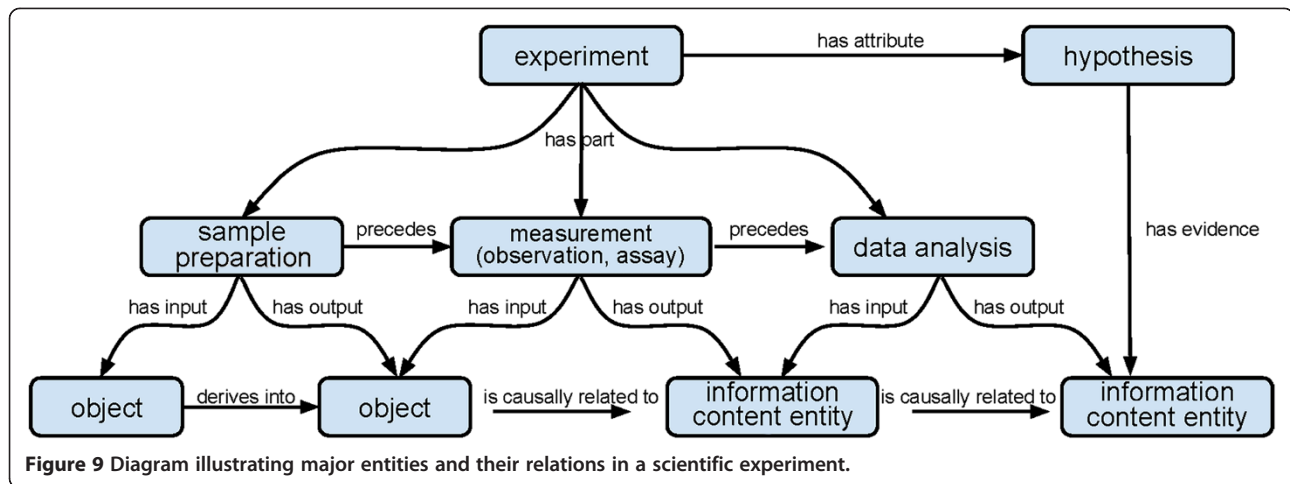
This query is possible because the BioModels type for biochemical reaction has been mapped as a subclass of SIO's **'biochemical reaction'**. Similarly, the BioModels predicate for *'is identical to'* has been mapped as a sub-property of SIO's *'is identical to'*.

##### *Semantic Web service interoperability*

The Semantic Automated Discovery and Integration (SADI) framework consists of a set of design patterns for producing stateless Web Services that natively consume and produce RDF data [24,25]. SADI services have been used to classify and annotate molecules based on their structure [26] and to uncover health information regarding drug-drug interactions [27]. The structure of the input and

```
'phenotype of an organism with a SNP at position 12'  
  
subClassOf  
  'phenotype'  
  and 'is attribute of' some  
    ('organism' that 'has part' some (  
      'gene'  
      and 'has part' some (  
        'snp'  
        and 'has value' value 'A'  
        and ('has attribute' some (  
          'sequence position' that 'has value' value '12')))))
```

**Figure 8** Description of phenotype linked to a particular genotype.



output data for SADI services are formally described by an input OWL class and an output OWL class respectively. Nearly 800 SADI services have been created as part of the C-BRASS (Canadian Bioinformatics Resources as Semantic Services) project. Consider for example, the abridged input and output descriptions for a SADI Web service [28] that executes BLASTN on the genome of *Prunus dulcis*. This service takes as an input a ‘**deoxyribonucleic acid sequence**’ and generates as output an instance of “BLASTed-Sequence that *has part* some (**“Subsequence”** that (*is part of* some (**‘biopolymer sequence’**)) and *is part of* some **‘BLASThit’**”). Table 1 shows the top 10 SIO classes and relations that are directly referred to in the SADI global service registry.

SADI services can also be orchestrated into a computational workflow by matching the outputs of one service with the inputs of another service [25]. The SADI-aware SHARE client decomposes a SPARQL query into an executable workflow by matching the query components with SADI services. SADI uses an OWL reasoner to find appropriate matches between service inputs and outputs by finding those that subsume one another. In Figure 12, we show a SPARQL query that can be interpreted by the SHARE client to find proteins and compounds in the caffeine metabolism pathway (has00232). To answer this query, the SHARE client invokes three SADI services that wrap 2 existing BioMoby services that use SIO predicates *has participant* and *encodes*.

```

sio: <http://semanticscience.org/resource/>
obo: <http://purl.obolibrary.org/obo/>
taxon: <http://bio2rdf.org/taxon:>

:p rdfs:label "Rob" . # Rob
:p a taxon:9606 . # Rob is human, as per the NCBI taxonomy in
Bio2RDF
:p sio:has-attribute :m1 . # Rob has an attribute m1

:m1 rdfs:label "Rob's mass on Jan 15, 2012"@en # Rob's mass
:m1 a sio:mass . # m1 is a mass
:m1 sio:has-value "74.5"^^xsd:float . # the value is 74.5
:m1 sio:has-unit obo:UO_0000009 . # the unit is kilogram as
# per the Unit Ontology
# mass measured at t1

:m1 sio:measured-at :t1 .

:t1 a sio:time-instant .
:t1 sio:has-value "2012-01-15T12:03:00-05:00"^^xsd:dateTime .

:mp a sio:measuring . # measuring process
:mp sio:has-agent :robscale . # measuring involved rob's scale
:mp sio:has-output :m1 . # measuring resulted in a measurement value

:robscale rdfs:label "Rob's scale"@en # Rob's scale
:robscale a obo:MMO_0000217 . # body measurement scale as per the Measurement
# Method Ontology
    
```

**Figure 10** Description of a mass measurement and value for an individual.

```

SELECT ?go ?label count(distinct ?x)
WHERE {
  {
    # get all the biochemical reactions labelled with protein catabolic process
    ?go rdfs:label ?label .
    FILTER regex(?label, "^protein catabolic process")
    SERVICE <http://biomodels.bio2rdf.org/sparql> {
      ?x <http://semanticscience.org/resource/is-identical-to> ?go .
      ?x a <http://semanticscience.org/resource/biochemical-reaction>
    } # end service
  } UNION {
    # get all the biochemical reactions that are
    # more specific than "protein catabolic process"
    ?go rdfs:label ?label .
    ?go rdfs:subClassOf+ ?tgo . # get all the subclasses of the target to term
    ?tgo rdfs:label ?tlabel .
    FILTER regex(?tlabel, "^protein catabolic process")
    SERVICE <http://biomodels.bio2rdf.org/sparql> {
      ?x <http://semanticscience.org/resource/is-identical-to> ?go .
      ?x a <http://semanticscience.org/resource/biochemical-reaction>
    } # end service
  } # end union
} # end where

```

**Figure 11** SPARQL query that uses SIO to obtain biochemical reactions from the BioMODELS database where the reactions are annotated with the Gene Ontology term “protein catabolic process” or one of its subclasses.

SIO is also being used in the Earth Life and Semantic Web (ELSEWeb) project to streamline the flow of heterogeneous geospatial data in order to ease the task of creating multi-source models of species-distribution [29]. ELSEWeb translates a family of industry standard XML geospatial metadata (e.g., OGC WCS, FGDC, CF) into RDF that is based on constructs defined by SIO and the Extensible Observation Ontology (OBOE) [30]. Geospatial satellite data is automatically discovered, transformed, and integrated with species distribution models services using the ELSEWebData ontology. The alignment of SIO, OBOE, ELSEWebData allows geospatial data to be queried and integrated with both data from the bio and environmental communities, providing a wider spectrum of modeling potential.

**Table 1** Top 10 classes and relations used in SADI services registered at [sadiframework.org](http://sadiframework.org)

| Class                          | Frequency | Property        | Frequency |
|--------------------------------|-----------|-----------------|-----------|
| Deoxyribonucleic acid sequence | 159       | Has part        | 289       |
| Protein sequence               | 41        | Is about        | 71        |
| Ribonucleic acid sequence      | 21        | Has attribute   | 67        |
| Definition                     | 2         | Is attribute of | 17        |
| Name                           | 2         | Is part of      | 9         |
| Sequence motif                 | 2         | Has output      | 9         |
| Answer                         | 1         | Is derived from | 9         |
| Common name                    | 1         | Derives into    | 9         |
| Description                    | 1         | Is similar to   | 9         |
| Preferred name                 | 1         | Overlaps with   | 9         |

### Nanopublishing

The publication of structured research data on the internet is an emerging area of interest. The nanopublication [31] is one effort that offers an RDF framework to capture assertions along with their provenance. Nanopublications have been used in enabling publication of genetic data [32] and more recently to arbitrary statements [33]. SIO is now being used to capture protein-protein interactions and gene-disease associations obtained through text mining [34]. To accommodate computed associations, we extended SIO with ‘**association**’ and more specific types including ‘**gene-disease association**’. In Figure 13 we show a portion of a nanopublication that expresses an association between the gene CENPJ and Seckel Syndrome that was obtained through text mining. SIO is used to assert the type of association, the entities that are in the association (identified using Bio2RDF identifiers), and the associated p-value.

### Related work

The OBO Foundry is a collaborative effort to construct a set of orthogonal interoperable Open Biomedical Ontologies (OBO) [35]. OBO Foundry ontologies use the Basic Formal Ontology (BFO) as an upper level ontology for domain independent types and the Relation Ontology (RO) as a source of domain-independent relations. The BFO is a small (36 class) ontology that is intentionally limited by its realist philosophy to classes with at least one known instance and whose instances only exist in real space and time [36,37]. In contrast, SIO simplifies the declaration and characterization of hypothetical, theorized or virtual entities (simply by virtue of



```
PREFIX sio: <http://semanticscience.org/resource/>
PREFIX kegg: <http://lsrn.org/KEGG_PATHWAY:>
SELECT ?participant ?protein ?chemical
WHERE {
  kegg:hsa00232 sio:SIO_000132 ?gene . # caffeine_metabolism has-participant?gene
  ?gene sio:SIO_010078 ?protein .      # ?gene encodes ?protein
}
```

**Figure 12** SPARQL query to obtain proteins encoded by genes in KEGG pathways.

having such a quality) and is thus more broadly applicable to situations of interest to the health care and life sciences including the presumed existence of underlying agents in medical disease or the existence of entities or attributes that are computationally predicted. SIO allows processes to have characterizing attributes, whereas the BFO does not [38]. The RO was initially [39] comprised of a collection of 8 domain-independent (e.g. has part) relations which has since been expanded to 160 relations, although these do not include all relations used in all OBO ontologies. OBO Foundry's approach to building an interoperable set of ontologies can be contrasted with that of SIO, where instead of coordinating needs and duplication across dozens of ontologies, SIO serves as a single point of interoperability capable of addressing needs that go beyond its current scope. In order to foster semantic interoperability between SIO and BFO + RO, we have mapped 9 BFO classes and 24 RO relations to SIO (mapping available at [40]).

BioTop [41] is an upper level ontology for biology and medicine that features 390 classes and 82 object properties. The class top-level is characterized by a flattened set of basic categories (material object,

immaterial object, information object, process, quality, role, condition, disposition, time, value region) while the object hierarchy provides type-specific relations around physical, processual and abstract nature (e.g. has physical part, has processual part, has abstract part). BioTop includes relatively sophisticated formalization for selected terms, for example pathological disposition is defined as "disposition that ('inheres in' some ('bearer of some (canonicity and ('quality located' some 'noncanonical value region'))))", where SIO would simply express it as a 'biological disposition' that ('is attribute of' some ('entity' that 'has attribute' some 'pathological quality')). BioTop has been used to provide a number of ontology design patterns [42,43] and to identify semantic type errors in the UMLS network [44].

The Translational Medicine Ontology (TMO) is a unifying ontology for chemical, genomic and proteomic data with disease, treatment, and electronic health records [13]. The TMO acted as a central schema that mapped basic types to dozens of bio-ontologies and linked open data. The utility of the TMO was demonstrated by answering a series of questions pertaining to diagnosis, prescription, drug mechanism of action, alternative

```
@prefix nanopub: <http://www.nanopub.org/nschema#> .
@prefix rdfs: <http://www.w3.org/2000/01/rdf-schema#> .
@prefix sio: <http://semanticscience.org/resource/> .
@prefix xsd: <http://www.w3.org/2001/XMLSchema#> .
@prefix :
<http://rdf.biosemantics.org/vocabularies/gene_disease_nanopub_example#> .

:NanoPub_1_Assertion {
  :Association_1
  a sio:gene-disease-association ;
  sio:has-measurement-value :Association_1_p_value ;
  sio:refers-to <http://bio2rdf.org/ncbigene:55835>,
<http://bio2rdf.org/omim:210600> ;
  rdfs:comment "This association has p-value of 0.00066, has attribute gene
CENPJ (NCBI gene id 55835) and attribute disease Seckel Syndrome (OMIM
210600)."@en .

  :Association_1_p_value
  a sio:probability-value ;
  sio:has-value "0.0000656211037469712"^^xsd:float .
}
```

**Figure 13** The assertion portion of a nanopublication that uses SIO to express a text-mined association between the CENPJ gene and Seckel Syndrome, along with its probability-value.

therapeutics, and biomarkers. As SIO emerged from considerations in the TMO effort, SIO can be seen as the supported successor to TMO.

## Conclusion

The SemanticScience Integrated Ontology (SIO) is an ontology of basic types and relations to capture a wide span of knowledge through a set of emerging domain-specific patterns using RDF/OWL. SIO has emerged to support the demands of the bioinformatics community, with a special emphasis on biological knowledge representation as well as ontology, data and service interoperability.

## Availability

The SIO homepage is <http://sio.semanticscience.org>. SIO is freely available under a Creative Commons by Attribution license at <http://semanticscience.org/ontology/sio.owl>. Version 1.0 of SIO is available as Additional file 1. The base namespace for SIO entities (classes, properties) is <http://semanticscience.org/resource/>. SIO entities are identified using resolvable HTTP URIs, initially formulated as an alphanumeric identifier e.g. [http://semanticscience.org/resource/SIO\\_000001](http://semanticscience.org/resource/SIO_000001), but is alternatively accessible using a label-based identifier e.g. <http://semanticscience.org/resource/is-related-to>. These and other generated subsets are available from <http://goo.gl/OLgN8>.

## Additional file

### Additional file 1: The SemanticScience Integrated Ontology, v1.0.

This file in the format of OWL2, the Web Ontology Language.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

MD conceived and implemented SIO. MD drafted and finalized the manuscript. All authors either directly contributed or have provided substantial discussion to the development of the ontology. All authors have read and approved the manuscript.

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## References

1. Gardner SP: **Ontologies and semantic data integration.** *Drug Discov Today* 2005, **10**(14):1001–1007.
2. Goble C, Stevens R: **State of the nation in data integration for bioinformatics.** *J Biomed Inform* 2008, **41**(5):687–693.
3. Bodenreider O, Stevens R: **Bio-ontologies: current trends and future directions.** *Brief Bioinform* 2006, **7**(3):256–274.
4. Noy NF: **Semantic integration: a survey of ontology-based approaches.** *SIGMOD Rec.* 2004, **33**(4):65–70.
5. Wache H, Voegele T, Visser U, Stuckenschmidt H, Schuster G, Neumann H, Hübner S: **Ontology-Based Integration of Information—a Survey of Existing Approaches.** In *IJCAI-01 Workshop: Ontologies and Information Sharing*, Vol. 2001. 2001:108–117.
6. Shadbolt N, Hall W, Berners-Lee T: **The Semantic Web revisited.** *IEEE Intell Syst* 2006, **21**(3):96–101.
7. **Resource Description Framework**, November 25, 2013. 2004. Available from: <http://www.w3.org/tr/rdf-concepts/>.
8. **RDF Vocabulary Description Language 1.0: RDF Schema.** 2004. Available from: <http://www.w3.org/TR/rdf-schema/>.
9. Hitzler P, Krötzsch M, Parsia B, Patel-Schneider PF, Rudolph S: **OWL 2 Web Ontology Language Primer.** 2009. cited 2011; Available from: <http://www.w3.org/TR/owl2-primer/>.
10. Hoehndorf R, Dumontier M, Gennari JH, Wimalaratne S, de Bono B, Cook DL, Gkoutos GV: **Integrating systems biology models and biomedical ontologies.** *BMC Syst Biol* 2011, **5**:124.
11. Hoehndorf R, Schofield PN, Gkoutos GV: **PhenomeNET: a whole-phenome approach to disease gene discovery.** *Nucleic acids research* 2011, **39**:18: e119.
12. Hoehndorf R, Dumontier M, Gkoutos GV: **Identifying aberrant pathways through integrated analysis of knowledge in pharmacogenomics.** *Bioinformatics* 2012, **28**(16):2169–2175.
13. Luciano JS, Andersson B, Batchelor C, Bodenreider O, Clark T, Denney CK, Domarew C, Gambet T, Harland L, Jentsch A, Kashyap V, Kos P, Kozlovsky J, Lebo T, Marshall SM, McCusker JP, McGuinness DL, Ogbuji C, Pichler E, Powers RL, Prud'hommeaux E, Samwald M, Schriml L, Tonellato PJ, Whetzel PL, Zhao J, Stephens S, Dumontier M: **The translational medicine ontology and knowledge base: driving personalized medicine by bridging the gap between bench and bedside.** *J Biomed Semant* 2011, **2**(Suppl 2):p. S1.
14. Sahoo SS, Bodenreider O, Rutter JL, Skinner KJ, Sheth AP: **An ontology-driven semantic mashup of gene and biological pathway information: application to the domain of nicotine dependence.** *J Biomed Inform* 2008, **41**(5):752–765.
15. Gangemi A: **Ontology design patterns for semantic web content.** In *The Semantic Web—ISWC 2005*. Berlin Heidelberg: Springer; 2005:262–276.
16. Egaña M, Rector A, Stevens R, Antezana E: **Applying ontology design patterns in bio-ontologies.** In *Knowledge Engineering: Practice and Patterns*. Berlin Heidelberg: Springer; 2008:7–16.
17. Aranguren ME, Antezana E, Kuiper M, Stevens R: **Ontology design patterns for bio-ontologies: a case study on the cell cycle ontology.** *BMC Bioinformatics* 2008, **9**(Suppl 5):S1.
18. Brinkman RR, Courtot M, Derom D, Fostel JM, He Y, Lord P, Malone J, Parkinson H, Peters B, Rocca-Serra P, Rutenberg A, Sansone SA, Soldatova LN, Stoeckert CJ Jr, Turner JA, Zheng J, O.B.I. consortium: **Modeling biomedical experimental processes with OBI.** *J Biomed Semantics* 2010, **1**(Suppl 1):S7.

19. Belleau F, Nolin MA, Tourigny N, Rigault P, Morissette J: **Bio2RDF: towards a mashup to build bioinformatics knowledge systems.** *J Biomed Inform* 2008, **41**(5):706–716.
20. Callahan A, Cruz-Toledo J, Dumontier M: **Ontology-based querying with Bio2RDF's linked open data.** *J Biomed Semantics* 2013, **4**(Suppl 1):S1.
21. Knox C, Law V, Jewison T, Liu P, Ly S, Frolkis A, Pon A, Banco K, Mak C, Neveu V, Djoumbou Y, Eisner R, Guo AC, Wishart DS: **DrugBank 3.0: a comprehensive resource for 'omics' research on drugs.** *Nucleic Acids Res* 2011, **39**(Database issue):D1035–D1041.
22. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, Altman RB, Klein TE: **Pharmacogenomics knowledge for personalized medicine.** *Clin Pharmacol Ther* 2012, **92**(4):414–417.
23. Chelliah V, Laibe C, Le Novere N: **BioModels database: a repository of mathematical models of biological processes.** *Methods Mol Biol* 2013, **1021**:189–199.
24. Wilkinson MD, Vandervalk B, McCarthy L: **The semantic automated discovery and integration (SADI) Web service design-pattern, API and reference implementation.** *J Biomed Semantics* 2011, **2**(1):8.
25. Wilkinson MD, McCarthy L, Vandervalk B, Withers D, Kawas E, Samadian S: **SADI, SHARE, and the in silico scientific method.** *BMC Bioinformatics* 2010, **11**(Suppl 12):S7.
26. Chepelev LL, Riazanov A, Kouznetsov A, Low HS, Dumontier M, Baker CJ: **Prototype semantic infrastructure for automated small molecule classification and annotation in lipidomics.** *BMC Bioinformatics* 2011, **12**:303.
27. Vandervalk B, McCarthy EL, Cruz-Toledo J, Klein A, Baker CJ, Dumontier M, Wilkinson MD: **The SADI personal health lens: a Web browser-based system for identifying personally relevant drug interactions.** *JMIR Res Protoc* 2013, **2**(1):e14.
28. BLASTN P: *dulcis SADI web service*. 2013. Available from: <http://sadirframework.org/services/blast/Prunus+dulcis>.
29. Del Rio N, Villanueva-Rosales N, Pennington D, Benedict K, Stewart A, Grady C: **Elseweb meets sadi: Supporting data-to-model integration for biodiversity forecasting.** In *Discovery Informatics Symposium*. ; 2013.
30. Madin J, Bowers S, Schildhauer M, Krivov S, Pennington D, Villa F: **An ontology for describing and synthesizing ecological observation data.** *Ecol Informat* 2007, **2**(3):279–296.
31. Mons B, van Haagen H, Chichester C, den Dunnen JT, van Ommen G, van Mulligen E, Singh B, Hooft R, Roos M, Hammond J: **The value of data.** *Nat Genet* 2011, **43**(4):281–283.
32. Patrinos GP, Cooper DN, van Mulligen E, Gkantouna V, Tzimas G, Tatum Z, Schultes E, Roos M, Mons B: **Microattribution and nanopublication as means to incentivize the placement of human genome variation data into the public domain.** *Hum Mutat* 2012, **33**(11):1503–1512.
33. Kuhn T, Barbano PE, Nagy ML, Krauthammer M: **Broadening the scope of nanopublications.** In *The Semantic Web: Semantics and Big Data*. Berlin Heidelberg: Springer; 2013:487–501.
34. van Haagen HH, AC't Hoen P, Bovo AB, de Morrée A, van Mulligen EM, Chichester C, Kors JA, den Dunnen JT, van Ommen G-JB, van der Maarel SM: **Novel protein-protein interactions inferred from literature context.** *PLoS One* 2009, **4**(11):e7894.
35. Smith B, Ashburner M, Rosse C, Bard J, Bug W, Ceusters W, Goldberg LJ, Eilbeck K, Ireland A, Mungall CJ, Leontis N, Rocca-Serra P, Ruttenberg A, Sansone SA, Scheuermann RH, Shah N, Whetzel PL, Lewis S: **The OBO Foundry: coordinated evolution of ontologies to support biomedical data integration.** *Nat Biotechnol* 2007, **25**(11):1251–1255.
36. Smith B, Ceusters W: **Ontological realism: a methodology for coordinated evolution of scientific ontologies.** *Appl Ontol* 2010, **5**(3–4):139–188.
37. Antony G, Riichiro M (Eds): *Formal Ontology in Information Systems, Proceedings of the Sixth International Conference, FOIS 2010, Toronto, Canada, May 11-14, 2010*. IOS Press; 2010:387–399. *Frontiers in Artificial Intelligence and Applications* ISBN 978-1-60750-534-1.
38. Lord P, Stevens R: **Adding a little reality to building ontologies for biology.** *PLoS One* 2010, **5**(9):e12258.
39. Smith B, Ceusters W, Klagges B, Kohler J, Kumar A, Lomax J, Mungall C, Neuhaus F, Rector AL, Rosse C: **Relations in biomedical ontologies.** *Genome Biol* 2005, **6**(5):R46.
40. Mungall C, Dumontier M: *SIO-RO mapping*. 2013. Available from: <http://purl.obolibrary.org/obo/ro/bridge/sio-ro-bridge.owl>.
41. Stenzhorn H, Beisswanger E, Schulz S: **Towards a top-domain ontology for linking biomedical ontologies.** *Stud Health Technol Inform* 2007, **129**(Pt 2):1225–1229.
42. Schulz S, Spackman K, James A, Cocos C, Boeker M: **Scalable representations of diseases in biomedical ontologies.** *J Biomed Semantics* 2011, **2**(Suppl 2):S6.
43. Seddig-Raufie D, Jansen L, Schober D, Boeker M, Grewe N, Schulz S: **Proposed actions are no actions: re-modeling an ontology design pattern with a realist top-level ontology.** *J Biomed Semantics* 2012, **3**(Suppl 2):S2.
44. Schulz S, Beisswanger E, van den Hoek L, Bodenreider O, van Mulligen EM: **Alignment of the UMLS semantic network with BioTop: methodology and assessment.** *Bioinformatics* 2009, **25**(12):i69–i76.

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