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Bioassay Ontology to Describe High-Throughput Screening Assays and their Results

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Abstract. Huge amounts of high-throughput screening (HTS) data are generated in the pharmaceutical industry and more recently in the public sector. These are typically analyzed on a per-project basis. Comparison and analysis across many diverse HTS datasets are hindered by the lack of standardized descriptions of biological assays and screening results. Here, we present the BioAssay Ontology (BAO), which enables the categorization of biological assays by concepts relevant to interpret and compare HTS data and thus facilitates data analysis across many HTS campaigns. We used BAO to annotate assays from the largest public HTS data repository, PubChem. Here we demonstrate how BAO can be applied to access and analyze HTS data. BAO makes use of expressive description logic and has potential for discovering implicit knowledge using inference. BAO is publically available from the NCBO BioPortal at http://bioportal.bioontology.org/ontologies/44531.

Keywords: high-throughput screening, HTS, biological screening, assay ontology, bioassay ontology, description logic, bioassay, biological assay, semantic integration, data analysis

1 Introduction

High-throughput screening (HTS) has become the most commonly used approach to identify starting points for the development of novel drugs [1]. Increasingly complex biological systems and processes can be interrogated using HTS, leveraging innovative assay designs and new detection technologies. Driven by the NIH Molecular Libraries Initiative, HTS has become available to public research sector along with a public HTS data repository, PubChem [2]. Screening centers of the Molecular Libraries Probe Production Centers Network (MLPCN) have so far deposited thousands of HTS assays describing the effects of several hundred thousand compounds.

However, biological assays in PubChem currently lack standardized descriptions and standards to report the HTS results (endpoints). This hinders data analysis and integration, thus preventing researchers from utilizing these public resources to their fullest potential [3]. It is currently not possible to identify related assays, for example those based on the same design (assay principle), the same detection technology, or interrogate protein targets from the same family or in the same pathway. It is also difficult to compare the activity of compounds across assays (because screening outcomes are not standardized). The motivation behind the BioAssay Ontology (BAO) development was to address this problem and to enable categorization of assays by concepts that are relevant to interpret screening results, which would then facilitate meaningful data retrieval and analysis across diverse HTS assays. We examined existing biomedical ontologies and incorporated information from several of them. However, we could not simply re-use or extend existing ontologies, because they lack many concepts required to model HTS data, including detection technologies (e.g. fluorescent vs. label-free assay), assay design (e.g. viability vs. enzyme reporter assay), HTS platforms, and detailed bioassay specifications. In addition, existing biomedical ontologies are not

structured to describe HTS assays by major categories, which describe important characteristics of an assay and whose subset of possible combinations could potentially define the universe of simple HTS assays. In an effort to develop a useful knowledge model of HTS assays, BAO uses description logic (DL) in OWL 2.0 to define semantics among classes of the different BAO categories. Although BAO represents an abstract model of HTS assays, its design and development adheres to many, although not yet all, principles recommended by the OBO (Biological and Biomedical Ontologies) Foundry [4, 5]. BAO can and should be mapped to additional ontologies of the OBO Foundry. For example the Ontology for Biomedical Investigations (OBI) [6] contains many classes that are related and relevant to describe biological assays. This work is currently in progress. We aim to collaborate with the members of the OBO to accomplish this while further developing BAO.

Here we describe the design and main components of BAO and the application of BAO for annotating HTS data in PubChem, both for data retrieval and meta-analysis. We also illustrate semantic definitions of BAO concepts and how they can be useful. BAO is publically available from our website [7] and the NCBO website [8].

2 Methods

We use 'single quotes' to denote terms from BAO and *italic* font to denote the semantic relationships.

2.1 Ontology Development

BAO was constructed using Protégé version 4.1 [9] in OWL (Web Ontology Language) 2.0 [10]. A number of available plugins were used throughout the development process including OWLViz2 [11] and OntoGraf [12] for visualization and DL reasoning engines HermiT [13] and Pellet [14].

2.2 PubChem Assay Annotation

To aid in manual annotation, assays were first clustered based on textual descriptions[15]. Using the terminology from BAO, PubChem bioassays were annotated with ~100 concept descriptors. These fall into the main BAO categories 'assay format', 'design', 'detection technology', 'meta target', 'perturbagen', and 'endpoint'. Assays were grouped by screening campaigns and organized by an assay stage (e.g. 'primary', 'secondary', etc.), throughput quality (e.g. 'single concentration single measurement', 'concentration response multiple replicates', etc.), and assay relationships (e.g. *is confirmatory assay of* or *is counter assay of,* etc.), among other categories. We also standardized assay endpoints, e.g.: 'IC_{50}', 'EC_{50}', 'percent inhibition', etc.

2.3 Integrating External Ontologies

We used OntoFox[16] to integrate external ontologies such as Gene Ontology (GO), NCBI Taxonomy, Cell Line Ontology (CLO) into BAO. Namespaces were preserved for these ontology terms.

3 Results

BAO is an abstract description of a 'bioassay' for the purpose of categorizing assays by concepts that are relevant to interpret screening results. BAO is therefore organized by major categories, which each include multiple levels of subclasses and specification classes. A number of specific object property relationships were created to connect classes and develop a knowledge representation in the domain of biological assays and screening outcomes. The relevance of BAO for annotating and analyzing MLPCN assays has recently been demonstrated [15]. Table 1 shows examples of attributes captured from BAO for sets of assays that comprise screening campaigns (partial views).

3.1 Ontology Design

BAO is instantiated in a well-specified syntax and designed to share a common space of identifiers. The ontology has a formally specified and clearly delineated content. All terms in the ontology have textual definitions.

Fig. 1 illustrates the high level design of BAO's main components: 'format' and 'perturbagen' have direct relationships to 'bioassay'; 'meta target', 'detection technology', 'design', and 'endpoint' are linked to 'bioassay' via 'measure group', which is an abstract concept to group experimental outcomes into

sets and thus to allow modeling multiplexed and multi-parametric assays. These classes are connected by specific (abstract) relationships (*has a* and its inverse *is of*) in contrast to the subsumption *is a* relationships within each major class.

One of the objectives of BAO is to represent domain knowledge, which is accomplished using DL in OWL 2.0. BAO (v1.1b868) has SROIQ(D) [17] expressivity and consists of 730 classes, 72 object properties (relations), 7 data properties, and 25 individuals (not including individuals from annotated assays or endpoints).

3.2 Description of BAO Major Concepts

The assay 'format' describes the biological or chemical features common to each test condition in the assay and includes several broad categories: 'biochemical', 'cell-based', 'cell-free', 'tissue-based', 'organism-based', and 'physicochemical' format. Further details are captured as 'format specifications' (Fig. 2) including special 'reagent' conditions (e.g. 'redox reagent', 'detergent', etc.) and 'assay phase characteristic' ('homogeneous assay' or 'heterogeneous assay').

Assay 'design' describes the assay methodology and implementation of how the perturbation of the biological system is translated into a detectable signal. In BAO, 'design' is broadly classified into one of eight categories: 'binding reporter', 'enzyme reporter', 'inducible reporter', 'morphology reporter', 'viability reporter', 'redistribution reporter', 'conformation reporter' and 'membrane potential reporter'. All of these assay 'design' classes have further subclasses and specification classes (Fig. 2). BAO also describes the 'detection technology' used in bioassays, which includes 'spectrophotometry', 'fluorescence', 'luminescence', and others. Additional attributes of the assay technologies, such as standard screening kits (e.g. CellTiter-Glo) and pertinent parameters thereof are captured in the class 'detection technology specification'.

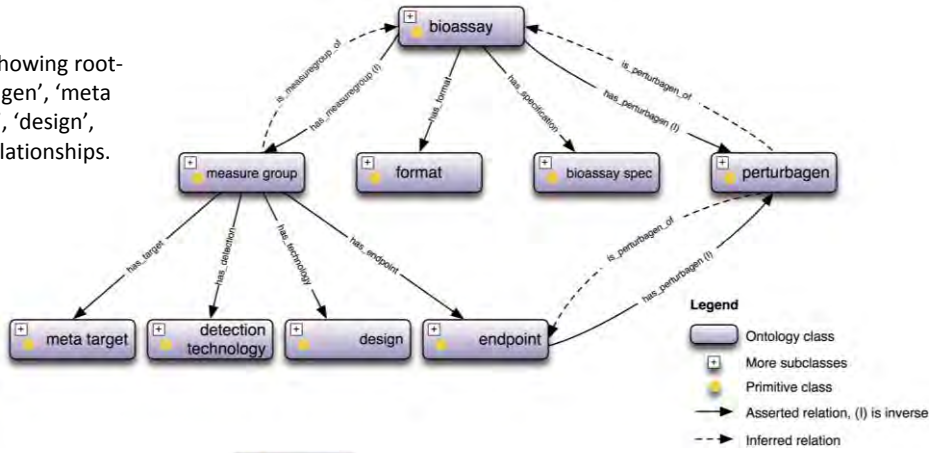

Figure 1. BAO ontology excerpt showing root-level classes: 'format', 'perturbagen', 'meta target', 'detection technology', 'design', 'endpoint', and some of their relationships.

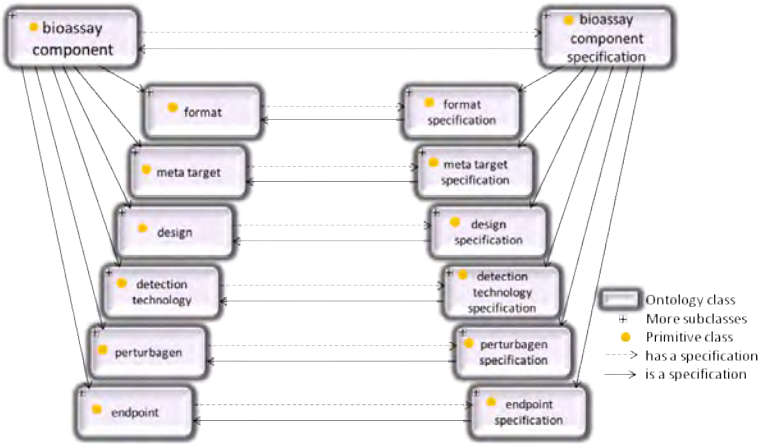

Figure 2. Illustration of the major bioassay components and corresponding specifications. Each bioassay component subclass has a corresponding specification subclass with a *has specification* and its inverse *is specification of* relationship.

Assay 'meta target' describes what is known about the biological system and / or its components interrogated in the assay (and influenced by the perturbagen). 'Meta target' can be directly described as a molecular entity (e.g. a purified protein or a protein complex), or indirectly by a biological process or event (e.g. phosphorylation). It includes information to enable linking external content, such as pathway databases, with the goal to infer the mechanism of action of perturbagens in an assay. The term "meta" is used to distinguish from the typical interpretation of target as a protein. Additional details about targets are captured as 'meta target specification'. For example 'protein specification' ('protein purity', 'protein form', 'protein preparation method') or 'cell specification', which includes assay-specific details about the cell line ('cell culturing component', 'cell modification', 'transfection specification').

An assay 'endpoint' describes a quantitative or qualitative result of the bioassay. The main classes are 'perturbagen concentration' and 'response' endpoints, e.g. 'IC_{50}' or 'percent inhibition', respectively. Because 'endpoint' typically infers other information (e.g. mode of action: 'inhibition'), in BAO the concept 'endpoint' is described semantically (using OWL DL) by specifying relationships between endpoints and other BAO concepts. The purpose is to enable the retrieval of inferred results that are not explicitly specified in a query (semantic equivalence) and which would otherwise not be retrievable or require complex Boolean endpoint queries (described in section 3.5).

3.3 Integrating BAO with External Ontologies

Some external ontologies contain information that define parts of concepts related to biological assays described by BAO (Fig. 3). We have imported relevant sections from Gene Ontology (GO) [18], Cell Line Ontology (CLO) [19], Unit Ontology (UO) [20] and others into BAO using OntoFox [16]. GO 'biological process' terms and CLO 'cell line' names and additional parameters are used in BAO 'meta target' and 'meta target specifications'. CLO is currently being extended as a collaborative effort to cover cell lines relevant for biological screening [21]. Organism names associated with targets were imported from NCBI taxonomy. Protein target names and IDs were referenced from UniProt. From UO we imported 'concentration unit' and 'time unit' terms. We also used terms necessary for curation of data from the Information Artifact Ontology (IAO), specifically, 'information content entity' and its sub-classes [22]. More work (in progress) is required to fully utilize IAO for BAO. We are currently working on mapping BAO to other OBO ontologies. For example, OBI includes relevant information to describe biological assays [6]. BAO was not developed as an extension of OBI because a different organization was required in BAO to allow categorization of assays and screening results for data retrieval and analysis. OBI links to many other resources and therefore mapping BAO to OBI will be of significant value as BAO and OBI take different but not incompatible approaches in describing assays. BAO can be seen as a more abstract description with the specific purpose to facilitate assay annotations by specific concepts and screening data analyses [15]; hence, many relationships are very specific (connecting two BAO classes; compare BAO design above). We have mapped some of the BAO relationships to the OBO Relationship Ontology (RO) and we aim to use more of RO relationships in the future. Additionally, we may be able to use RO to map BAO concepts to other ontologies.

3.4 Applications of BAO

Using BAO terms, we have manually annotated over 900 MLPCN assays in PubChem, based on their textual descriptions (see methods). These assays correspond to over 15 millions endpoints (screening results), which we also standardized. Assays were categorized into campaigns. Examples of assay annotation are shown in table 1.

Using BAO annotations, assays can be readily categorized. For example, after annotating the formats of 1961 PubChem assays, we found the majority of assays to be 'cell-based' (874) or 'biochemical' (798) with some 'organism-based' (245) and a few 'cell-free' (31) and 'tissue-based' (13) (Fig. 4A). This information is relevant to interpret screening results, for example, 'biochemical' assays provide direct evidence of the mechanism of action (e.g. inhibition of an enzyme), while

activity in 'cell-based' assays infers that a compound is cell permeable. In another example, we annotated the most widely used HTS assay designs, namely, luciferase- and β-lactamase-based assays. 350 of such assays from PubChem were further classified into assay 'design' sub-categories (Fig. 4B). We have demonstrated the utility of such annotations to identify promiscuously active compounds (i.e. their activity is related to the assay 'design', but not to the 'meta target') as well as the likely mechanism of action underlying such promiscuity [15].

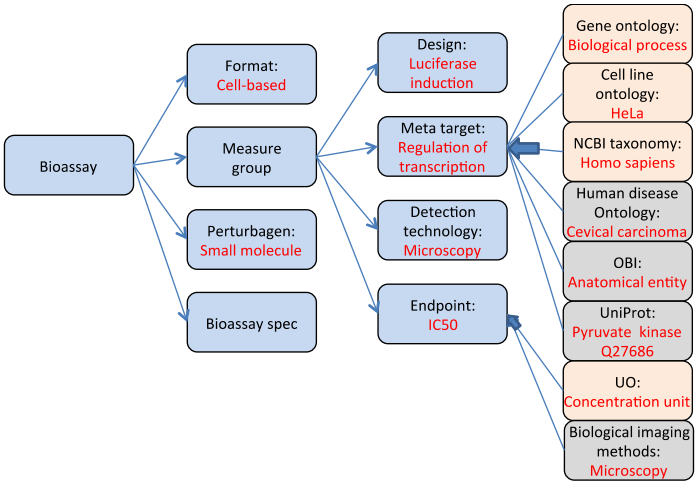

Figure 3. Examples of external ontologies that contribute to some BAO concepts. External ontologies are shown to the far right and are linked to BAO concepts shown in blue to their left. The ontologies from which terms were already imported are shown in red and those that will be imported in the future are shown in grey. Specific examples of terms in an ontology or BAO concept are shown in red letters.

Screen. campaign	"Identification of inhibitors of Kruppel-like factor 5"		
AID	1700	1973	1944
Assay Stage	Primary Assay	Confirmatory Assay	Secondary Assay
Relationship	has confirmatory assay 1973 has secondary assay 1944	has primary assay 1700	has primary assay 1700
Assay Measurement Throughput Quality	Single concentration single measurement (e.g. 1x%Inh)	Concentration response multiple replicates (e.g. 3xIC50)	Single concentration multiple replicates (e.g. 3x%Inh)
Endpoint std	% Inhibition	IC50	% Inhibition
Assay Format	Cell-based	Cell-based	Biochemical
Assay Design	Luciferase induction	Luciferase induction	Enzyme reporter
Assay Target	Transcription factor	Transcription factor	Hydrolase
Detection Technology	Luminescence	Luminescence	Luminescence
Measured Entity	Luciferase concentration	Luciferase concentration	Luciferin concentration
Screen. campaign	"Positive allosteric modulators of the M5 muscarinic receptor"		
AID	2665	2194	2206
Assay Stage	Primary	Confirmatory	Secondary Assay
Relationship	has confirmatory assay 2194 has secondary assay 2206	has primary assay 2665	has primary assay 2665
Assay Measurement Throughput Quality	Single concentration single measurement (e.g. 1x%Inh)	Concentration response multiple replicates (e.g. 3xIC50)	Concentration response multiple replicates (e.g. 3xIC50)
Endpoint std	Maximal response	EC50	EC50
Assay Format	Cell-based	Biochemical	Cell-based
Assay Design	Calcium redistribution	Radioligand binding	Calcium redistribution
Assay Target	Human M5	Human M5	rat M1
Detection Technology	Fluorescence intensity	Scintillation counting, filter assay	Fluorescence intensity
Measured Entity	Calcium flux	[3H]-NMS radioactivity	Calcium flux

Table 1. Annotations of PubChem assays using BAO

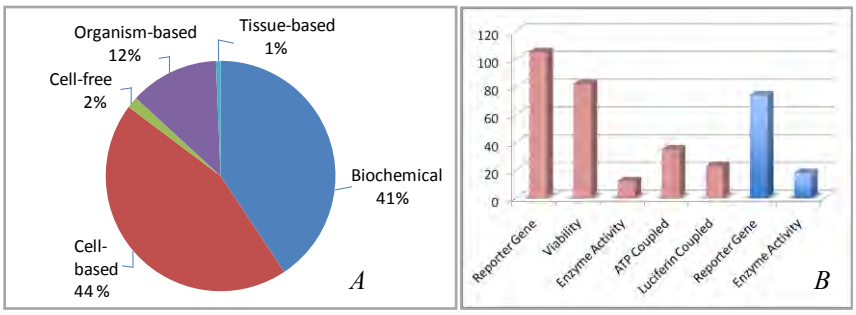

Figure 4.
Curation of PubChem bioassays.

A: Annotation of the bioassay 'formats' from PubChem.

B: Number of annotated PubChem assays by major assay platforms (luciferase (red) and β-lactamase (blue)) and relevant sub-categories.

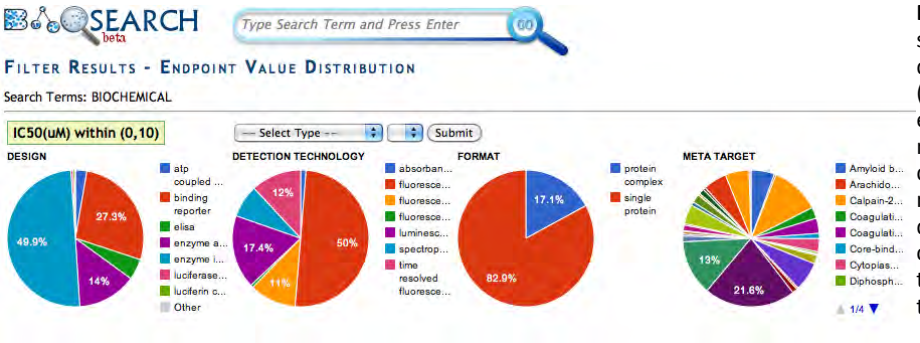

Figure 5. BAOSearch graphical summary example result page after querying for 'biochemical' assays (by concept search) with 'IC_{50}' endpoints of less than 10 micromolar activity. This page displays how the endpoints that match the search query are distributed among the major BAO concepts, 'design', 'detection technology', 'format' and 'meta target'.

We have also developed a software application that makes use of BAO. BAOSearch [23, 24] allows us to query and explore annotated PubChem assays and screening results in the context of BAO (Fig. 5).

3.5 An Example of DL to Define BAO Concepts

To illustrate how BAO classes are embedded with semantic information, we describe the BAO 'endpoint' concept 'IC_{50}', defined as the concentration of the perturbagen that results in '50 percent inhibition' (Fig. 6).

Definitions include equivalent classes (necessary and sufficient conditions) and superclasses (necessary conditions only). Necessary and sufficient conditions are used to classify individuals; for example, we might be able to infer that an individual endpoint must be an 'IC_{50}' because the 'mode of action' is 'inhibition' (among other criteria). With only necessary conditions, the definition is logically different, saying that if an individual is a member of the class 'IC_{50}', it is necessarily a subclass of 'perturbagen concentration'. The equivalent class 'IC_{50}' specifies *has mode of action* only 'inhibition'. "Only" denotes universal quantification, describing all the individuals whose *has mode of action* relationships refer to members of the class 'inhibition'; or conversely, the individuals that do not have *has mode of action* relationships to individuals that are not members of the class 'inhibition'. "Some" denotes existential restrictions, e.g. *has mode of action* some 'inhibition' specifies the existence of at least one relationship along a given property to an individual, which is a member of the class 'IC_{50}'. Existential restrictions can be seen as "among other things", and are used to "close" a given property, which is necessary for the reasoning process (open world assumption). In the BAO knowledge model, many relationships specifically connect two classes and must not be interpreted in any other way. For example *has mode of action* means that 'endpoint' is further specified by 'endpoint mode of action'. Certain specifications are inherited from classes that are higher up in the hierarchy. An example of this is the inherited anonymous class definition of individuals having the object property *has perturbagen concentration value*. There is also the relationship *has perturbagen*, describing that every individual of the 'IC_{50}' class must have at least one 'perturbagen'. The semantic description of 'IC_{50}' facilitates the retrieval of inferred results. For example querying for perturbagens with greater than '50 percent inhibition' at a defined 'perturbagen concentration' retrieves qualified 'IC_{50}' as well as 'percent inhibition' endpoints, as illustrated in the BAO SPARQL Examples on our web site [7]. (http://129.171.150.121/joseki/query.html)

```
Equivalent classes:
    ('has mode of action' some inhibition)
    and ('has mode of action' only inhibition)
    and ('has percent response' value '50
        percent inhibition individual')
Superclasses:
    'has curvefit spec' only 'curvefit spec'
    'perturbagen concentration'
Inherited anonymous classes:
    ('has perturbagen concentration unit' some
        'concentration unit')
    and ('has perturbagen concentration unit'
        only 'concentration unit')
    and ('has perturbagen concentration value'
        exactly 1 float)
    ('has specification' only endpoint spec)
    ('has perturbagen' some perturbagen)
    and ('has perturbagen' exactly 1 Thing)
```

Figure 6. BAO definition of the class 'IC_{50}'.

4 Summary

Large amounts of data are generated by HTS in private and public organizations. Nevertheless, large scale screening capabilities have so far not translated to increased numbers of approved drugs [25]. One likely reason is that available data is used inefficiently. It remains a challenge to effectively translate increasing amounts of data into actionable knowledge; at the very least this is the case for the current public domain data. To address this challenge, we have developed BioAssay Ontology (BAO). BAO describes biological assays and their outcomes by concepts that are relevant to interpret, analyze and integrate screening data. BAO addresses 1) development of standardized terminology and uniform standards to report HTS results; and 2) a semantic description of bioassays and their results to model domain knowledge and to facilitate semantic integration with diverse other resources [26, 27]. We have used BAO to annotate PubChem assays and showed that BAO concepts are useful to categorize and analyze screening results [24]. We have illustrated the use of DL to incorporate semantics into BAO concepts and to retrieve inferred query results.

BAO is under active development. Although BAO makes use of relevant information from several external ontologies, current effort is focused on incorporating content from several other resources with the potential of making BAO-annotated HTS data widely accessible via a "Linked Data" approach [28].

In summary BAO opens new functionality for querying and analyzing HTS data sets and has potential for discovering new knowledge (that is not explicitly described in the data) by inference.

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