

Phenotype Ontologies Traversing All The Organisms (POTATO) workshop aims to reconcile logical definitions across species

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Abstract

Logical definitions, in particular those following the Entity-Quality approach, are increasingly used to drive automated classification of phenotypes and integrate phenotypes across species semantically. Over the years, the lack of consistent and widespread use of common standards resulted in conceptually equivalent or similar phenotypes with logically divergent definitions. Recently, pattern-based approaches such as Dead Simple Ontology Design Patterns (DOSDP) have emerged as a way to reconcile such divergent definitions on a large scale. To facilitate the widespread adoption of DOSDP-based phenotype ontology development and to organise the reconciliation process involving key model organism communities, we have established the Phenotype Ontologies Traversing All The Organisms (POTATO) Workshop Series. These workshops are part of the NIH-funded “Forums for Integrative Phenomics” conference award, which provide a venue for phenotype ontology developers and phenomics informaticians to align their goals and technical approaches. The first POTATO workshop, in August 2018, provided training in cutting-edge tools and techniques for developing and releasing ontologies using design patterns and automated imports. This workshop also featured collaborative exercises in reconciling divergent logical definitions drawn from major phenotype ontologies that resulted in a set of general recommendations for how to improve phenotype ontologies and their development as well as a set of reconciled definitions. As a result of the workshop, many of the attendees have joined a phenotype ontology reconciliation effort, aimed at developing and

implementing common design patterns across a range of phenotype ontologies. We thus plan to hold additional POTATO workshops.

Introduction and Motivation for the Workshop

Phenotype ontologies now exist for a wide and growing range of species, from nematodes to humans, and have been used to annotate millions of individual phenotypes (1–6). Many of these ontologies are at least partly formalised using formal, logical definitions in Web Ontology Language (OWL). These logical definitions specify necessary and sufficient conditions for class membership, allowing class hierarchies to be constructed automatically using logical inference. They are typically constructed according to a semi-standardised framework (7) and use terms, directly or indirectly, from cross-species ontologies such as Uberon (8) and the Gene Ontology (9). With the use of standard reasoning technologies, we can leverage knowledge encoded in the referenced ontologies to automate classification of phenotypes, making phenotype ontology development more efficient, and classifications more accurate and complete.

Logical definitions can also be used to facilitate the development of tools for translational medicine that rely on cross-species phenotype grouping and mapping of phenotypes (10,11). By giving logical definitions to species-neutral phenotype terms, we can use reasoning to group related phenotypes from different species. This is one of the approaches being evaluated by the Alliance of Genome Resources (Alliance, (10)) for integration of phenotype data. Combining reasoning with the use of semantic similarity algorithms allows us to map phenotypes between species in biologically meaningful ways (12–14). This approach underpins the work of the Monarch Initiative to facilitate the discovery of candidate genes and animal models of human disease on the basis of phenotypic similarity (15).

At present, all of this potential is only partially fulfilled. Divergence in the design patterns used to construct logical definitions both within and between ontologies limits inferred classification and cross-species mapping. This divergence is unsurprising given that ontology developers have been keeping definition patterns for 10s of thousands of terms in sync manually.

We have recently developed tooling for centrally defining and applying templates for logical definitions (16) and integrated this into a popular ontology development system that supports many of the other needs of ontology developers such as automating imports, checking syntax and integrity, and making releases. This can be used to develop a central repository of phenotype design patterns and make it easy for phenotype ontology developers to apply these, overcoming the challenges of manually keeping definition patterns in sync. In addition to improving intra- and inter-ontology alignment, a central repository of patterns would be a valuable resource for accelerating the development of new phenotype ontologies and extending existing ones, as new terms can be added by applying and extending existing patterns.

Efforts to build and apply a central repository of design patterns for phenotype ontologies can only be successful with the collaborative effort of the phenotype ontology community to align design patterns so that they accurately reflect shared biology. At the International Conference on Biological Ontology (ICBO, August 7-10 2018) in Corvallis, Oregon, we held a workshop that hosted 40 ontology curators, developers, and biomedical experts who study diverse taxa to learn about our updated tools for pattern-based development, and to discuss strategies for

aligning logical definitions across phenotype ontologies. Here we describe the outcomes of this workshop.

The increasing divergence of logical definitions across phenotype ontologies

Logical definitions are increasingly used to classify concepts in OWL (17) ontologies with automated reasoners (18). Most phenotype ontology terms with formal definitions use a common framework (EQ) that combines reference to an entity (E) - a biological process such as “gene expression” (GO:0010467) or a material entity such as “eye” (e.g. UBERON:0000970) - and an affected quality (Q), such as weight (PATO:0000128), size (PATO:0000586) or increased rate (PATO:0000912) (7). For example, the phenotype ‘*abnormal eye muscle development*’ could be defined using the OWL class expression:

'has part' some (quality and 'inheres in part of' some ('muscle organ development' and 'occurs in' some camera-type eye) and 'has modifier' some abnormal).

The EQ approach resulted from an earlier phase of community standardization to which many Model Organism Databases and ontology development groups contributed, including the Mammalian Phenotype Ontology (MP) (2), the Human Phenotype Ontology (HP) (3), the Drosophila Phenotype Ontology (4) and ZFIN (6,7,19) who pioneered the direct use of the EQ framework to formalise phenotype curation. The adoption of the EQ framework led to some significant advances in interoperability between major phenotype ontologies, particularly HP, MP and a pre-coordinated version of the ZFIN EQ annotations (ZP) (20). However, manually co-ordinating the process of developing and applying compatible sets of logical definitions does not scale well. Despite regular meetings, working groups and shared documentation, efforts to maintain consistent definitions within and between phenotype ontologies has had limited success. Changing specifications and dispersed documentation led to an increasing divergence in definition patterns. This resulted in many cases where terms referring to very similar phenotypes in different ontologies are defined using logically-incompatible patterns. For example, the logical definitions for necrosis phenotypes in MP and HP, which are internally consistent in each ontology, are sufficiently different between HP and MP that there is no biologically meaningful inferred classification relationship between the two sets of phenotypes. A comparison of the logical definitions of 'myocardial necrosis' in HP and MP illustrates the problem.

Myocardial necrosis (HP:0001700)	myocardial necrosis (MP:0006085)
<i>has part some (having extra processual parts and inheres in part of some myocardium and towards some necrotic cell death and has modifier some abnormal)</i>	<i>has part some (increased amount and inheres in part of some (necrotic cell death and occurs in some myocardium) and has modifier some abnormal)</i>

Neither the affected entities nor the qualities in these two definitions are related. In the HP the entity affected (the entity that the Quality inheres in) is an anatomical structure, the myocardium (defined in Uberon), whereas in MP it is the process of necrotic cell death (defined in GO)

occurring in the myocardium. Similarly, the qualities chosen by the MP and HP are in entirely different parts of the PATO classification hierarchy. Given this, automated reasoning will not place these terms anywhere near each other in the classification hierarchy and semantic similarity scores (used for cross-species inference) will be low. For more details and other examples see (21).

Pattern-based ontology development provides a scalable methodology for developing logically compatible definitions across communities.

In recent years a number of pattern- or template-based ontology development systems, have been developed. These include Dead Simple OWL Design Patterns (DOSDP) (16), TawnyOWL (22) and ROBOT templates (23), which have all been successfully applied to improve the curation of biomedical ontologies. While the various approaches cater to different use cases, the general idea is to distinguish the pattern or template, which is a blueprint for the generation of OWL statements, from the actual instances (application) of a pattern. Dead Simple Ontology Design Patterns (DOSDP) (16) is a generic framework for specifying and applying OWL design patterns. Patterns containing logical axioms with variable slots are represented as YAML files. Applications of the patterns are represented as rows in tab-separated values (TSV) files, which contain fillers for the variables in the pattern. The Ontology Development Kit (24) (ODK) is a toolkit for jump-starting ontology development and managing ontology release cycles. As of August 2018, the ODK fully supports DOSDP-based ontology curation. Before the POTATO workshop, a significant amount of work was invested to develop the methods and tools to support DOSDP-based development and to create an initial repository of community-curated patterns for phenotype development (25). This was adapted from documentation created by HP and MP curators, hosted as part of the UPHENO ontology repository (25). The aim of the repository is to centralise discussion and representation of phenotypes that are general enough to be useful for cross-species inference. So far UPHENO has concentrated on defining phenotypes affecting morphology and key processes, representing these as DOSDP patterns (e.g. *abnormalMorphology*). This provides a flexible and scalable approach to curating these phenotype definitions. The use of such patterns across species-specific phenotype ontologies would result in more logically compatible definitions across communities.

The POTATO workshop: reconciling definitions, developing patterns and practicing the new methods and tools

At the International Conference on Biological Ontology (ICBO, August 7-10 2018) in Corvallis, Oregon, we held a workshop that hosted 40 ontology curators, developers, and biomedical experts who study diverse taxa to learn about our updated tooling for pattern-based development and to discuss discrepancies between logical definitions across various phenotype ontologies. The workshop, with 5 sessions across 2 days, attracted developers from phenotype ontologies including the Human (HP), Mammalian (MP), Zebrafish (ZP), *C. elegans* (WBPhenotype) (1), *Xenopus* (XPO), *Drosophila* (DPO), Planarian (PLANP) and Cellular Microscopy (CMPO) phenotype ontologies and the Plant Trait Ontology (TO) (26). The first day was divided into the following sessions:

- Session 1: The EQ approach - Background & methodology (M. Haendel, D. Osumi-Sutherland, C. Mungall) and hands on session (N. Matentzoglou).
- Session 2: EQ definitions in the wild (N. Matentzoglou), overview of pattern-based development (D. Osumi-Sutherland), state of individual phenotype ontologies (L.

Carmody, S. Bello, D. Osumi-Sutherland, C. Grove, Y. Bradford, E. Segerdell, M.-A. Laporte) and introduction to reconciliation framework (N. Matentzoglou).

- Session 3: Reconciliation group session (led by N. Matentzoglou and Nicole Vasilevsky)
- Session 4: Reconciliation results, open discussion (led by D. Osumi-Sutherland), feedback collection.
- Session 5: Hands on tutorial for DOSDP-based development (D. Osumi-Sutherland)

The primary goals of this workshop were to establish an ongoing effort committed to the continuous reconciliation of logical definitions across phenotype ontologies and introducing the community to new methods and tools for DOSDP-based ontology curation. The practical Session 3 aimed to jump-start this process through negotiating suitable patterns for a select number of reconciliation problems (i.e. divergent definitions that refer to the same real-world concept) drawn from HP, MP and ZP (for a list see <https://bit.ly/2QAteZz>). The 40 participants gathered in six groups to work through those reconciliation problems and were asked to 1) determine whether the definitions actually refer to the same real-world concept 2) develop a suitable EQ definition to replace both definitions and 3) identify a suitable pattern from the UPHENO repository, or, if none existed, develop a new one.

Outcomes of the workshop

The main goals of the meeting were:

- Enable the members of the community to curate their ontologies using the DOSDP-approach.
- Enlist key curators for the continuous reconciliation effort over the coming years and foster a sense of community
- Reconcile the interests and goals of the various groups in the community and start characterising and prioritising modelling-related problems to develop community-wide solutions
- Practice definition reconciliation and pattern negotiation and observe potential pitfalls.

Reconciling thousands of definitions across multiple species is a very difficult problem that requires method and tool support that, after almost a decade of development, has only now reached sufficient maturity for mainstream adoption. We introduced key curators of phenotype ontologies to the process of DOSDP-based ontology curation during the POTATO workshop, and also uncovered some technical obstacles that will require our attention in the near future. Half (20) of the workshop participants felt committed to the ongoing reconciliation effort after the workshop (a few more being undecided), with more than 15 being willing to dedicate one hour or more per week to the effort (on top of their normal curation activities). The open discussion session revealed a number of shared concerns by the community, for example:

- The idiosyncrasies of PATO, e.g. the lack of textual definitions, 'strange' hierarchies and inconsistent grammatical forms of term labels (e.g. 'increased curvature' and 'curved') which cause confusion among curators and frustration among developers of automated labelling approaches.
- Difficulties with UBERON, the anatomy ontology that integrates the species-specific anatomy ontologies, in particular overly strict restrictions that do not necessarily apply to the domain models of all species, and the need for open, community-based curation.

- The necessity of capturing causality properly, in particular distinguishing abnormal biological processes from their consequences. This is a major concern, as currently abnormal processes and abnormal effects are interleaved in the same classification hierarchies across major phenotype ontologies (e.g. ‘abnormal thyroid gland morphology’, is a superclass of ‘abnormal thyroid gland development’). This mix is a potential cause of inference errors. These classifications were added in order to group annotations to process phenotypes under their consequences. We can achieve the same result without causing inference errors by replacing these classifications with casual relationships that can be used for grouping annotations.
- The occasionally ambiguous human-readable definitions and labels make it hard to determine the exact phenotype the author intended to describe. For example, does “abnormal glycosylation” refer to a “physical abnormality in the structure or composition of a glycan, or their attachment to conjugation targets” or the glycosylation process - “the attachment of glycan molecules to a substrate”? This can be a problem for community-driven ontology development when the label and the definition do not agree and the author’s original intent is lost.
- A methodology and detailed instructions are needed for how UPHENO and species specific EQ definitions can be exploited in applications such as search engines.
- Better documentation of our patterns and guidelines for the design of EQ definitions are needed.
- Some ontologies like HP make use of **phenotypic profiles** (sets of co-occurring phenotypes merged into one compound phenotype), which has not yet been vetted formally. A related issue is that of **phenotype extension** (for example deafness phenotype vs unilateral deafness), which has also not been incorporated in the methodology.

The practical reconciliation session sensitised the participants to the fact that logical divergences exist that do not reflect differences in intended meaning, and gave them a sense of how to develop better, more standardised definitions. Across groups, around 20 reconciliation problems were discussed thoroughly and documented, and 5 concrete patterns proposed or adjusted as a result. All 6 groups independently discussed the reconciliation example for ‘unilateral deafness’ (for details see (21)), and came to quite comparable but not necessarily equivalent pattern proposals for the problem.

Fully reconciling all phenotype ontologies is a hard problem which is likely to take several years. As there is no objective way to determine which concepts need to be reconciled in the first place, quantifying the progress and the impact (such as downstream effects on dependent tools and algorithms, e.g. semantic similarity) of the reconciliation process is going to be a major part of our effort. Another challenge will be to develop tool support for at least partially automating the process of identifying reconciliation candidates, for example based on string-matching techniques or through a mix of syntactic and semantic approaches that exploit the increasing degree of semantic integration as we continue to reconcile definitions. In preparation for the POTATO workshop, we have started developing the Ontology Pattern Reconciliation Workbench, which provides a graphical user interface for identifying suitable candidates across ontologies and prioritising them by potential impact (27). In the three months since the workshop, the phenotype ontology community has:

- Re-established a bi-weekly phenotype editors call with 13 to 20 participants

- Established an ongoing program for training the individual groups in advanced usage of DOSDP and the ODK in weekly video calls.
- Migrated or developed from scratch four ODK-based ontology repositories (Xenopus, *C. elegans*, Planarian, Zebrafish) and moved many thousands of EQ definitions to the DOSDP approach. The effort is ongoing: by the end of 2018 our goal is to have most other phenotype ontologies participating in the phenotype reconciliation effort implementing at least one, but likely more, collectively negotiated phenotype pattern(s).
- Collected and discussed two of the major obstacles of the community: the class hierarchy and annotations of the Phenotype and Trait Ontology (PATO) and the compatibility issues with UBERON, the species-independent anatomy ontology

Due to the success of this year's edition of the POTATO workshop, we are currently planning the next workshop in the series, most likely to be co-located with Biocuration 2019 in Cambridge, United Kingdom, where we will focus on the top pressing issues identified by the phenotype community this year, such as the need to re-design the PATO and problems caused by some of the logical assumptions made by UBERON in a multi-species setting.

To join this effort or for any other questions, please contact Nico Matentzoglou: nicolas.matentzoglou@ebi.ac.uk or Nicole Vasilevsky: vasilevs@ohsu.edu

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