June 12th, 2010.

Dear Editors of Applied Ontology,

Please find here attached the revised manuscript “MIREOT: the Minimum Information to Reference an External Ontology Term” authored by Mélanie Courtot, Frank Gibson, Allyson L. Lister, James Malone, Daniel Schober, Ryan R. Brinkman and Alan Ruttenberg, and assigned tracking number 09-116.

We appreciate the time and efforts of the reviewers and would like to thank them for their constructive feedback, which helped us reach the current improved stage of our manuscript. Detailed replies to the reviewers’ comments are provided below, in italics.

We would like to mention that we extended the MIREOT mechanism since the original submission to address more uses cases from our community of users. To illustrate this we added the section *3.3. Use Case Three - Unit instances* to the originally submitted manuscript*.* We believe this addition doesn’t alter the substance of the paper, but rather provides more guidance as suggested by reviewer #1.

On behalf of all co-authors, I would like to thank you for considering our manuscript for publication in Applied Ontology.

Sincerely,

Mélanie Courtot

TFL- BCCRC

675 West 10th Avenue

Vancouver, BC

V5Z 1L3, Canada

On behalf of all the co-authors:

Frank Gibson, Abcam plc, 332 Cambridge Science Park, Cambridge, CB4 OWN, UK

Allyson L. Lister, CISBAN and School of Computing Science, Newcastle University, Newcastle upon Tyne, UK

James Malone, The European Bioinformatics Institute, Cambridge, CB10 1SD, UK

Daniel Schober, Institute of Medical Biometry and Medical Informatics (IMBI), University Medical Center, 70104

Freiburg, Germany

Ryan R. Brinkman,  BC Cancer Agency, and Department of Medical Genetics, University of British Columbia Vancouver, BC, Canada

and

Alan Ruttenberg, Science Commons, Cambridge, MA, USA.

**Responses to reviewers’ comments**

**---Review #1---**

[…]

How would the mechanism for for OBO format ontologies?

*We updated the “Future Work” section to illustrate that while the mechanism implemented for OBI is geared towards OWL, a mechanism with a similar effect could be applied to OBO format ontologies.*   
  
Could a concrete example be given of the problems that are to be avoided by using MIREOT (I think I understand this myself but this is not really made clear in the manuscript)? What exactly is the advantage of MIREOT over just using a Perl script to compare IDs/names/definitions of the imported terms with those in the external ontology? I for one am a bit wary of using an automatic MIREOT scheme that will automatically update definitions (what if the external ontology does make some silly mistake) and think that some amount of manual curation is necessary. It would be quite easy to keep my external terms in a separate file and to run a script as a cron job and get some message if there has been a change in an external ontology. The MIREOT method seems to have the same capabilities but seems to be rather more complicated. So what do I get in return for the added complication? This is something that is missing from the manuscript at present.

*MIREOT provides the guideline as to which information is required to perform a lightweight import of selected terms into a target resource. The implementation itself is independent, and any mechanism providing the required functionalities would be acceptable. We however believe that the implementation we propose is better suited for the job: it relies on SPARQL queries on a remote server, providing a standard way to access a service, which is maintained and updated on a regular basis. We updated the manuscript to explain the choice of a SPARQL endpoint.*

There are especially two areas that are somewhat opaque in the current manuscript that would benefit from a more detailed description:

1) The authors write, „ during the development of the Ontology of

Biomedical Investigations (OBI) (OBI Ontology), importing the root class of the Common Anatomy Reference Ontology (CARO) (Haendel et al., 2008) was not desired as its definition intersected multiple classes in OBI..."

It would be interesting to have an example of what is meant, as it is not clear to me. I was not aware that OBI has an anatomy hierarchy.

What terms are overlapping?

*Specifically, here the root of CARO, anatomical entity, encompasses material and immaterial material entity. The latter doesn't fit under material entity, subclass of BFO independent continuant, as it currently is in OBI.*

2) „We tried several modularization tools (Grau et al., 2007; Jimenez-Ruiz et al., 2008; Seidenberg, Rector, 2006; Sirin et al., 2007). All of them discarded annotations, resulting in modules containing only the class declarations and no annotation properties, such as labels or definitions."

It would be useful to describe how these modularization tools work.

At least it is not familiar to me that there are tools that can automatical extract submodules of an ontology in any useful way that would not require a lot of manual curation. And if on the other hand only a subhierarchy of terms is desired, it is unclear to me it should be difficult to do so while retaining the annotation properties.

*Modularization tools rely on specific algorithms aiming at extracting minimal modules while preserving entailments in the importing resource. As presented in the manuscript, this is currently an active area of research, and those tools are still in infancy. Detailed explanations depends on the tool considered and a complete review would not be possible within this paper, however specific information is available in the papers describing each tool.*

*The implementation we provide queries different resources via resource-specific SPARQL queries that allow us to be more flexible and retrieve selectively the information desired, for example retrieving annotation properties in resources using different schemes.*

As a minor point, the definition

Class: electroporation

SubClassOf: 'cell permeabilization'

and has\_specified\_input some cell

and has\_participant some 'power supply'

seems suboptimal. Since most cells do not survive the electroporation procedure, and a small minority actually successfully take up the vector, one uses hundreds of thousands of cells. I realize that this sort of thing is difficult to define in OWL, but perhaps there is a better solution?

*OBI is still evolving and we hope that this definition will improve with time. This is a typical example of class for which the textual definition is much more accurate than its logical restrictions.*

**---Review #2---**

Content revisions:

p.2, "In this instance, wholly importing such ontologies could lead to inconsistencies or unintended inferences.": I am not questioning the statement per se, but an actual example or a citation of a piece of work that actually shows this would make this statement more compelling than simply asking the reader to "trust us on this".

*We added a citation to Bernardo Cuenca Grau, Ian Horrocks, Yevgeny Kazakov and Ulrike Sattler, Ontology Reuse: Better Safe than Sorry, Proc. of the 2007 Description Logic Workshop*

p.5, Figure 2: 1) Shouldn't this figure precede all others, and be put near the Policy and Implementation sections?

*We moved the figure up as per the reviewer's suggestion.*

2) The diagram and the figure legend depict the SPARQL endpoint as a required component of a MIREOT mechanism. But isn't this really only an implementation detail of the MIREOT implementation for OBI? Couldn't I easily have an implementation that does not use a SPARQL endpoint, or are you suggesting that one should really have one for the ontologies one wishes to import from?

*We updated the legend to make it clear that we here refer to the OBI implementation of the MIREOT guideline, which relies on a SPARQL endpoint. Any other way to retrieve the information needed would be acceptable.*

p.6, " and IAO developers therefore chose to MIREOT it"

This is the first time that MIREOT, an acronym, is used as a verb. I think it's fine to introduce this as a convenient new short-hand jargon term, but this should be done explicitly somewhere before (maybe in Policy?) rather than surreptitiously.

*We agree and chose to remove use of MIREOT as a verb.*

p.7, first paragraph. I may be misreading or misunderstanding the text here, but it looks like no solution, not even an outline of what a solution could be, is presented. If this issue is currently

unresolvable, wouldn't that put a rather serious damper on considerations of adoption? What would it take to find a solution? If it is resolvable, restructure the paragraph so that this is clear.

*We restructured the paragraph as per the reviewer's suggestion to emphasize that we believe the tool solution to be the best way to proceed.*

p.7, second paragraph. There seems again be an implication that an implementation of MIREOT must include a SPARQL endpoint. It seemed earlier in the manuscript that this is an implementation detail; if it is indeed pretty much required for a sound implementation, that should be made clear early on.

*While a SPARQL endpoint is not absolutely required, we believe that it is the best way to have easy access, in a standard way, to the information needed, and would recommend using one whenever possible. Other options are possible, such as downloading external resources' files on a regular basis and parsing them locally. We added an explanatory sentence to the implementation section to make this clearer.*

p.7, " correct inference using the external classes is only guaranteed if the full ontology, or a module, is imported." It is not clear to me why that has to be true. Provided that the imported assertions are correct, how is it possible that these imply something in the target ontology that they would not imply in the source ontology? It is of course possible that the target ontology contains assertions that are in conflict with not imported assertions in the source ontology, but even if those conflicting assertions were imported, wouldn't the result only be conflict, but not "correct" inferences? I would in fact argue that if there can be no expectations in regard to correctness of inferences, the practical appeal of MIREOT would be substantially lowered. Please clarify if the statement in the text is correct, otherwise revise.

*We updated the manuscript to further explain that MIREOT is a lightweight import mechanism, and that by importing only parts of a resource we may be missing on axioms needed to preserve the full semantics of the source ontology.*

p.7, "In adding axioms, such as the subclass axiom when importing the external term, the aim is to only assert true statements." Why? I can imagine why (false assertions have a higher chance of contradiction in the source ontology?), but this should be explained rather than leaving the guesswork to the reader.

*We updated the text as per the reviewer’s suggestion.*

p.7, " In our experience with the better OBO ontologies, the denotation of the term, as explained in the definition or documentation, is clearer and more correct than the axiomatization." What are the "better OBO ontologies", and what makes them better?

*We here refer to the more mature OBO ontologies.*

Besides, the sentence doesn't make sense to me. How can something be less or more correct in logic reasoning, and how can a free-text definition be logically more correct than axiomatic statements?

*Curators tend to spend more time writing free text definitions (which are quicker and easier to formulate). Those therefore often have more semantically-correct information than their equivalent axiomatization.*

*We updated the text to reflect these.*

p.7, " If additional restrictions are required"

Restrictions such as? Not sure what you mean here.

*In some cases we may want to add extra logical restrictions on the imported terms that relate them to other OBI classes. This usage is however anecdotal and we removed this sentence.*

p.7, "When deciding to import an external term the textual definition is reviewed and, if required, discussion with the original editor is undertaken." Why? This seems to be a reaction or resolve to an encountered issue that is left unsaid.

Explicitly state what motivated this.

*When importing a term it is important to ensure that the term we decide to import actually matches the use we foresee in the target ontology. In some cases, even though the label and hierarchy of the term in its source ontology seemed to match our intended use, the textual definition was ambiguous. In order to avoid any error in our interpretation we prefer to consult with the original creators of the term. This example has been added into the text.*

p.7, " As we are importing from OBO Foundry candidate ontologies we have a community process for monitoring change" This sounds like people not importing from OBO Foundry candidate ontologies are going to be out of luck re: MIREOT. Are you indeed recommending that for now MIREOT is only practicable between OBO Foundry and its candidate ontologies? If so, this should be stated, along with why this is so.

*An important aspect of the MIREOT mechanism is maintaining the term's meaning, and ensuring that if it changes the term gets deprecated. We therefore recommend to use resources adhering to a deprecation policy, and consequently to consider OBO Foundry and candidates ontologies.*

*This statement has been added to the manuscript.*

p.7, "The current implementation of the MIREOT guidelines relies on command-line scripts, making it difficult for some curators to use." Be more specific about what the things or capabilities are that, if a curator lacks them, will make it difficult to use.

*We added the mention of needed programmatic skills.*

Minor typographical and stylistic revisions: […]

*We thank the reviewer for those, which have been corrected as suggested.*

p.2, "and the logical axioms need to be accurate.": This suggests that there are logical axioms that are inaccurate, which sounds like an oxymoron. If it's not, what distinguishes a logical axiom that is accurate from one that is inaccurate?

*Some axioms, while logically correct, represent inaccurate knowledge.*

p.2, first paragraph: Are "slims sensu OBO" also ontology modules? If yes, this should probably be mentioned, as a reader from the OBO community will surely wonder about that. In fact, if OBO slims are not, or not strictly speaking, ontology modules, that should probably be clarified therefore, too.

*OBO slims are sets of terms extracted based on user requirements for example, but they do not constitute a module stricto sensu, i.e. there is no check that entailments are preserved. We added a statement w.r.t. to OBO format resources in the future work section.*

p.3, "The logical URI" (3 times): What is the difference between a "logical URI" and a "normal URI"? Use a different term, or explain what criteria the URI needs to meet in order to be a logical URI.

*We added an explanation logical vs. physical URI to the text.*

p.5, "which are in turn mapped from the NCBItaxonomy." You probably mean the NCBI taxonomy \*ontology\*? BTW this ontology is not maintained nor endorsed by NCBI, and so should be cited with its URL.

*Updated based on instructions at http://www.ncbi.nlm.nih.gov/Taxonomy/taxonomyhome.html/index.cgi?chapter=howcite*

**---Review #3---**

This paper presents a very important and practical technique that will greatly benefit efforts to scale up the size of ontologies, increase collaboration, and avoid reduplication of effort in constructing ontologies.  I believe MIREOT represents an important early step in what may become a suite of next-generation tools for easily importing and reasoning with terms from external resources (potentially, even non-OWL resources).

Just a few comments (all minor):

p.1 identifier mapping systems are not only "error prone", but also create a new system that must be maintained, debugged, and evolved...as such MIREOT has a great advantage that it is not an outside software system that needs its own software lifecycle, but rather, it is built out of the same formalism (OWL) as the ontology itself.

*Indeed.*

p.2 It would be good to show quantitative benchmark data (or ref papers) for how many assertions are needed before tools like Protégé and Pellet begin to deteriorate/crash.

*We don’t have any reference of benchmark data. We rely here on our own experience with several resources, discussion with colleagues and general knowledge from users and developers of these tools.*

p.3 Oftentimes there will be a request made for a particular term in an existing ontology, but until the term is added, it will not have an id...does MIREOT support a "NoIDYet" option that might be used once an external group has agreed to add the term (but, say, doesn't have a good definition for it yet)

*We believe that in such a case this "NoIDYet" wouldn't be stable or unique enough to allow to unambiguously refer to one specific term in a specific resource, e.g., 2 terms are requested from the same resource. Instead we would rather see a mechanism allowing resources to quickly assign IDs to terms, even if those may not be fully curated yet. An early draft for this has been elaborated within the OBI project, under the name "Quick ID"*

p.6 Fig 3, It seems to me that exhaustively filtering unwanted superclasses via a list of disjuncts is a very heavy burden and unmaintainable for very complicated ontologies.  It wasn't clear to me whether the creation of the filter statement was automated (i.e., generated from the script).  My particular concern is when one is importing from an ontology with good terms and definitions, but whose structure is not stable or known by the importers.

*This is a very specific case: we wanted to import extra information from the NCBI taxonomy database, while stopping at a specific set of parent classes, which union defines the class organism in OBI. It has been a conscious decision from the OBI developers to restrict to this specific set of classes, and the script merely implements this decision.*

p.7 Just speculation, but perhaps an RSS update mechanism could be used to keep the SPARQL endpoint synced to the latest ontologies

*Only few resources currently publish their updates as RSS feed. Also this would require an incremental update mechanism on the triple store, and access to the specific triples that have been added/modified. The current server used in our case is updated nightly with distributions from the OBO Foundry website.*

p.7 Ideally, the source ontology would be able to discover when the importing ontology is making axiomatic assertions about its terms.

Again, this is speculation and might require some message passing/update mechanism.

I thought the use cases were realistic and the technical limitations were clearly stated.  Great paper.