Response to reviewers of

ICBO 2012 paper 31

Wanting what we don't want to want:
Representing addiction in interoperable bio-ontologies
Janna Hastings, Nicolas Le Novere, Werner Ceusters, Kevin Mulligan and Barry Smith

----
*** REVIEW #1
Overall score (out of 10): 7

Quality of work:

The authors discuss preliminary work on using a more or less existing framework of ontologies, that together, are intended to represent the range of entities that are the focus of addiction research. These entities would range from biochemicals to cognitive and behavioral symptoms that might be indicative of addiction.

→ that is correct

The "work" in the paper is an analysis rather than an empirical or descriptive study.

→ We do not understand why this reviewer placed quotes around the word "*work*". Is he arguing that performing an analysis is not work? Is he implying that an analysis is less scientific than an empirical or descriptive study? We did not spot any indication in the call for submissions that only empirical or descriptive studies are allowed. That would be strange since, after all, ontology development, the core of our work and a topic explicitly solicited for in the call for papers, requires a thorough analysis of the domain to be covered by the ontology.

The authors argue that the ontology framework has the potential to support very wide ranging queries across the various domains of addiction research. While certainly not an extravagant claim, the claim seems reasonable simply because there is no hard evidence to disprove it.

→ We believe this claim is reasonable because hard evidence for improved querying through ontology has been published in many other domains and in our paper we document how this works for addiction as well. That said, we do not follow this reviewer in his reasoning that a "claim seems reasonable simply because there is no hard evidence to disprove it"; we suggest this reviewer to study Russell's teapot argument: "*If I were to suggest that between the Earth and Mars there is a china teapot revolving about the sun in an elliptical orbit, nobody would be able to disprove my assertion provided I were careful to add that the teapot is too small to be revealed even by our most powerful telescopes*".

However, the authors appear to have in mind a certain conceptual framework for addiction which relies on causal assertions described in the work of Koob and Volkow. It is unknown to this

reviewer how valid the assumptions of this biochemical/molecular causal model are, or how completely substance addict ion is covered by this model.

→ The citation of Koob and Volkow is a recent review of the field, not a "certain conceptual framework" based on their "work". Section 3 of our paper represents a fairly consensus vision of the neurobiological basis of addiction. The role of the mesolimbic reward system in the addiction to drugs of abuse has been known for three decades, and has been confirmed by an overwhelming body of evidence from molecular biology to cognitive science, on human and animal models. Debates exist in the scientific community, but on points of details that are far out of the scope of this paper (e.g. respective roles of different monoamines, subcellular locations of the receptors, role of the genetic background etc.). For one of the authors, who spent 10 years working on nicotine addiction, this sentence feels very similar to let's say: "However, the authors appear to have in mind a certain conceptual framework for evolution which relies on causal assertions described in the work of Darwin. It is unknown to this reviewer how valid the assumptions of this genetic/molecular causal model are, or how completely evolution is covered by this model".

I am also concerned that the role of environment on addiction is never mentioned and this seems like a fairly significant ommission. Assuming the ontologies have complete coverage of symptoms, biological processes, and material entities, would that be sufficient to represent important elements of the broad scientific literature on addiction?

→ We absolutely agree with the reviewer that environment is not insignificant, in particular for the onset of addiction, where social interactions are very important. We mentioned it now in the paper. Nevertheless, it is not a major feature of the mechanism of addiction itself. Whatever the substance, once access is granted, the proportion of addiction is roughly the same, whatever the country or the social circle. The mean of absorption is the main difference. Added to section 'Representing Addiction'.

For example, many individuals who periodically use mind altering substances never present with addiction symptoms, while others may quickly move from simply trying the same substance to addiction as they come to rely on the substance to help them cope with traumatic issues which primarily result from environment (e.g., abuse, traumatic stress, sexual molestation, great personal loss). If it is true that environment is key component of addiction (or at least a significant modifying or confounding factor), then I think the authors would need to demonstrate how environment can be modeled in the proposed ontology framework.

→ The first example given by the author does not relate to the role of environment on addiction. According to the current scientific knowledge, the fact that "many individuals who periodically use mind altering substances never present with addiction symptoms" is primarily due to different genetic backgrounds.
The second example does not relate to addiction at all. The *use* of substance to cope with traumatic issues does not affect possible following addictions. The trauma just lowers the barrier to move from use to abuse. The abuse is due to the mind altering (euphoria, analgesia, amnesia etc.) effects of some of the substances, and as not much to do with their addictive properties.

Page 3, first column, "In particular, substance addiction is often characterised by repeated failed efforts to control or give up the use of the substance , in which case, we might say, the organism wants not to want to use the substance , or suffers a weakness of will (Stroud, 2008)." -- I would be concerned about how this statement will be received by the intended audience, especially because the citation that one would look to for further information is written by a philosopher rather than a mental health professional or an addiction scientist. While the aforementioned statement links the reader back to the title, I do not think that it adds anything to the logical flow of the writing. Its my understanding that many decades ago, starting about the time that Alcoholics Anonymous was achieving remarkable success with alcoholics, addiction began to be recognized as an complex illness involving psychological, physical, and spiritual (sic) components. This was a dramatic paradigm shift from the old conventional wisdom that addiction was a "will power deficiency". Thus, The authors' statement, unless more carefully presented, seems to be an anachronism.

→ We agree with the reviewer here, at least on the misunderstanding by a non-specialist public. Since the quotation [Stroud 2008] is not relevant for the paper, we removed it.

Page 3, second column, considering the use of DispositionToCauseAlteredMentalFunctioning. The explanatory statement below the definition that uses this term leads me to wonder if the would apply to children who are born addicted to drugs because of maternal drug use during pregnacy. What does "their life history" mean in this context. I think that is an issue because, as written, the statement "normal functioning" seems to imply a characteristic of the organism at the instance level rather than a characteristic of the organism at a class level. Is this intended? Another thing that might be worth considering -- if an athlete's "normal function" is healthy eating, excercise, and supplements, is this functioning altered if he/she becomes inadvertantly addicted to supplements that enhance performance (such as steroids)? What would be different about the athlete's functioning in this case? I think that there must be something that is different but I think that it would be challenging to model and suggests that the authors should spend some more time clarifying these meanings. Perhaps this type of addiction is not substance addiction as defined in Section 3 but it doesn't appear to fit as a "process addiction" either (though this phrase is not clearly defined in the paper).

→ We have changed to an axiom referring to reward-system-related mechanisms of action of addiction instead, which helps us later when we suggest that we might be able to link together the mental disease ontology with biochemical ontologies representing mechanisms.

My other concerns are below and in the "minor points" section of this review.

Quality of presentation: The paper is well presented. Minor points listed below.

1. Page 1, second column, last paragraph - "the Chemical Entities of Biological Interest ontology de Matos et al. (2010)" --> the ChemicalEntities of Biological Interest ontology (de Matos et al. 2010)

→ this has been corrected

l2. Page 2, first column, "While we will reserve the term 'addiction' to refer to the mental disease so defined, we emphasize that the term as commonly used is ambiguous between the disease and the disease course that results therefrom and which varies in type from patient to patient." -- Please simplify this sentence as it is hard to follow.

→ Done

3. "Such substances are described in databases such as DrugBank (Wishart et al., 2006) and included in ChEBI (de Matos et al., 2010)." -- This is of course true but I would expect that there is certainly an unknown number of substances that are not described in these resources. For example, the so called "bath salts" <http://www.webmd.com/mental-health/features/bath-salts-drug-dangers> include methylone, mephedrone, and pyrovalerone dirivatives. Neither methylone nor pyrovalerone appear in either ChEBI or DrugBank as a drug entity, while mephedrone is in ChEBI but not DrugBank. Moreover, there are always going to be new illicit drugs that neither of these resources have explicitly (especially DrugBank which, as I understand it, is only periodicly updated). Perhaps it would be appropriate to state that 1) many common chemical substances the people get addicted to are present in these resources and 2) ChEBI has the parent compounds from which many new illicit drugs are likely to be derived.

→ Done

4. I think that it would be nice if Figure 1 could be enlarged perhaps by moving the DSM-IV criteria to a table.

→ we did so Enlarged slightly, can't be made larger due to space restrictions

5. Page 4, column 2, "Sahoo et al. (200)" --> "Sahoo et al. (200???)" PROBLEM WITH CITATION

→ this has been corrected

*** OVERALL EVALUATION: 0 (borderline paper)
→ our paper was accepted, and the revised submission improved on all relevant points

*** REVIEWER'S CONFIDENCE: 2 (medium)
→ we agree

REVIEW #2
Overall score (out of 10): 9
Quality of work

This is a description of preliminary efforts to define addiction on the basis of the MFO. I found the first part of the text, in which ontological definitions are given that correspond to part of the checklist of the DSM-IV, quite interesting and well done. I suspect that the framework that the

authors are developing is a promising way of capturing information about mental diseases in ontologies, and look forward to seeing how this project progresses for other diseases.

→ we agree and will do so

The section on the biochemistry of addition does not add much to the paper, other than saying that there are terms from various ontologies that could be used to describe some of the components of addiction. However, no ideas are put forward on how to connect this with the clinical descriptions in the first part of the results (and indeed, this would be a very hard task at present). Optionally, I would encourage the authors to provide more detail in section 2 and less in section 3 (or provide a road plan of how to connect the biochemical aspects to the clinical aspects of addiction).

→ We have modified the paragraph in section 3 to hint at a roadmap for linking the disease to the mechanisms.

Quality of presentation
Minor points
'Following (Ceusters and Smith, 2010), we regard mental disease as a disposition to pathological processes rather than as itself an example of a pathological process.'
=> This definition seems very reasonable in the case of addiction, but perhaps less so for types of mental diseases such as dementia, in which there is a lack of the ability for the mind to perform „normal" mental processes such as remembering items. A disposition implies that there is some option as to whether an abnormal event occurs or not. This model is not really suitable for all types of mental disease. (This is a remark about something that is peripheral to the current paper and does not have to be addressed in the revision of the paper).

→ indeed, outside the scope of this paper. No further action taken, although we disagree in part with this reviewer's analysis: in the case of dementia, there are for sure pathological processes, for sure those that caused the brain to lose the cited ability.

"The key missing ingredient in this picture is the link from these annotations involving mechanism of action to the disease itself. This link will be created as a relationship has mechanism of action from the disease to the encompassing biological process that best describes the mechanism."
=> It should probably be stated that we are very, very far away from understanding the mechanism of most mental diseases such as depression or schizophrenia at anything but a very superficial level.

→ We certainly disagree about that. While we do not understand much of the etiology of those diseases (although a lot of progress has been made), we made enormous progress in understanding the symptomatology. The proof is that the two last decades showed much improved treatments. Anyway, there is no relation with our paper, so no further action taken.

*** OVERALL EVALUATION: 1 (accept)
*** REVIEWER'S CONFIDENCE: 3 (high)

*** REVIEW #3

Overall score (out of 10): 7

Quality of work

This is a well-reasoned and well-written paper that details the issues and approach to development of an application

→ thanks. We agree, though improved the final submission nevertheless.

Quality of presentation
Minor points
----
1. The title is too funky for my taste. I would drop the first phrase.

→ The title is funky on purpose, so we left it.

2. In the Introduction, the second paragraph sentence that starts 'The estimated death toll…' should more readably be constructed as 'In the year 2000, the estimated death toll…..'

→ Done

3. In the second sentence, first paragraph of discussion, missing a zero in Sahoo reference statement …(2000) rather than (200). This error repeated in the REFERENCES.

→ Done

*** OVERALL EVALUATION: 1 (accept)
*** REVIEWER'S CONFIDENCE: 3 (high)

*** REVIEW #4

Overall score (out of 10): 7

Quality of work : 7

The paper presents the preliminary work for the ontological framework for representing data on substance addictions.   Such framework is built leveraging the MFO (Mental Functioning

Ontology) - also presented, it seems for the first time, in this paper - and linking it with other existing ontology. It is certainly a good start that well fit this conference. However, the work will require some validation on the field in order to be proven really helpful.

→ that is correct, but not in the scope of this paper.

Quality of presentation: 8

The paper reads well and is mostly clear.

In the several examples (for instance the first snippet in section 2.3), the classes are all represented in the same format. It would be helpful to understand what comes from MFO and what is defined for the purpose of this work or elsewhere.

→ Added ontology-scope prefixes throughout all axioms. Not sure about some of them, though, as some of the named entities may be "mere" defined or anonymous classes in the end result? Especially the distribution of terms between MF (mental functioning ontology) and MD (mental disease ontology) is not clear to me.

To improve the readability I would suggest to spend a few words about the 'process profiles', While reading the linked document, I understand the explanation is not trivial but it is worth trying

→ Added a sentence of explanation.

Where is the relationship 'has mechanism of action' - introduced on page 4 - coming from? Is that a planned new relationship?

→ We have modified that paragraph to be less suggestive that there would be a single relationship and more vaguely set out a vision of the cross-ontology relationships that might be captured in the future using this framework.

- On page 1 (six lines above the section 1. title) the word 'addition' is probably 'addiction'

→ Done

- On page 4 (second line after section 4 title) the citation year is missing a digit.
→ has been corrected.

*** OVERALL EVALUATION: **1 (accept)**
*** REVIEWER'S CONFIDENCE: 3 (high)