Wanting what we don't want to want: Representing addiction in interoperable bio-ontologies

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ABSTRACT

Ontologies are being developed throughout the biomedical sciences to address standardization, integration, classification and reasoning needs against the background of an increasingly data-driven research paradigm. In particular, ontologies facilitate the translation of basic research into benefits for the patient by making research results more discoverable and by facilitating knowledge transfer across disciplinary boundaries.

Addressing and adequately treating mental illness is one of our most pressing public health challenges. Primary research across multiple disciplines such as psychology, psychiatry, biology, neuroscience and pharmacology needs to be integrated in order to promote a more comprehensive understanding of underlying processes and mechanisms, and this need for integration only becomes more pressing with our increase in understanding of differences among individuals and populations at the molecular level concerning susceptibility to specific illnesses. Substance addiction is a particularly relevant public health challenge in the developed world, affecting a substantial percentage of the population, often co-morbid with other illnesses such as mood disorders. Currently, however, there is no straightforward automated method to combine data of relevance to the study of substance addiction across multiple disciplines and populations.

In this contribution, we describe a framework of interlinked, interoperable bio-ontologies for the annotation of primary research data relating to substance addiction, and discuss how this framework enables easy integration of results across disciplinary boundaries. We describe entities and relationships relevant for the description of addiction within the Mental Functioning Ontology, Chemical Entities of Biological Interest Ontology, Protein Ontology, Gene Ontology and the Neuroscience Information Framework ontologies.

1 INTRODUCTION

Ontologies are increasingly designed to support scientific research through annotation and integration of research results, with the goals of enabling sophisticated querying and disambiguation of the terminology employed in scientific literature. Furthermore, ontologies, when designed with not only logical consistency but also faithfulness to reality in mind (Smith and Ceusters, 2010; Brochhausen *et al.*, 2011), help facilitate the translation of primary research into therapeutic endpoints by easing the transfer of knowledge between different specialist disciplines. In the various fields investigating mental health and related issues, the problem of terminology and integration is particularly severe, as much of the terminology employed refers to subjective experiences on the side of the patient and subjective judgements on the side of the caregiver, for which it is difficult to design standardised measurements across different disciplines and to integrate results arising from different methodological and technological approaches. Research into mental illness needs to be correlated with research on the associated canonical mental processes and with underlying biological and neurochemical pathways in order to better understand conditions and mechanisms of action, and ultimately to lead thereby to the discovery and design of novel therapeutics for challenging conditions (Ceusters and Smith, 2010; National Advisory Mental Health Council Workgroup, 2010).

Addiction is a primary mental health problem affecting an increasing percentage of the population in the developed world (National Institute on Drug Abuse, 2007). In the year 2000, the estimated death toll due solely to use of tobacco was around 5 million worldwide (Ezzati and Lopez, 2009). Furthermore, addiction is often co-morbid with other mental health conditions such as bipolar disorder and depression. We will limit the ensuing discussion to substance addiction, leaving process addictions (such as addiction to gambling) to one side. The DSM-IV description for patients with alleged substance addiction (or dependence) reads: *'When an individual persists in use of alcohol or other drugs despite problems related to use of the substance, substance dependence may be diagnosed. Compulsive and repetitive use may result in tolerance to the effect of the drug and withdrawal symptoms when use is reduced or stopped.' (APA, 2000).*

While the DSM, controlled vocabularies such as SNOMED CT and patient classification systems such as ICD include references to various sorts of mental illness, as yet none of these provides the facility to smoothly interlink the results of relevant related research from different domains such as psychology, psychiatry, biology, chemistry and neuroscience. The OBO Foundry (Smith *et al.*, 2007) promotes the development of interoperable domain-specific public domain ontologies that – in contrast to the above-mentioned resources – can be interlinked with bridging relationships that have been termed *cross-products* (Mungall *et al.*, 2010). Within each domain, the domain-specific ontology is applied to annotation of research results. For example, the Gene Ontology (The Gene Ontology Consortium, 2000) is used to annotate gene products, the Chemical

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Entities of Biological Interest ontology (de Matos *et al.*, 2010) is used to annotate chemicals. Bridging relationships (for example, chemical participation in a biological process) then are able to span different resources based on the relationships between the ontology entities. This strategy allows automated reasoning to retrieve relevant results across disciplines with different primary entities and annotation standards – without necessitating that each resource provide additional primary annotation to the ontologies which are outside of its core domain.

The purpose of this paper is to illustrate such a framework for the overlapping disciplines of mental health, mental illness and chemical biology, focusing on data pertaining to addiction. In the next section, we discuss the definition and symptoms of addiction, and how these can be described in ontologies of mental functioning and disease. Thereafter, we describe how underlying mechanisms of action for addiction and the substances which are the objects of addiction are described in other bio-ontologies. Finally, we discuss the framework in comparison to related work and prevailing methods.

2 REPRESENTING ADDICTION

Addiction is an example of a mental disease. 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 can be seen as corresponding to the sense in which a patient with nicotine addiction is still addicted even if he has not smoked in the last week, and for some severe addictions such as heroin, relatively few substance use events can be enough to confer the addiction for the remainder of the patient's life. The process of ongoing substance use by an organism eventually results in changes to the organism such that the disposition – the addiction – is created. In the remainder of this paper, we will use the term 'mental disease' exclusively as a technical term in this sense, and use 'mental disorder' to denotes the physical basis that brings a mental disease into existence and 'mental disease course' for the totality of processes that realizes a mental disease (Scheuermann *et al.*, 2009). We will reserve the term 'addiction' to refer to the mental disease so defined, although in common language 'addiction' is ambiguous: it can be used to mean either *the disease* or *the disease course* (the latter being something which varies in type from patient to patient, for example according to presence or absence of treatment).

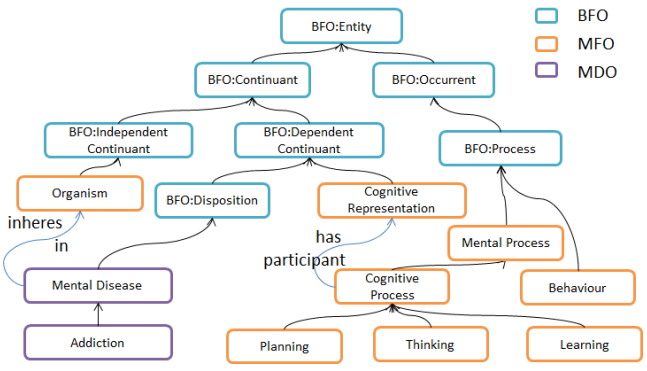

Fig. 1. Upper levels of the Mental Functioning Ontology

In what follows, we will work within the Mental Functioning Ontology (MF) as the context for our representation. MF is an ontology for all aspects of mental functioning, including mental processes such as cognition and traits such as intelligence (Hastings *et al.*, 2012). Disorders and diseases of mental functioning are included in a separate module, the Mental Disease Ontology (MD). They are being developed beneath the upper-level ontology Basic Formal Ontology (BFO) (Grenon and Smith, 2004). Figure 1 illustrates the upper levels of the ontologies.

2.1 Types of Addiction

The type *substance addiction* can be further refined by reference to the substance that determines its subtypes. Such substances are described in databases such as DrugBank (Wishart *et al.*, 2006) and included in ChEBI (de Matos *et al.*, 2010). Although these resources may not be fully comprehensive, many common addictive substances are already included, and the bulk of addictive substance chemistry is represented in ChEBI in the form of parent compounds from which many new illicit drugs are likely to be derived.

Addiction is a disposition to, *inter alia*, use of the substance in question. Substance use is characterised by intake of some sort (eating tablets or injecting fluids, for example). We can describe substance use as a bodily process that has as participant some portion of the substance in question (OWL Manchester syntax (Horridge and Patel-Schneider, 2009)):

MF:Nicotine Use `subClassOf` (*MF:Bodily Process* `and` **hasParticipant**[1] `some` *CHEBI:Portion of Nicotine*)

CHEBI:Portion of Nicotine `subClassOf` (*CHEBI:Chemical Substance* `and` **hasGranularPart**[2] `some` *CHEBI:Nicotine Molecule*)

MD:Nicotine Addiction `subClassOf` (*MD:Addiction* `and` **isRealizedIn**[3] `some` *MF:Nicotine Use*)

This description is necessary, but certainly not sufficient to *define* substance use, as there are many bodily processes in which substances participate that would not qualify as substance use (for example, accidental inhalation of secondary smoke). However, the axiom nevertheless serves as a link between 'addiction' and 'nicotine' that can be reasoned over.

2.2 Symptoms of Addiction

Addiction – or rather, in our terminology, the disease course of addiction – is described in the DSM-IV as having the following symptoms, three or more of which in a 12 month period are required for a positive diagnosis (APA, 2000):

1. Preoccupation with use of the chemical between periods of use.
2. Using more of the chemical than had been anticipated.
3. The development of tolerance to the chemical in question.
4. A characteristic withdrawal syndrome from the chemical.
5. Use of the chemical to avoid or control withdrawal symptoms.
6. Repeated efforts to cut back or stop the drug use.

[1] **hasParticipant** is defined in (Smith, 2012), section entitled 'Relation of participation'.

[2] As described in (Batchelor *et al.*, 2010), we follow (Bittner and Donnelly, 2006) in using **hasGranularPart**, a sub-property of **hasPart**, to link bulk portions of chemical substances to the molecules from which they are composed.

[3] **isRealizedIn** is defined in (Smith, 2012), section entitled 'Relation of realization'.

7. Intoxication at inappropriate times (such as at work), or when withdrawal interferes with daily functioning (such as when hangover makes person too sick to go to work).
8. A reduction in social, occupational or recreational activities in favor of further substance use.
9. Continued substance use in spite of the individual having suffered social, emotional, or physical problems related to drug use.

Cognitive processes are mental processes that manipulate cognitive representations, such as thinking and planning. Many of the symptoms listed above can be characterised in part as mental processes, and in part as behaviour. Preoccupation with use of the chemical is an uncontrolled form of *thinking* about the chemical – a cognitive process. Using more of the chemical than had been anticipated is behaviour (using the chemical) as well as an implicit description of a historical anticipation or *plan* for how much of the substance to use (even if the plan involved is very vague, e.g. 'use less' or 'try to quit'). While tolerance and withdrawal are best characterised in physiological terms, deliberate use of the chemical to avoid or control withdrawal symptoms is again behaviour, as are repeated efforts to cut back or stop the drug use. Similarly, interference of intoxication or withdrawal in daily functioning, reduction in social or other activities in favour of further substance use, and continued substance use in spite of related problems suffered, can all be characterised as contrasts between behaviour affected by substance use and what would have been the canonical or normal behaviour of the organism. 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.

In what follows we sketch how some of the symptoms can be represented with explicit relationships to mental functioning terms, which will allow bridging from disease annotations to annotations of research into normal mental processes.

2.3 Thinking

The primary altered form of thinking that is characteristic of addiction is the preoccupation, in which the content of the thinking process is use of the substance in question:

MF:Thinking `subClassOf` *MF:Cognitive Process*
MF:Preoccupation With Substance Use `subClassOf` (
  MF:Thinking `and` **hasParticipant** `some` (
    MF:Cognitive Representation `and`
      isAbout[4] `some` *MF:Plan to Use Substance*))

Missing from the above description is a characterization of the thinking process that merits the description 'preoccupation'. In order for a thinking process to be described as a preoccupation, it needs to be *regularly recurring* and be *uncontrolled*. It is implied that the patient cannot help undergoing this thought process, despite the existence of efforts to think about other things instead. These attributes of the thinking process are *process profiles*. Process profiles are structural dimensions of processes, such as rates and other attributes, recently introduced in BFO 2 (Smith, 2012).

[4] **isAbout** is defined in the Information Artifact Ontology (IAO, Ruttenburg *et al.* (2012)) as that relation which holds between a representation and the entity that it is a representation of.

2.4 Planning

Planning is a cognitive process that has as output a realizable plan that the organism develops about its own future behaviour. The plan is realized if the corresponding behaviour is executed.

MF:Planning `subClassOf` *MF:Cognitive Process*
MF:Planning Substance Use `subClassOf` (*MF:Planning*
  `and` **hasParticipant** `some` (*MF:Cognitive Representation* `and`
    isAbout `some` *MF:Plan for Quantity of Substance to Use*))

Here, the *Plan for Quantity of Substance to Use* would be, for the individual, further specified in terms of the quantity of the substance and a time-frame over which the quantity is to be distributed. For example, a plan could involve a specification such as *'I want to smoke no more than five cigarettes per day'*. Planning is also implicated in the symptom where the use of the chemical is taken to avoid or control withdrawal symptoms. Here, though, the plan, to control withdrawal symptoms, is in fact realized.

2.5 Behaviour

Most of the processes described in the list of symptoms are behaviour, and most of these have to do with taking the substance in question. This is in itself unsurprising, since the DSM-IV is designed as a tool to aid diagnosis, and behavioural symptoms are those which are easiest to observe. A further elucidation of the use of the substance in question could include the following:

MF:Substance Use `subClassOf` (*MF:Behaviour*
  `and` **hasParticipant** `some` *CHEBI:Addictive Substance*)
CHEBI:Addictive Substance `subClassOf` (
  CHEBI:Portion of Chemical Substance `and`
    hasDisposition `some`
      CHEBI:Disposition to Alter Reward System Functioning))

Here, *Disposition to Alter Reward System Functioning* needs to be further annotated in the ontology by reference to the various known *mechanisms* by which addictive substances alter the functioning of the brain reward system (Berridge and Robinson, 2003). We discuss some of these mechanisms in Section 3.

2.6 Linking the symptoms to the disease

It is important to note that the existence of any of the above symptoms in isolation does not imply the presence of an addiction, in particular as some of them may also be symptoms of different diseases. Neither does addiction imply the existence of any one of the symptoms, as only a subset of symptoms need be present. Therefore we cannot assert an existential restriction on a relationship between the symptoms and the disease without creating incorrect implications (Boeker *et al.*, 2011). Rather, the inference from symptoms to disease is made on the judgement of a clinician in the case of a *particular* patient (Ceusters and Smith, 2006). Nevertheless, we can assume – if the DSM-IV criteria are taken to be correct – that there are at least *some* cases of addiction in which *some* of these symptoms are displayed as manifestations of the disease. To link the symptoms and the disease for purposes of automated reasoning, we could create a subtype of the disease which displays the relevant symptom, for example:

MD:Addiction with Preoccupation `subClassOf` (*MD:Addiction*
  `and` **realizedIn** `some` *MF:Preoccupation With Substance Use*)

This strategy will allow the symptoms of mental diseases to be linked to the corresponding 'normal' mental functionings such as ordinary thinking and planning, thus enabling automated retrieval of relevant results across the boundary of research into normal and

abnormal functioning. However, DSM-IV does not refer explicitly to any information at the biochemical or neurobiological levels of description. The next section addresses this shortcoming.

3 BIOCHEMISTRY AND NEUROBIOLOGY

Substance addictions are caused by the highjacking of the reward system of the brain (Koob and Volkow, 2010). This system, part of the basal ganglia, is a crucial relay of the cortico-striato-thalamic loop, involved in learning, motivation and control of voluntary locomotion. Most psychostimulant drugs of abuse – the mechanism of action for depressants such as alcohol is slightly different – stimulate the global activity of the mesocorticolimbic dopamine system, causing an increase of extracellular dopamine in the striatum. The exact mechanism to achieve this differs from substance to substance: nicotine mimics acetylcholine and stimulates the release of dopamine; cocaine and amphetamine inhibit the re-uptake of dopamine; dopamine agonists – such as those used to treat Parkinson's disease – mimic dopamine; while opioids, cannabinoids and caffeine amplify the effect of dopamine receptors by mimicking respectively the effect of enkephalines, anandamine and adenosine.

As a consequence of these effects of substance use, the mesocorticolimbic system adapts to the drug intake, through molecular, cellular and tissular mechanisms, causing withdrawal symptoms when the drug consumption is interrupted. Onset and maintenance of addiction involves the response of neurotransmitter receptors to the drug, recruitment of signalling pathways and disregulation of transcription factor cascades, but also chromatine remodeling via histone modification (Robison and Nestler, 2011). This leads to a complete cell reprogramming of the dopaminergic neurons and their targets, including protein production and targeting, synapse generation and dendritic remodeling.

This mechanism of action can be amply described using existing ontologies such as the Chemical Entities of Biological Interest Ontology (CHEBI, de Matos *et al.* (2010)), Protein Ontology (PR, Natale *et al.* (2011)), Gene Ontology (GO, The Gene Ontology Consortium (2000)), NeuroLex and BIRNlex (Bug *et al.*, 2008). For instance, when a portion of heroin is consumed, the molecule heroin (CHEBI:27808), participates in a binding process (GO:0031628), to μ-opioid receptors (PR:000001612). Similarly, when a portion of tobacco is smoked, the molecule nicotine (CHEBI:27808), participates in a binding process (GO:0033130), to nicotinic acetycholine receptors (GO:0005892). Those receptors are present on the dopaminergic neurons (NeuroLex – nlx:144018), of the nucleus accumbens, described in BIRNlex (birnlex:727).

Heroin is assigned to the 'biological role' class 'μ-opioid receptor agonist' (CHEBI:55322). As described in (Batchelor *et al.*, 2010), ChEBI biological roles are functions that are realized in biological processes, in this case 'regulation of opioid receptor signaling pathway' (GO:2000474), in which process both the chemical and the μ-opioid receptor participates. Those receptors are present on the striatal medium-sized spiny neurons (NeuroLex – nifext:141), of the nucleus accumbens, described in BIRNlex (birnlex:727). This binding potentiates the dopamine (CHEBI:18243) receptor (PR:000001107) signaling pathways (GO:0007212). In particular, the protein kinase A signaling cascade (GO:0010737) activates the transcription factor CREB (PR:000005854; GO:0032793).

Furthmore, the entire opioid signaling pathway is described in the pathway database Reactome (Matthews *et al.*, 2009) (REACT_15295), and some models of the relevant signaling pathways are present in the BioModels (Li *et al.*, 2010) database (e.g. BIOMD0000000153, MODEL9079740062). In both resources, the processes are annotated by GO terms and the physical entities.

These inter-ontology interlinkages to describe the biochemistry and neurobiology of addiction facilitate enhanced querying across all resources in which any of the ontologies are applied as annotations. For example, rather than querying pathway databases for heroin alone, a query can retrieve results for all molecules that act with the same mechanism of action. 22 molecules have **hasRole** 'μ-opioid receptor agonist' (CHEBI:55322) in the January 2012 release.

The key missing ingredient in this picture is the link from these annotations involving mechanism of action to the disease itself. Linking entities in ontologies describing mental disease to the entities described in ontologies for the underlying mechanism of action, which are in turn linked to ontologies for biological entities such as chemicals and proteins, will allow automated retrieval of biological knowledge in relevant databases and automated linking of these data to the corresponding medical and psychiatric data for addiction, facilitating the translation of basic research into clinical applications. Such links will take the form of ontology cross-products linking specific types of addiction to specific known pathways (biological processes), representing the best of current scientific knowledge.

4 DISCUSSION

Interlinking of entities across different domains has been popularized in Semantic Web approaches. For example, Sahoo *et al.* (2008) provide an ontology-based semantic 'mash-up' of nicotine dependence related pathways and genes. While our approach is compatible with use within the Semantic Web, it is not restricted to such usage, and the ontologies we mention are in most cases already being applied to many different application scenarios including primary data-driven research. Ontology annotations are becoming an essential tool in life sciences data management and comparison, and have been used to compare systems biology models as a clustering method for retrieval (Schulz *et al.*, 2011).

Existing lexicons in the domain of mental functioning and disease have by and large been designed with one application or community in mind, and the result has been the proliferation of distinct and overlapping ontologies, none of which is appropriately interlinked in the way we have described for addiction, and in which the classification of entities has been ad-hoc and application-specific. A search for 'addiction' in BioPortal returns 12 exact matches from different vocabularies and 462 partial matches and synonyms. Yet, none of these occur in contexts where the disease is explicitly related to its mechanisms of action or symptoms in the fashion we have described. Mental processes such as thinking and planning are also described in multiple resources, for example the Cognitive Atlas (Poldrack *et al.*, 2011), but this resource does not include a term for addiction (although it does in fact include a task for the measurement of nicotine dependence, not related to any cognitive terms). The NIF vocabularies include terms for mental disorders such as heroin dependence (nlx:89410) and opioid-related disorder (birnlex:12713), but do not link these to the chemicals in question nor to any of the other related vocabularies. In short, the proliferation of standard vocabularies within specific domains and application scenarios has hindered rather than facilitated data integration and enhanced querying thus far.

Following the OBO Foundry approach and creating an interlinked framework of ontologies will address this issue, allowing annotations to be exploited in a cross-disciplinary fashion without requiring that data maintainers provide annotations outside of their own discipline. The framework we have described surrounding the Mental Functioning Ontology will interlink the domains of neuroscience, psychology, medicine and biochemistry. The work here described is in the preliminary stages and future work will involve making the cross-linkages between the ontologies available as mapping files and extending the approach to other subject areas than addiction.

5 CONCLUSION

A new generation of bio-ontologies are increasingly interlinked, in support of a new holistic methodology for data-driven science that focuses on what data are about rather than on narrow disciplinary boundaries. Addiction is a public health condition of particular severity in the developed world. Our approach is to facilitate research through interdisciplinary data aggregation and interoperability. We have shown that interlinked ontologies allow this aggregation in an automated fashion, enabling discoverability across disciplines.

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