miRNAO: An Ontology Unfolding the Domain of microRNAs

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Abstract. We describe here an application ontology for microRNAs, written in OWL, which is also available in the OBO format. The miRNAO is freely available and it abides by the OBO Foundry's principles and rules such as full technical definitions of terms and complete *is_a*. It is based on the Basic Formal Ontology and it entirely follows the principle of orthogonality: almost 100% of the terms in the ontology have been imported from other ontologies and new relations have been included for them. This results in a maximized interoperability for databases using miRNAO for annotation or other functions. Moreover, this also facilitates data annotation and database development. The ontology can be accessed in repositories such as the OBO Foundry and the NCBO BioPortal, and it is free for use to drive pertinent databases or to serve any other purpose in information technology.

Keywords: microRNAs, Ontology

1 Introduction

Ontologies are widely recognized as informatics tools that help describe a domain in a way that is understood by both computers and humans. Thus, machines and software using such enhanced comprehension tools are in position, among others, to perform more efficient searches of domain-specific databases. Moreover, if ontologies are widely adopted by database designers, interoperability between different databases is achieved, enhancing this way the power of knowledge sharing [30]. In life sciences, the most successful ontology in terms of its usage is the Gene Ontology (GO) [2], which was initiated with the explicit goal to "unify biology". Whether this goal was, or will ever be achieved remains to be seen, yet, the fact is that in the fewer than 15 years since the GO was made available in its first version over 96 million annotations in 347778 species have been performed using the GO [35].

The fast adoption of the GO by the genome annotating community was the catalyst that led, early on, to the establishment of the OBO Foundry [33], a loose

consortium of groups and scientists involved in the construction of bio-ontologies. The OBO Foundry set up rules that govern the development and the architecture of these tools and played a key role in the development of OBO-Edit [6], a software application that facilitates the construction of ontologies using the OBO Flat File Format [26]. By December 11, 2013, the OBO Foundry listed in its web site 128 open biological and biomedical ontologies, while 368 ontologies, partially overlapping with the former set, can be found in the NCBO Bioportal [38], a resource of the National Center for Biomedical Ontologies. In addition to their "classical" function in advancing the efficiency of databases through enhanced searches and interoperability, bio-ontologies have also provided improvements in other areas. The most prominent example for this is the fact that genetic/genomic databases cooperating under the umbrella of GMOD [34] decided to develop and use the Chado database schema [27], which is completely dependent on ontologies for operation.

For the last few years our group has been involved in the development of ontologies for the domain of vector-borne diseases and their arthropod vectors [36]. The fact that microRNAs (miRNAs) are now being recognized as potential molecular "mediators" of dengue infection [11, 21], but also as potential tools for dealing with some aspects of that same disease [16, 17], led us to the decision to develop an ontology of microRNAs. Although a specific Ontology of miRNA Targets prediction (OMIT) does exist [20], no such dedicated tool is publically available for miRNAs as such; as a matter of fact, OMIT concentrates on the potential roles of miRNAs in (human) cancer. A general ontology for RNA (RNAO) does also exist [19], but as declared in its home page[4], its aim is general, i.e. to "...[capture] all aspects of RNA - from primary sequence to alignments, secondary and tertiary structure from base pairing and base stacking to sophisticated motifs"; miRNA-specific information is, thus, not to be found in the public domain. This is in contrast to the number of miRNA-specific databases (including their targets), which may well exceed 10, and which cover either general miRNA and miRNA target information such as, for example, miRBase [15], miRGEN 2.0 [1] and TarBase 6.0 [37], or organism specific ones such as PMRD for plants [40] and mirFANs [24], a specific database for *Arabidopsis thaliana* miRNAs.

In order to provide an additional tool for the "unification" of miRNA research, we developed the miRNA ontology (miRNAO), and describe it here.

2 Methodology

For the construction of the ontology, we have used Protégé[5], a popular open-source ontology editor.

In the biomedical domain, the vast majority of ontologies are structured according to the OBO Flat File Format [26]. However, in the Semantic Web community, the Web Ontology Language (OWL) specifications [25] are recommended by the World Wide Web Consortium (W3C) as a standard for developing

[4] `http//www.rnao.org`
[5] `http://protege.stanford.edu`

Ontology (Prefix)	Terms in miRNAO	Percentage
Sequence Ontology (SO)	348	51.5%
NCBI organismal classification (NCBITaxon)	261	38.6%
Gene Ontology (GO)	28	4.2%
Basic Formal Ontology (BFO)	16	2.4%
RNA Ontology (RNAO)	9	1.3%
miRNAO-specific terms (miRNAO)	5	0.7%
Chemical Entities of Biological Interest (ChEBI)	4	0.6%
Gene Regulation Ontology (GRO)	2	0.3%
NCI Thesaurus (NCIThesaurus)	1	0.1%
Ontology for General Medical Science (OGMS)	1	0.1%
Ontology for Biomedical Investigations (OBI)	1	0.1%

Table 1. Origin and number of the terms included in the miRNAO. The percentage refers to the total number of terms in the miRNAO.

ontologies across different domains of research. Due to the high expressivity and the well-defined semantics of the OWL syntax, the miRNAO has been developed using that language, but a version in OBO format is also available upon request. That version is not the product of primary development, but it has been engineered using the OWLtoOBO conversion tool that we previously developed [8].

The miRNAO was constructed as a true application ontology. The purpose was that it can be applied to any database, or related tool, that contains or uses information on microRNAs as well as the regulation of gene expression that these mediate. As such, one of our main goals while developing miRNAO was to facilitate interoperability and reusability across different knowledge areas. A common practice in order to achieve interoperability is to rely on a more generic ontology that defines the upper concepts. The more specific classes of the application ontology would then be classified at lower levels. Ontologies that share a common upper layer can then be used for the exchange of information more easily. The Basic Formal Ontology (BFO) [14], a generic, domain independent ontology, is one of the most popular upper level ontologies used in the biomedical domain for such purposes. Having been used by several bio-ontologies as an upper layer ontology (as for instance, at the RNA ontology (RNAO) [19], which was initiated by the RNA Ontology Consortium [23], the Gene Regulation Ontology (GRO) [4] and the Ontology for Biomedical Investigations (OBI) [5]), we chose as well to rely on BFO for the upper concepts of miRNAO.

The miRNAO is freely available for browsing and downloading at the NCBO Bioportal[6] and the OBO Foundry[7].

[6] `http://bioportal.bioontology.org/ontologies/MIRNAO`
[7] `http://obofoundry.org/cgi-bin/detail.cgi?id=miRNAO`

3 The miRNA Ontology (miRNAO)

3.1 The miRNAO basics

Many of the concepts that are required to express the information regarding miRNAs, such as the processes they're involved in, have been previously defined by other popular ontologies. Therefore, an additional decision we had to make before developing the miRNAO was whether we should use new identifiers (IDs) and, most importantly, definitions for these concepts or "borrow" the existing ones from other broadly known ontologies, specifically ontologies listed by the OBO Foundry. In the first case, we could offer definitions that, potentially, best describe the concepts for people actively working with miRNAs. In the second case, i.e. the tedious procedure of identifying and using the identical terms incorporated in other bio-ontologies, as also dictated by the OBO Foundry rules [12], we would make sure that all terms in the miRNAO would provide interoperability among different knowledge domains. We decided to follow the latter road. To do this we used the MIREOT (Minimum Information to Reference an External Ontology Term) approach [39]. Besides the terms that come from BFO together with their IDs, the IDs of the remaining terms of miRNAO are obtained from ten popular ontologies. These are the Sequence Ontology (SO) [9], the NCBI Organismal Classification [10], the NCI Thesaurus [32], the Gene Ontology [2, 35], the RNA Ontology [19], the Chemical Entities of Biological Interest [7], the Gene Regulation Ontology [4], the Ontology for Biomedical Investigations [5] and the Ontology for General Medical Science [13]. The exact number of borrowed IDs from each of the aforementioned ontologies is shown in Table 1.

In total, 671 out of the 676 terms (i.e. ∼99.3%) of the miRNAO are defined using shared IDs, while 2 terms (*DNA Sequence* and *RNA Sequence*) have their definition imported from the NCI Thesaurus along with a cross-reference to this controlled vocabulary (i.e. without importing their IDs from it). The reason for this is that no OBO Foundry ontology lists these two classes, which, we thought, had to be listed in the miRNAO. Furthermore, while the term *Transcription Factor* is listed by the Gene Regulation Ontology, we disagree with the term being listed as a child of *Protein*, maintaining that *Transcription Factor* is a *Role* and not a *Material Entity* (it should be noted that throughout this report classes, terms and relations are always indicated in italics). Of course, although this decision follows the Aristotelian reasoning (no multiple *is_a* relations), this matter is something that could (or, better, should) be later unequivocally solved by the community.

However, merging the necessary terms from the aforementioned ontologies does not suffice, in order to express all the information regarding the function of miRNAs. Indeed, the borrowed terms would remain unrelated if we used them exactly as they were defined in the originating ontology. Since the goal of miRNAO is to express this additional information that describes the processes in which miRNAs participate and the results of their interference, new relationships have been used to link terms among these different ontologies that would otherwise be unrelated. These new relationships are capable of expressing the

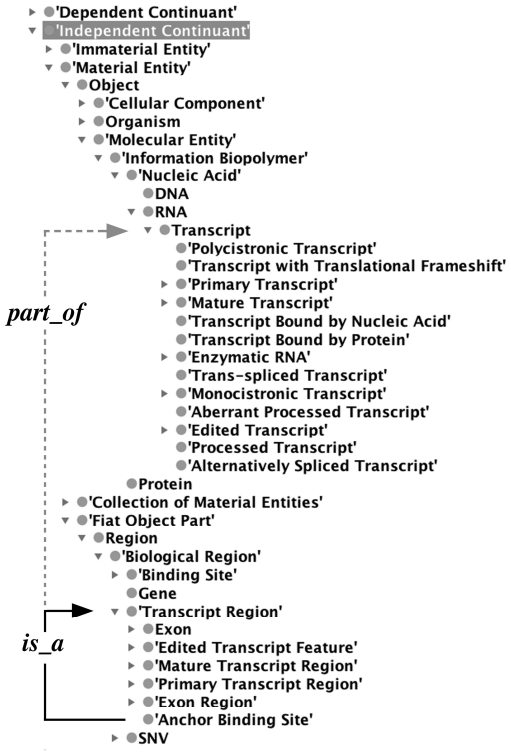

Fig. 1. Summary of the children terms of the class *Material Entity* showing *Object*, *Collection of Material Entities* and *Fiat Object Part*. The arrows point to the example mentioned in Section 3.2 (black arrow: *is_a* path, grey, stippled arrow: *part_of* path of the *Anchor Binding Site*).

additional information and enable the extraction of the latter when populating a miRNA database according to miRNAO. A detailed example of this fact is provided in Section 3.2. It should also be noted that two of the ontologies we used for the construction of the miRNAO, namely ChEBI and GO, have recently undergone "mutual editing" in order to achieve a consistent representation of shared terms at both the chemical and the biological level [18].

3.2 The structure of the miRNAO

Since the miRNAO follows the adopted structure of the BFO, all terms are classified under the BFO's two upper classes, namely *Continuant* and *Occurent*. Continuants consist of *Immaterial Entity* and *Material Entity*; the latter class contains different kinds of *Objects* and is one of the most heavily populated classes. This is due to the dense population of the class *Molecular Entity*, which comprises *Nucleic Acids* and *Proteins*. Regarding *Nucleic Acid*, a very detailed

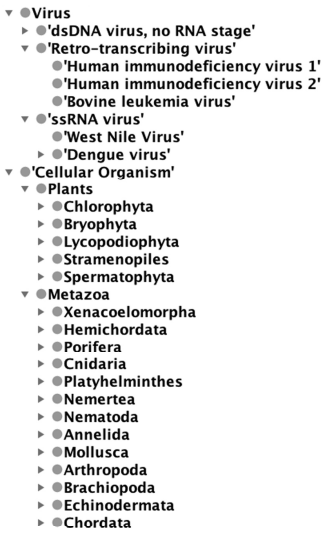

Fig. 2. The *Organism* path in the miRNAO.

hierarchical structure containing 266 terms is provided under the term *RNA* giving the ability to distinguish RNAs among the different existing types. A summary of the *Molecular Entity* sub-hierarchy is shown in Figure 1. It is apparent that in contrast to the heavily populated *RNA* class, *DNA* and *Protein* have no children. This is so in order to keep the ontology relatively simple. Of course, should we obtain feedback requiring specific children in these two classes, we will populate these easily.

Besides the description of the different types of nucleic acids, specific parts of these molecules are also of great interest when expressing or annotating information on miRNAs. For instance, when describing the regulation induced by a miRNA, researchers need to capture the information regarding its *Target Site*, which is a part of a messenger RNA. Such parts of *Material Entity* (as a rule, RNA), which are required to be conceptualized within the ontology, are classified as descendants of the class *Fiat Object Part* and are related to their corresponding *Material Entity* by using the relation *part_of*. For example, the term *Anchor Binding Site*, imported from the SO, has a *part_of* relation relative to *Transcript* (grey, stippled arrow in Fig.1), but an *is_a* relation relative to *Transcript Region* (black arrow in Fig. 1). The class *Collection of Nucleotide Residues* is also used to refer to a secondary structure of a nucleic acid such as, for example, the *Internal Loop* or the *Stem Junction* of a *pre-miRNA*; all of these terms also have *is_a* paths to *Material Entity*.

Figure 2 shows a summary of the descendants of class *Organism* (the second child of *Object*); these are organisms in which miRNA-induced regulation of gene expression has previously been described (stand December 2013) and all of them have been imported from the NCBI Taxon controlled vocabulary. The

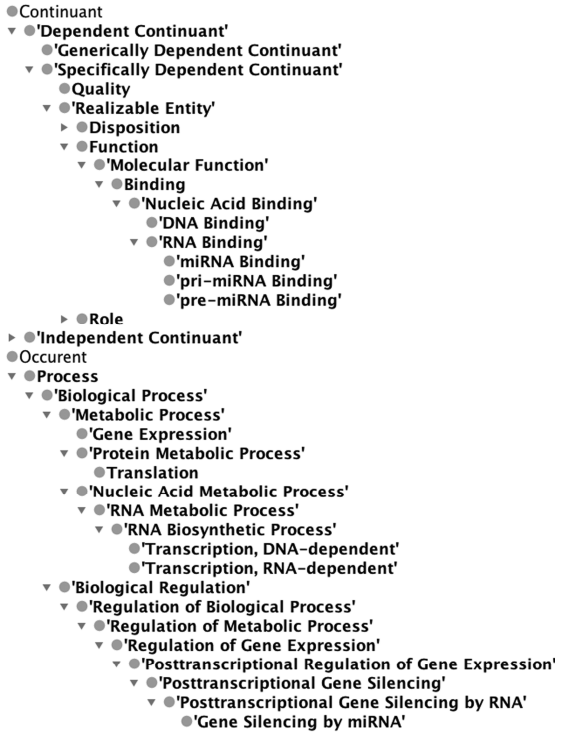

Fig. 3. The classes *Process* and *Function* in the miRNAO. The complete paths are shown for these two classes in all cases relating to RNA and shown in the ontology.

terms presently include 33 viruses, 106 animal species, 74 plants and one amoeba. It is planned to update regularly the organism class, as more species are reported in the miRNA published literature.

The main feature of miRNAs that also needs to be captured by an ontology is that of their function and the biological processes that they are involved in; the corresponding paths in miRNAO are shown in Figure 3. The function of these RNA molecules is obviously their binding to messenger RNAs, resulting in translational repression or in target degradation [3]. This function (*Binding*) is fully expressed in miRNAO, regardless of whether it refers to a binding of a pre-miRNA, a pri-miRNA or a mature miRNA. The class of *Function*, alongside with *Disposition* and *Role*, comprise together the term *Realizable Entity*. Figure 3 also shows the actual processes miRNAs are involved in, listed as a direct child of *Occurent*. Here, we have included all biological processes that miRNAs take part in, or interfere with. These include processes entailing *Biological Regulation* and *Metabolic Process*; they were all taken over from the GO.

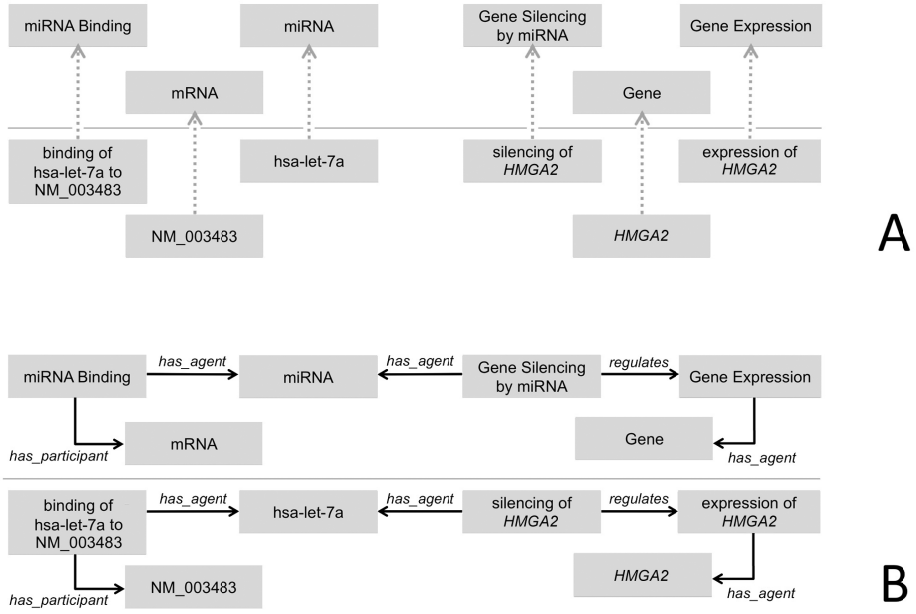

Fig. 4. A model of miRNA action using the miRNAO. A: Instances of individual molecules and processes are shown below the grey line, linked to their corresponding ontological term through stippled arrowed line. B: The same instances as in A, above, are now linked to one another by defined relations (italicized, next to the black arrows) modeling the entire process of the suppression of the human gene HMGA2 by the binding of the miRNA let-7a (hsa-let-7a) to the transcript of the gene (NM_003483).

As we have already stated above, the structure of the miRNAO as such (i.e. the structure resulting by importing all the required terms from different ontologies within a single one) does not provide all means to extract the needed additional information regarding the role that miRNAs play. Consider a scenario, for example, in which we want to keep track of a specific miRNA that, by binding to an mRNA, manages to induce the silencing of a specific gene. Such a scenario is given in Figure 4. Here we show the usage of the miRNAO ontology for the modeling of the action of the human miRNA let-7a; the respective entry in the microRNA.org [29] database is hsa-let-7a. The microRNA let-7a has been found to target, among others, the mRNA of the gene HMGA2, silencing its expression [22, 31, 28]. A simple model of this interaction is depicted in Figure 4A. The boxes under the grey line show the actual interacting molecules (instances) that are linked to their ontological terms by the grey stippled arrowed lines. However, these molecules would then remain unrelated, neglecting this way an important part of the available information. Indeed, the most interesting part of the information is the exact relationship among the individual instances of miRNAs, mRNAs, their bindings and the genes that are found to be down-regulated

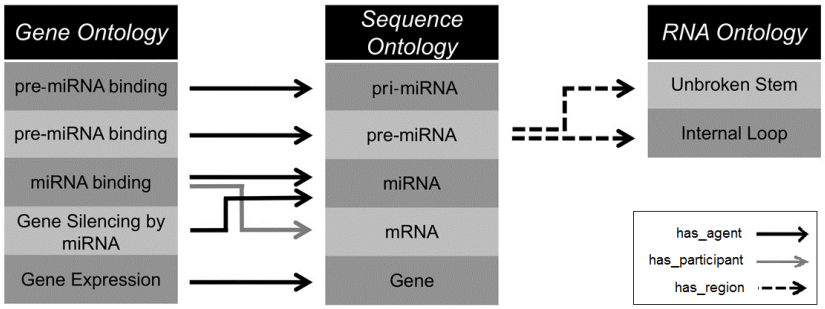

Fig. 5. Relationships added to miRNAO in order to capture all the desired information. Each term is placed under the ontology name where it was originally borrowed/imported from. The three types of arrows represent different relationships (black arrow: *has_agent*, grey arrow: *has_participant*, black stipped arrow: *has_region*).

or silenced by these bindings. This ontology derived information, imported from miRNAO is now shown in Figure 4B. It becomes obvious that the simple listing of all necessary terms from existing ontologies does not suffice to capture all the information and, instead, the creation of a new ontology in which the terms are successfully and logically inter-related is of immense help to model any kind of interaction.

We have introduced into miRNAO 8 new relationships among terms derived from different ontologies. These relationships are illustrated in Figure 5. For example, the process of *binding* of miRNAs (coming from the GO) is defined within miRNAO as having as agents the corresponding *RNAs* (term coming from the SO). Moreover, the *miRNA Binding* is also related to its target *mRNA* by utilizing the relationship *has_participant*. Finally, the *pre-miRNA* is related to its regions *Unbroken Stem* and the *Internal Loop* (coming from the RNAO). Using the same example and by exploiting the new relationships incorporated in miRNAO, we are able to extract all the captured information.

4 Conclusions

The ontology for microRNAs presented here follows the rules set by the OBO Foundry, in particular, the one of orthogonality [12], and is so far, to our knowledge, the only bio-ontology available in the public domain that uses terms from other OBO Foundry ontologies and OBO Foundry candidate ontologies to a level higher than 99%. The obvious question of why develop a new ontology when almost all terms could be found in other ontologies can be simply answered by the ease of using such a tool; this applies to both developers who would like to include pertinent ontological terms in their databases as well as putative annotators who would only have to deal with a single, rather than

several ontologies. The high level of orthogonality achieved, thus, allows for a potentially maximum interoperability for people and systems using this tool. The utilization of the defined relationships among terms of different ontologies enhances the ability of capturing the desired information regarding miRNAs and the processes they take place in. This is further enhanced by the introduction of additional relations in the miRNAO, than the ones originally described in the "source" ontologies. This enhancement, offered by miRNAO, can best be exemplified by its usage in the modeling of biological pathways/processes, as shown in Section 3.2. Finally, although this ontology was originally developed for direct usage by the TarBase [37], its format/structure is such that it could be used by anybody interested in an ontology of miRNAs. According to the OBO Foundry rules miRNAO is freely available to everyone under the conditions that its origin should be acknowledged and, if altered, not be subsequently redistributed under the name miRNAO and its own identifiers. The miRNAO clearly remains open for additions and corrections upon feedback from the research and users community.

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