RNA-KG: An ontology-based knowledge graph for representing interactions involving RNA molecules

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ABSTRACT

The "RNA world" represents a novel frontier for the study of fundamental biological processes and human diseases and is paving the way for the development of new drugs tailored to the patient's biomolecular characteristics. Although scientific data about coding and non-coding RNA molecules are continuously produced and available from public repositories, they are scattered across different databases and a centralized, uniform, and semantically consistent representation of the "RNA world" is still lacking. We propose RNA-KG, a knowledge graph encompassing biological knowledge about RNAs gathered from more than 50 public databases, integrating functional relationships with genes, proteins, and chemicals and ontologically grounded biomedical concepts. To develop RNA-KG, we first identified, pre-processed, and characterized each data source; next, we built a meta-graph that provides an ontological description of the KG by representing all the bio-molecular entities and medical concepts of interest in this domain, as well as the types of interactions connecting them. Finally, we leveraged an instance-based semantically abstracted knowledge model to specify the ontological alignment according to which RNA-KG was generated. RNA-KG can be downloaded in different formats and also queried by a SPARQL endpoint. A thorough topological analysis of the resulting heterogeneous graph provides further insights into the characteristics of the "RNA world". RNA-KG can be both directly explored and visualized, and/or analyzed by applying computational methods to infer bio-medical knowledge from its heterogeneous nodes and edges. The resource can be easily updated with new experimental data, and specific views of the overall KG can be extracted according to the bio-medical problem to be studied.

Background & Summary

The involvement of RNAs in various physiological processes has been ascertained by several studies[1–3] that have revealed the pervasive transcription of an unexpected variety of RNA molecules[4] that can lead to a significant breakthrough in the treatment of cancer, genetic, and neurodegenerative disorders, cardiovascular and infectious diseases[5]. The study of RNA is also one of the most promising avenue of research in therapeutics, as evidenced by the recent success of mRNA-based vaccines for the COVID-19 pandemic[6], for the treatment of melanoma[7], for the development of new drugs that can target both proteins and mRNA, as well as other non-coding RNA, and for encoding missing or defective proteins, regulating the transcriptome, and mediating DNA or RNA editing[8]. Thus, RNA technology significantly broadens the set of druggable targets, and is also less expensive than other technologies (e.g., drug synthesis based on recombinant proteins), due to the relatively simple structure of RNA molecules that facilitate their biochemical synthesis and chemical modifications[9]. Non coding RNAs (ncRNAs) comprise a large range of RNA species, and a large set of scientific data representing different kinds of interactions among them and with other bio-entities (e.g., genes, proteins, chemicals, diseases, and phenotypes) are made publicly available by several genomics laboratories.

The possibility of integrating the interactions that they made available would be of great relevance for knowledge discovery and also for the development of new RNA-based drugs. However, these sources adopt different data models, formats, and conventions for the representation of the bio-entities, and different semantics can be assigned to the proposed interactions. The extraction and integration of information from even two data sources for conducting knowledge discovery activity would require a lot of effort from researchers. To address these issues, KGs[10] have emerged as a compelling abstraction for organizing interrelated knowledge in different domains and a way for integrating heterogeneous information extracted from multiple data sources with the aim of highlighting complex interdependencies and uncovering hidden relationships. KGs can be

represented both with property graphs (e.g., Neo4j[11]) or according to the Resource Description Framework (RDF[12]) with different advantages and disadvantages[13]. When a KG is generated according to an ontology, it contains a schema part (denoted TBOX or terminologies) and a data part (denoted ABOX, facts, or assertions) on top of which different kinds of reasoning activities can be conducted using expressive languages (like OWL[14], DL[15], or SPARQL[16]). KGs have started to play a central role also in the life sciences[17] for the representation of bio-entities and their interactions and for the application of AI approaches for discovering new knowledge and eventually for explaining it. Different ontologies have been proposed for systematizing the corpus of terms used to describe the function and localization of bio-entities and for offering a formal framework to represent biological knowledge. Specific biological KGs (e.g., PrimeKG[18], Human Disease benchmark KG[19], ReproTox-KG[20], Monarch Knowledge Graph[21], and Knowledge Base of Biomedicine[22]) have been recently constructed for conducting different kinds of analysis and supporting the research activities.

In this paper we describe *RNA-KG*, the first ontology-based knowledge graph for representing coding and non-coding RNA molecules and their interactions with other biomolecular data as well as with pathways, abnormal phenotypes and diseases to support the study and the discovery of the biological role of the "RNA-world". RNA-KG contains RDF triples extracted from more than 50 public data sources and also integrates related bio-medical concepts. RNA-KG can be exploited for the study of RNA molecules and the development of innovative graph algorithms to support knowledge discovery in data science. A big effort has been dedicated to the characterization of the data sources and to the identification of the bio-medical ontological concepts that better represent the information provided by the considered data sources and the interactions involving RNA molecules. This work culminated in the construction of a meta-graph that represents all the possible interactions that can be devised from the considered data sources and that can be represented by means of the Relation Ontology (RO[23]), which ensures common semantics for the different relationships that can be extracted from the sources. Relying on the generated meta-graph and exploiting the Phenotype Knowledge Translator (PheKnowLator[19]) tool, we extracted 578,384 nodes and 8,768,582 edges of good quality according to the metrics provided in each data source. We also experimentally evaluated the main statistical and topological characteristics of the generated KG. RNA-KG can be exported according to different knowledge models and can be accessed through a SPARQL endpoint.

Related Work
For a better understanding of the approach that we have followed in the construction of RNA-KG, we first outline the methods developed for integrating graph-based biomedical heterogeneous data sources and then summarize the main characteristics of the different types of RNA molecules. Finally, we outline the bio-ontologies that can be exploited for the characterization of RNA molecules and the bio-entities with which they are related.

Approaches for the construction of bio-medical knowledge graphs
The data integration issue is a well-known problem in data management and many approaches have been devised to deal with relational data[24]. However, the explosion of data formats (like CSV, JSON, XML) and the variability in the representation of the same types of information[25, 26] has pushed the need to exploit ontologies as global common models both for accessing (OBDA – Ontology-Based Data Access) and integrating (OBDI – Ontology-Based Data Integration) data sources[27].

In OBDA, queries are expressed in terms of an ontology, and the mappings between the ontology and the data sources' schema are described in the form of declarative rules. Two approaches are usually proposed to enable access and integration of different data sources: *materialization*, where data are converted from the local data format according to the ontology concepts and relationships; *virtualization*, where the transformation is executed on the fly during the evaluation of queries by exploiting the mapping rules and the ontology. In this case, only the data from the original sources involved in the query are accessed. Materialization can provide fast and accurate access to data because already organized in a centralized repository. However, data freshness can be compromised when data sources frequently change. On the other hand, virtualization allows access to fresh data but requires the application of transformations during query evaluation and can cause delay, and inconsistency when the structures of the local sources change. Several approaches are available for the specification of mapping rules like R2RML[28] (a W3C standard for relational to RDF mapping), and RML[29] that extends the standard for dealing with other formats. Moreover, SPARQL-Generate[30], YARRRML[31], and ShExML[32] were also proposed for dealing with data heterogeneity.

In the biological context, many efforts are nowadays devoted to the construction of KGs by integrating different public sources that exploit the materialization and virtualization approaches previously described. For instance, Zhang and colleagues[33] applied a Connecting Ontology (*CO*) to integrate all external ontologies that describe the data sources involved. By exploiting algorithms for fusing and integrating annotations, an enriched KG is obtained that spans multiple data sources and is annotated by the integrated biological ontology obtained by gluing together the Gene[34], Trait[35], Disease[36], and Plant[37] ontologies. The Precision Medicine KG (PrimeKG)[18] was developed to represent holistic and multimodal views of diseases. PrimeKG integrates more than 20 high-quality resources with more than 4 million relations that capture information like disease-associated perturbations in the proteome, biological processes, and molecular pathways. The considered data were collected and annotated using diverse ontologies such as Disease Gene Network, Mayo Clinical Knowledgebase, Mondo, Bgee, and

DrugBank. ReproTox-KG[20] combines information about genes, drugs, and preclinical small molecules with knowledge about the association of genes and drugs with birth defects with the aim of predicting the likelihood that preclinical compounds induce specific birth abnormalities, and whether these compounds are likely to cross the placental barrier. The information is extracted from scientific publications by considering several ontologies including HPO[38], CDC birth-defect terms[39], Geneshot[40] for connecting genes with birth-defect terms, DrugCentral[41] for connecting drugs with birth-defect terms, and LINCS L1000 data[42] for drug–gene associations. Sima and colleagues[43] proposed a virtualization approach based on an ontology-based federation of three data sources (Bgee, OMA, and UNIProtKB), i.e., starting from the GenEx semantic model for gene expression, the authors proposed mapping rules to deal with the different formats of the three sources and faced the issue of joint queries across the sources by leveraging SPARQL endpoints. A preliminary version of the RNA-KG meta-graph[44] was recently presented and here deeply enhanced with the description of the methodology and the generation of RNA-KG. A fully automated Python 3 library named PheKnowLator was recently proposed for the construction of semantically rich, large-scale biomedical KGs that are Semantic Web compliant and amenable to automatic OWL reasoning, and conform to contemporary property graph standards. The library offers tools to download data, transform and/or pre-processing resources into edge lists, construct knowledge graphs, and generate a wide-range of outputs[19].

All these papers point out the difficulties that arise when trying to integrate different data sources that exploit different data models, formats, and ontologies. Specifically, data redundancies, data duplicates, and lack of common identifier mechanisms must be properly addressed. In the case of RNA data integration, we also have to consider the lack of specific ontologies for the description of all possible non-coding RNA sequences, and the presence of ontologies that are not well-recognized by the community because still in their infancy. All these aspects must be properly addressed in the generation of RNA-KG.

RNA molecules

The wide variety of RNA molecules, which can be classified as sketched in Figure 1, can be translated into proteins, can regulate gene expression, have enzymatic activity, and can modify or regulate other RNAs.

Coding RNA. In Eukaryotes, messenger RNA (mRNA) primary transcripts follow a cascade of biological processes to transform them into mature functional mRNA molecules that are read by ribosomes, translated into amino acid chains and finally assembled in proteins through peptide bonds[45].

Non-coding RNA. Transcripts that are not translated into proteins are named non-coding RNAs (ncRNAs). They can be further classified into long non-coding RNAs (lncRNAs – with more than 200 nucleotides) and small non-coding RNAs (sncRNAs – with less than 200 nucleotides)[46]. lncRNAs are the majority of transcription products and play a pivotal role in disease development and progression[47]. Circular RNAs (circRNAs) are lncRNAs produced from alternative splicing events, and may play a role as splicing event regulators. circRNAs have been involved in many human diseases, including cancer and neurodegenerative disorders such as Alzheimer's and Parkinson's disease, due to their aberrant expression in different pathological conditions[48].

Small non-coding RNA (sncRNA). sncRNAs are involved in several cellular biological processes, including: translation processes; RNA interference (RNAi) pathways; splicing and self-cleavage processes; catalysis of biochemical reactions, and targeted gene editing.

sncRNAs involved in the translation process. Several sncRNAs are involved in this process, including ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), and Small Cajal body-specific RNAs (scaRNAs, snoRNAs specific to the Cajal body). While rRNA constitutes the core structural and enzymatic framework of the ribosome, tRNAs are characterized by a structure consisting of an acceptor stem that links to a particular amino acid and of a specific anticodon sequence of 3 bases complementary to the corresponding mRNA codon, thus assuring the translation from the mRNA codon triplets to the corresponding sequence of amino acids. snRNAs and snoRNAs primarily guide chemical modifications of other RNAs, mainly rRNAs and tRNAs, and control chromatin compaction and accessibility.

sncRNAs associated with RNA interference pathways. RNA interference pathways play a central role in gene expression and their misregulation is associated with several diseases[49]. sncRNAs associated with RNAi pathways include: microRNAs (miRNAs), short interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), antisense oligonucleotides (ASOs), piwi-interacting RNAs (piRNAs), tRNA-derived fragments (tRFs), and tRNA-derived small RNAs (tsRNAs). Mature miRNAs, siRNAs, shRNAs, and ASOs regulate the mRNA expression by blocking translation or promoting degradation of the target mRNA (complementary base pairings). Unlike siRNAs, each miRNA can simultaneously regulate the expression and the activity of hundreds of protein-coding genes and Transcription Factors (TFs). miRNAs from various exogenous sources, which are present in human circulation, are named xeno-miRNAs[50]. By contrast, ASOs are more effective to knock down nuclear targets, whereas siRNAs are superior at suppressing mRNA cytoplasmic targets by recruiting, via Watson-Crick base paring, the RNA-induced Silencing Complex (RISC) that catalyzes the mRNA cleavage. Similarly, throughout RNAi, piRNAs and tRFs promote genome integrity, avoiding potential threats to cellular homeostasis, by silencing transposons, retrotransposons and repeat sequences[51].

Aptamers, riboswitches, ribozymes and guide-RNA. The tertiary structure of RNA sequences can also be investigated to

identify interferences. Aptamers are short single-stranded nucleic acids that can bind to a variety of targets (e.g., proteins, peptides, carbohydrates, DNA, and RNA) thanks to their 3D conformation. Riboswitches are small non-coding RNAs involved in alternative splicing and self-cleavage processes that cause gene expression control and mRNA degradation, critical for survival of the cell[52]. Some RNAs, such as ribozymes, even possess enzymatic activity therefore catalyzing biochemical reactions (e.g., mRNA and protein cleavage). Synthetic ribozymes can and have already been designed to target viral RNA. Synthetic guide RNAs (gRNAs) are usually involved in the application of CRISPR-Cas9 technique, used for gene editing and gene therapy[53].

Biomedical ontologies for the semantic characterization of RNA-KG

Several standard biomedical ontologies can be used to set up common semantics in the considered data sources. Table 1 shows those considered during RNA-KG construction (their specifications are made available in the web portals `ebi.ac.uk/ols4` and `bioportal.bioontology.org`). We selected these ontologies because their terms and hierarchical structures are commonly accepted by the scientific community to unequivocally describe biological classes and entities such as diseases, phenotypes, chemicals, biological processes, proteins, and relations between them. In the case of RNA-KG, we have also taken into account the lack of specific ontologies for the description of all possible RNA sequences (especially non-coding ones), and the presence of bio-ontologies that are yet not well-recognized by the community.

Results

RNA-KG is open-source and available through a SPARQL endpoint (hosted at http://fievel.anacleto.di.unimi.it:9999). The code for generating and maintaining RNA-KG is available on GitHub (https://github.com/AnacletoLAB/RNA-KG). RNA-KG comprises a comprehensive collection of relationships involving RNA molecules from various recognized RNA sources. The considered data sources have been characterized from different perspectives and compared (see Tables 2-3). These tables also provide the different kinds of relationships that can be established and their respective occurrences are summarized in Figure 6. Data sources might contain similar relationships and their possible overlapping has been visually highlighted in Figure 7. Relationships have been represented according to the Relation Ontology (RO) and the resulting meta-graph (Figure 8) has been used for the generation of an ontological description of RNA-KG. Different analyses have been conducted to characterize the types of nodes and interactions that are represented in RNA-KG (Figure 10), their distribution (Figures 11-12), and the topological structure analysis (Table 5). Details on the obtained results are discussed in the *Data Records* section.

The methodology we employed to construct RNA-KG enabled us to generate a high-quality knowledge graph that includes reliable interactions, validated through experimental methods and/or strongly endorsed by data providers, and whose meaning was meticulously verified to ensure a consistent representation of domain knowledge.

In the supplementary section, we have also included further figures and tables that better describe RNA-KG. Specifically, Supplementary Table 1 delineates the bio-ontologies that have been exploited for representing concepts in each RNA source. Supplementary Tables 2-5 report the descriptive statistics of the triples that have been extracted from the different data sources. Moreover, Supplementary Figures 1-2 show bio-entities present in RNA sources and their mapping to RO terms we used to represent relationships within the sources. Supplementary Table 7 highlights the primary node types and their corresponding identifiers with an instance sample. Finally, Supplementary Listings 1-3 provide a few examples of SPARQL queries, illustrating the kind of information that can be extracted from RNA-KG.

Discussion

The structure of the obtained KG has been analyzed by computing various graph metrics that provide a macroscopic description of the network topology derived from the entity relations (see Table 5). By means of a t-SNE representation of an embedding of the nodes/edges in RNA-KG (Figure 13) we have highlighted that the embedding of the node type is able to effectively identify the similarities among the nodes of the same type, thus capturing their function in the network. Moreover, the edge embedding is able to capture, in most cases, the similarity between edges. In our analysis we have also identified the nodes having the highest out-degree and observed that the (undirected) degree distribution follows a heavy-tailed distribution (see Figure 14). Moreover, we computed bounds for the treewidth and the closeness centrality distribution, which suggest a sparse yet well-connected structure. All of these characteristics are commonly found in networks with a scale-free structure, which is often seen in networks representing complex interactions. Further investigation will be conducted in this direction to confirm such a structure. This property would yield benefits in the network analysis both in terms of structure understanding and algorithmic design. Finally, we have investigated the presence of isomorphic node groups, that is nodes that are topologically indistinguishable because they present exactly the same neighbors. These nodes deserve further investigation to check whether the involved molecules are duplicates and should thus be collapsed to improve the information quality of RNA-KG. A detailed discussion of the results is reported in Section *Technical Validation*.

RNA-KG can generate heterogeneous biomedical graphs in different formats that can be processed by graph-based computational tools to infer biomedical knowledge, provide insights into biomolecular mechanisms and biological processes

underlying diseases, support the discovery of new drugs, especially those based on RNA, and evaluate biomedical hypotheses in silico. In particular, RNA-KG is specifically designed to deal with computational tasks involving RNAs, by e.g. exploiting the information about ncRNA interactions for gene and protein expression regulation, collected from tens of publicly available databases. By leveraging the biomedical concepts represented in the biomedical ontologies embedded in the KG, RNA-KG can be also analyzed to predict associations and causal relationships of the "RNA world" with diseases and abnormal phenotypes. We also observe that the rich information embedded in the RNA-KG can be leveraged for classical biomedical prediction tasks, including e.g. gene-disease prioritization, drug-target prediction, and drug repurposing.

Most of these biomedical tasks can be modeled as link or node-label prediction problems in heterogeneous graphs. Even if, in principle we could apply methods developed for homogeneous graphs[54], to leverage the rich information scattered across the different types of modes and edges of the RNA-KG, we suggest applying methods specifically designed for heterogeneous graphs[55]. To this end, several AI graph-based methods have been recently proposed to deal with heterogeneous graphs, also in the context of biomedical Knowledge Graphs[56]. In particular we foresee that Graph Representation Learning methods, by leveraging the topology of the complex bio-medical heterogeneous graphs to embed them into compact vectorial spaces, could be the most promising choice to properly analyze the complex heterogeneous structure of RNA-KG[57].

We are currently working on enhancing the proposed KG in different directions. First, we are identifying key properties associated with RNA molecules and their interactions to be included in RNA-KG. This is a tough problem because we need to integrate and make uniform the information about the same bio-entity obtained from different sources. However, we have already identified the main properties characterizing the same molecule. Moreover, we have established systematic rules for aligning the representation and fusing records representing the same bio-entities. In this line of research, we are also considering the possibility of proposing an RNA Ontology for describing RNAs with a particular emphasis on non-coding RNA molecules. We aim to craft this ontology on the data that we have identified in the sources considered in this study. This could be a relevant contribution toward the definition of a standard representation of RNA molecules and the interactions that might be determined among them. Another research direction is the use of Transformers[58] in combination with RNA-KG for the extraction of new triples from textual documents. In this direction, we are currently leveraging the SPIRES engine[59] which enables the user to guide OntoGPT on the kinds of interactions that we are interested in, by specifying our meta-graph in terms of LinkML[60]. The identified triples can be validated by using RNA-KG as a gold standard in this domain. This approach can limit the hallucination issue that is typical of large language models, ensuring the reliability and accuracy of the extracted information. We would like also to analyze RNA-KG with cutting-edge AI graph representation learning algorithms[61] to support the discovery of novel RNA drugs. Finally, we are developing graphical facilities for supporting the user in the data acquisition and maintenance processes and thus reducing the manual effort required for mapping the data available in the different data sources into RNA-KG[62] and also for showing the graph at different granularities[63, 64].

Methods

The creation of a KG is a complex task that requires facing several phases that can be organized in a workflow such as the one reported in Figure 2. In the remainder of the section, we provide a detailed description of the different issues and adopted solutions for each phase of the creation of our RNA-based KG.

RNA sources characterization

In this phase, we have identified and analyzed the characteristics of relevant data sources from which the information for feeding the KG has been extracted. This is a well recognized critical initial step in constructing a KG[65].

To this aim, an extensive literature review was carried out to identify repositories dealing with RNA sequences and annotations developed by well-reputed organizations, published in top journals, periodically updated, and containing significant amounts of RNA molecules and relevant relationships with other types of molecules and bio-entities. Furthermore, RNA sources that are included in other bigger repositories have been considered, as well as those that are used as collectors of other repositories. We have also identified the presence of controlled vocabularies, thesauri, reference ontologies that formally describe the repository content, and the presence of well-recognized identification schemes.

Sources provide data in different formats (e.g., CSV, TSV, gaf, hpoa, reactome, xlsx, JSON, and HTML) or by issuing queries on content management systems. Once the data were downloaded, Pandas[66] DataFrames were used to transform the data into a common format (TSV files) and remove syntactic inconsistencies. The data obtained can be then processed through PheKnowLator to extract the relationships among bio-entities.

For the characterization of the relationships that can be extracted from the different data sources, we applied the Relation Ontology. Moreover, the hierarchical organization of concepts in RO allows the expression of different kinds of relationships at different granularities (e.g., the general term `interacts with` can be substituted with more specific terms such as `molecularly interacts with` or `genetically interacts with`). Moreover, in case of a lack of specific terms for describing relationships identified in a data source, two strategies have been devised. The first one is to approximate

the concept/relationship type with a term already present in RO. This implies a better coherence with RO semantics but misses details that the concept/relationship can carry. The second strategy is to extend the RO ontology with new terms specifically tailored for the representation of the concept/relationship. In this case, non-standard, more precise terms can be introduced for the representation of the concept/relationship. In the construction of RNA-KG, we adopted the first strategy for a larger agreement on the meaning of the used terms and uilized the `interacts with` relationship for representing any connection among bio-entities when a more specific one is missing.

The adoption of different types of molecular identifiers represents another issue. Indeed, the identification scheme encountered in the considered data may vary from the source and target of the relation and could be characterized by different accuracy levels. Four levels have been detected: *Well-Reputed* (denoted `WR`), when the identifiers are widely accepted by the scientific community (e.g., NCBI Entrez Gene identifiers); *Ontology-based* (denoted `O`), when the identifiers are directly represented with ontological terms; *Mapping-based* (denoted `M`), when the identifiers can be obtained by exploiting look-up tables; and *Proprietary* (denoted `P`), when all the previous techniques cannot be applied. Once the identification scheme adopted in a source has been classified, appropriate *look-up* tables for their mapping into the reference ontology have been realized by analyzing synonyms in the reference ontology or by examining the ones provided by the sources themselves to facilitate interoperability with other sources dealing with the same entities. For instance, we employed *NCBI Gene Entrez* identifiers to represent genes in RNA-KG, but many sources provide the correspondent *Gene Symbol*. In this case, a look-up table has been used to map gene identifiers into the chosen representation (Figure 3).

To guarantee a high level of homogeneity in the KG, a few tuples have been omitted when the mapping to the reference ontology was not possible. For some types of RNA molecules (especially ncRNA sequences), the look-up tables cannot be adopted because of the lack of a reference ontology with which these molecules can be represented. In these cases, the *NCBI Entrez Gene* identifiers of the gene from which the specific RNA is transcribed have been extended with a suffix that corresponds to the type of non-coding RNA (e.g., in case of small nucleolar RNA molecules the suffix is `?snoRNA`). We remark that the lack of a common ontological representation among heterogeneous sources can cause the duplication of molecules. At the current stage of development, we decided to admit the presence of duplicates for this kind of molecule, but we will consider de-duplication techniques[67,68] that rely on the use of similarity measures on the molecule sequences in future releases.

To guarantee a high-level of reliability of the relationships to be included in RNA-KG, only *meaningful* relationships have been considered, that is those satisfying constraints that take into account p-values or FDR – False Discovery Rate (e.g., $p_{val} < 0.01$), experimental validation of results, or scores (denoted with σ) defined as reliable in the considered data source.

All of these activities led to the identification of the reference ontologies for each data source and the relationships that can be extracted and represented according to the RO ontology. Moreover, by studying the organization and format of the data sources, the extraction patterns and the look-up tables to apply have been realized. Finally, pruning strategies have been devised specifically tailored to the characteristics of each data source.

Ontological description of the KG

In this phase, we identified the classes of bio-entities that need to be managed and of the kinds of relationships that can exist among them (*schema layer*). Moreover, specific instances and the properties that need to be maintained have been identified (*data layer*). This design activity plays a fundamental role in the hierarchy, structure and content filling of the knowledge graph, and it is the basis for determining the kind of reasoning that can be supported.

Starting from the knowledge gained from the characterization of RNA sources, we moved toward the construction of the ontological schema underlying RNA-KG. A *meta-graph* was built to include all the kinds of bio-entities and relationships between them outlined in the previous phase. The meta-graph provides both direct and inverse relationships that are considered to guarantee bi-directional navigation of the generated KG.

Once classes of bio-entities and their relationships have been identified, we determined the properties that should be kept for them. At the current stage, only fundamental properties of bio-entities have been collected (identifiers, node types, and source provenance). This choice has the advantage of avoiding the explosion of the KG size. However, in future implementations, we wish to enhance the properties that can be stored within RNA-KG.

Ontological alignment specification

In this phase, we identified the KG representation and the kind of storage system to adopt. RDF triples have turned out to be suitable because of their common, flexible, and uniform data model. These properties result in an ontologically-grounded knowledge graph for conducting different kinds of analysis and reasoning.

Since a standardized formal definition for the concept of a KG is still lacking, we considered the one adopted by Callahan and colleagues[19] where a KG is a pair $< T, A >$, where T is the TBox and A the ABox. The TBox represents the taxonomy of a particular domain including classes, properties/relationships, and assertions that are assumed to generally hold within a domain (e.g., a miRNA is a small regulatory ncRNA located in an exosome as depicted in Figure 4). The ABox describes attributes and roles of class instances (i.e., individuals) and assertions about their membership in classes within the TBox

(e.g., *hsa-miR-125b-5p* is a type of miRNA that may cause *leukemia*). Non-ontological entities (i.e., entities from a data source that are not compliant to a given set of ontologies such as RNA molecules) can be integrated with ontologies using either a TBox (i.e., class-based) or ABox (i.e., instance-based) knowledge model. For the class-based approach, each database entity is represented as `subClassOf` an existing ontology class, while for the instance-based approach it is represented as `instanceOf` an existing ontology class.

For the construction of the KG we have employed the PheKnowLator ecosystem[19] because it offers both approaches for the representation of bio-entities and their relationships, and also because of its simplicity in the identification of the columns containing the molecules' identifiers and for the specification of their relationships in terms of the RO ontology. PheKnowLator also provides tools to easily generate the ontology that better describes the content of the KG that, besides the terms and relationships of the meta-graph, also includes other ontological terms for supporting the reasoning.

KGs can be easily exported according to different kinds of models offered by PheKnowLator depending on the analyses to be conducted. Even if RNA-KG is made available in all the supported knowledge models, we think that the instance-based, inverse relation, semantically abstracted (OWL-NETS[69] without harmonization) configuration is the most suitable to be processed by different kinds of ML algorithms for node and link prediction. This solution ensures that RNA molecules (which lack semantic characterizations in bio-ontologies) and other non-ontological data can be specified as `subClassOf` specific ontological classes. Moreover, this approach enables the automatic specification of inverse relations among the involved bio-entities. Lastly, OWL-NETS reversibly abstracts ontological biomedical knowledge into a network representation containing only biologically meaningful concepts and relations. Figure 5 shows a small toy-example subgraph extracted from RNA-KG according to the proposed set-up. We can notice the presence of inverse relationships (`located in` and its inverse `location of`), and the relation RDF `subClassOf` connected to entities that do not have a corresponding term in a reference ontology (miRNA molecules are specified as `subClassOf` the SO term `miRNA`).

By studying the characteristics of the data sources, specific mapping rules have been devised through PheKnowLator to extract triples compliant with the adopted ontologies. Mapping rules contain the position of the source and object in the TSV file, the two human-readable labels for subject and object (e.g., mRNA and disease), the type of relationship that holds/exists between them according to RO (e.g., `RO_0003302` corresponds to `causes or contributes to condition` relation), and further detailed options (e.g., thresholds for considering the tuple, row filtering options, transformation options according to the look-up table). These rules will be exploited for the extraction of the triples according to the reference ontology.

Since many ontologies are used in our context, we adopted the PheKnowLator tools to clean ontology files (i.e., remove and normalize errors, eliminate obsolete and/or deprecated entities, remove duplicate classes and class concepts) and merge cleaned ontology files into a single ontology file. The so-obtained merged ontology describes entirely the structure of RNA-KG and is compliant with our meta-graph.

RNA-KG generation

In this final phase, the PheKnowLator mapping rules have been issued on the pre-processed data with the aim of generating a KG compliant with the meta-graph identified in Phase 2 (ontological description of the KG).

In order to evaluate the characteristics of the generated KG, we used the GRAPE library that we recently developed for fast and efficient graph processing and embedding[70]. By importing RNA-KG into the GRAPE environment, we were able to retrieve relevant topological information and topological oddities that can be useful in identifying biological and biomedical KG inconsistencies. Moreover, GRAPE can be exploited to implement different types of graph embedding techniques that cannot be realized by means of other tools because of the size of the generated KG.

Finally, a Blazegraph endpoint[71] has been realized to make RNA-KG freely available and accessible. Using SPARQL, it is possible to extract portions of the graph and use it for different kinds of analysis (see the examples reported in the Supplementary Listings 1- 3). Moreover, the entire RNA-KG can be downloaded from our lab website.

Data Records

Identification and characterization of RNA entities and relationships

By applying the method discussed in the previous section, we identified more than 50 public repositories. The papers describing these data sources were published in top bioinformatics, bio-medical, and database focused journals between 2008 and 2023 but the majority were published in the last 5 years. The main characteristics of the identified repositories are reported in Tables 2-3, whose entries are organized according to the main type of RNA molecules made available by the source. Sources with `miRNA` entities can contain hairpin miRNA, xeno-miRNA, and mature miRNA molecules (last ones, in turn, can be classified in `-3p` and `-5p` transcripts). `Inter RNA` sources are those that do not focus on a single RNA type but propose multiple relationships among different types of RNA molecules and bio-entities (e.g., disease in the case of RNADisease or cellular component in the case of RNALocate). Note that no species is present for aptamers because they are synthetic and none of the databases are specific for piRNA molecules related to *Homo sapiens* (although relationships involving piRNA sequences are stored in

`Inter RNA` sources). Regarding the format, the majority of the considered data sources ($\geq$ 80%) export data in a flat-file format (*CSV*). Only a small fraction of them (around 20%) provide an API for accessing data stored in a relational database. Only DrugBank offers a RDF data representation coupled with a SPARQL endpoint.

Figure 6 summarizes the available relations involving RNA molecules and bio-entities (i.e., gene, protein, chemical, and disease) that we have identified in the different data sources. miRNA-lncRNA interactions are the most numerous. We can retrieve around 150 million distinct relationships of this type from public RNA-based data sources. In terms of cardinality, they are followed by lncRNA-mRNA interactions ($\sim$28 million) and miRNA-mRNA interactions ($\sim$12 million). Around 800 thousand distinct relationships can also be identified for protein-lncRNA interactions. These categories of molecules often interact with each other in specific diseases. RNA aptamer-disease is the less represented one because at the current stage only two approved (or under-investigation) RNA aptamer drugs are present in DrugBank and, in general, RNA drugs are less represented than others because they are synthetic (DrugBank siRNA and mRNA vaccine categories contain only 4 approved or under-investigation drugs, ASO drugs are only 12, and RNA aptamer drugs only 2). In addition to the so far discussed data sources, RNAcentral[72] is a collector coordinated by the European Bioinformatics Institute (EBI[73]), which imports non-coding RNA sequences from multiple databases and enables integrated text search, sequence similarity search, bulk downloads, and programmatic data access through a reliable API.

Starting from the need to understand whether the content of the different data sources overlap, we examined the entities and relationships made available in the considered data sources and identified containment (or overlapping) data sources. The result of our study is reported in Figure 7 where bubbles represent the relationships made available by the data sources. We can note the presence of two prominent clusters (miRNet and RNAcentral) that properly include or overlap the relationships made available by other data sources. The identification of these containments has been exploited to reduce the issue of semantic compatibility. Furthermore, many miRNA and lncRNA sources contain relations that either overlap or are properly included within other sources. For the sake of readability, we have included some of these RNA sources in a legend. We remark that the `Inter RNA` sources RNAInter, RNALocate, RNAdisease, ncRDeathDB, cncRNAdb, and ViRBase are nicknamed "Sister Projects" because they are updated and maintained by the same research team. Common semantics in "Sister Projects" result useful for data handling because they share a practically identical structure.

Construction of the RNA meta-graph and ontological description of the KG

Besides the sequences, these data sources also contain different kinds of relationships that can be exploited for the KG construction. Table 4 reports the main relationships that have been identified in the considered data sources according to the RO ontology. For each relation, Table 4 reports the RO identifier, the corresponding meaning, and, whenever feasible, we have introduced the inverse relationships in case only a unidirectional relationship is available in the data source (e.g., `develops from` and `develops into`). The general relationships `interacts with` available in RO with the meaning "A relationship that holds between two entities in which the processes executed by the two entities are causally connected" have been specified in the most specific relationships `molecularly interacts with` in our classification to represent the situation in which the two partners are molecular entities that directly physically interact with each other (e.g., via a stable binding interaction or a brief interaction during which one modifies the other). We use this relationship to represent a specific interaction process at the molecular level (e.g., aptamer-protein binding interaction or tRNA molecule charged with a specific amino acid). We remark that some authors[74,75] suggest that miRNA molecules are `involved in negative regulation of` complementary miRNA molecules by forming base-pairing interactions. However, this kind of relationship is not present in the considered data sources.

The content of Tables 2–4 is the groundwork for the generation of the meta-graph reported in Figure 8. The graphical representation provides a global overview of the richness of information that is currently provided. To simplify the visualization of the meta-graph, we omitted most of the non-RNA bio-entities that are known to play an important role in studying the biology (and supporting the discovery) of novel RNA drugs. Moreover, we have omitted some of the relationships extracted from the `Inter RNA` data sources (see Table 3) because of the limitation of their occurrences. The meta-graph in Figure 8 can be further extended to include other nodes representing other bio-entities (e.g., diseases, epigenetic modifications, small molecules, tissues, biological pathways, and cellular components) and relationships relevant to the analysis. This "enlarged" meta-graph is quite complex and difficult to be graphically represented. Figure 9 shows a very abstract representation by clustering in a single RNA node all the kinds of RNA molecules described in Figure 8. Then, this node is connected with various bio-entities based on insights extracted from RNA sources and literature. It is worth noting that RNA-KG has the potential for expansion by integrating additional KGs, and to set the basis for an RNA ontology thanks to the hierarchical structure introduced by the `subClassOf` relationship.

RNA-KG statistical analysis

The current version of RNA-KG has a single connected component containing 578,384 nodes and 8,768,582 edges. The number of nodes and edges has been deeply reduced by considering only the relationships with a high reliability. The construction

process of the graph is designed to be periodically updated, including data from other public RNA and related biomedical sources. Moreover, thresholds can be tuned for enlarging or reducing the KG size. Table 5 depicts the main macroscopic topological and structural properties of the current RNA-KG.

Figure 10a shows the distribution of nodes contained in RNA-KG. Nodes can be classified into nodes representing bio-entities and those that represent the ontological terms. Bio-entities have been further subdivided into RNA nodes (gathering together sncRNA, mRNA, lncRNA, viral RNA, and unclassified RNA nodes), and non-RNA nodes (named `other bio-entities`) that contain, for instance, gene and variant (SNP)-typed nodes. Furthermore, Figure 11a presents the distribution of nodes according to the main type of RNA molecules, detailing the different categories of sncRNA. mRNA, lncRNA, and miRNA available in RNA-KG. These RNA molecules are the most represented in RNA-KG because they are well-studied (many RNA sources have been categorized/typed as lncRNA and miRNA, and mRNA are in relationships with many other ncRNAs as already discussed in the characterization of the data sources). Also tRF molecules (that are classified in the sncRNA category) are very numerous because they are "fragments" of tRNAs (one tRNA can generate more than one tRF or tsRNA). The `unclassified RNA` category includes 692 RNA nodes for which a better semantic characterization cannot be assigned because, in the original sources, they are specified as "other RNA", "miscellaneous RNA", "unknown RNA", "ncRNA", or "RNA molecules to be experimentally confirmed". Finally, the `other` category includes sncRNA molecules whose distribution is negligible in RNA-KG (64 sncRNA molecules among ribozymes, piRNAs, enhancer RNAs, vault RNAs, Y RNAs, retained introns, mitochondrial RNAs, small conditional RNAs, and scaRNAs). The total number of mRNA, and in general, RNA, is consistent with experimental studies regarding the number of genes in human ($\sim$ 22-25K protein coding genes and more than 100K total genes[76]). Ontological terms shown in Figure 10a are introduced in the generation of the KG for supporting reasoning activities and can be further classified according to the specific bio-ontology from which they are extracted (e.g., ChEBI for chemicals and HPO for phenotypes). Among them, chemical and protein nodes cover around 42.5% of the total amount of nodes in RNA-KG. This is due to the fact that ChEBI and PRO both contain many terms representing chemical entities and proteins for *Homo sapiens*. Figure 11b further details the distribution of ontological terms. Since the considered ontologies contain also terms that do not follow the usual pattern for their identification (e.g., terms representing glycans belong to PRO but their identifier starts with the prefix `GNO` which differs from the usual one adopted for identifying proteins), we have introduced the category `species`, with the terms representing the species (all species start with the prefix `NCBITaxon`), and the category `other terms`, generally containing all the others.

Figure 10b shows the distribution of edges in RNA-KG. Edges have been subdivided into three categories: *i*) edges representing RO terms that have been further classified in those that describe the interactions among RNA molecules and RO terms introduced by the integrations of the bio-ontologies; *ii*) edges representing the `subClassOf` relationships; and *iii*) edges representing other kinds of relationships not included in RO (e.g., `has gene template` belonging to PRO). Figure 12a details the distribution of the types of edges involving RNA molecules. As reflected by the organization of the meta-graph, `interacts with` is the most represented edge type because it is symmetric, whereas the presence of many `regulates activity of` edges is justified by the vast majority of miRNA molecules within RNA-KG that indeed regulate the activity of, for example, pseudogene and mRNA molecules. Moreover, Figure 12b shows the distribution of the remaining edges included in RNA-KG. We can notice the prevalence of many `subClassOf` due to the integration of the bio-ontologies, and because we specified each RNA molecule as `subClassOf` an appropriate class within SO (e.g., `SO_0000276` for miRNA molecules).

Technical Validation

In order to evaluate the quality of the generated KG, several analyses have been performed whose results are reported in the following paragraphs.

t-SNE representation.   Figure 13 shows the t-SNE representation of an embedding of the nodes/edges in RNA-KG by using the GRAPE implementation of Node2Vec with CBOW, a random walk-based second-order embedding algorithm[77], with walk length equal to 5. Figure 13a shows how the embedding of the node type is able to effectively identify the similarities among the nodes of the same type, thus capturing their function in the network. On the other hand, Figure 13b depicts the edge embedding for RNA-KG. Also in this case, the embedding is able to capture the similarity between edges with the only exception of the `interacts with` relation which seems to overlap several other edge types. This fact is not so surprising considering that this relation is also used to denote a generic relation between nodes.

Topological analysis.   The topological analysis led to the identification of top-5 nodes with the highest degree centrality: *microvesicle* (`GO_1990742`) with degree 27.11K (whose type is `GO`); *nucleus* (`GO_0005634`, degree 20.15K), *hcmv-miR-US25-1-5p* (`human cytomegalovirus hcmv-miR-US25-1-5p mature miRNA`, degree 18.18K and node type `miRNA`), *hFOXA1* (`PR_P55317`, degree 31.80K and node type `protein`), and *cytosol* (`GO_0005829`, degree 17.26K). We remark that the nodes cytosol, nucleus, and microvesicle represent cellular components used for aggregating different

bio-entities existing in the context of a cell and this is the main reason for the high node degree within RNA-KG. Moreover, the RNA relationships with these kinds of cellular components are enhanced by the semantics `contained in` and `location of` together with their respective RO inverse `contains` and `located in`. On the other hand, *hcmv-miR-US25-1-5p* is a human cytomegalovirus (HCMV)-encoded -5p miRNA transcript, whose diagnostic and prognostic value has been proved valid for several human diseases and their clinical implications[78]. Finally, hFOXA1 is a forkhead TF known to be the main target of insulin signaling, to regulate metabolic homeostasis in response to oxidative stress, and to interact with chromatin. The central role assumed by hFOXA1 in RNA-KG is quite interesting since this TF is implicated in various human malignancies characterized by altered expression of ncRNAs[79].

Degree distribution. As can be seen in Table 5, the average degree of the undirected version of RNA-KG is relatively small (9.65). Despite the graph sparsity, the diameter of the KG is also relatively small (36). On the other hand, as shown in Figure 14a, the degree distribution suggests a heavy-tailed distribution. All of these properties are usually associated with scale-free graphs, which is a common structure in real-world complex systems. These properties motivate the computation of the empirical *complementary cumulative distribution function* (CCDF) for the degree reported in Figure 14b. This curve approximates the probability distribution that a randomly selected node has a degree greater than or equal to x. The linear trend in the plot is usually associated with a powerlaw distribution, where the CCDF is given by a function proportional to $x^{1-\alpha}$. We estimate the power of the distribution using[80], obtaining a value of $\alpha = 1.832$. The theoretical powerlaw obtained for the degrees is shown in Figure 14b together with other common heavy-tailed distributions. Among these alternatives, we found that the powerlaw distribution fits better according to the log-likelihood ratio criterion[81] with *p*-values smaller or equal than 10^{-6}. Further exploration should be made to confirm the powerlaw properties of the graph since they are usually associated with a hierarchical modular structure of the network, entailing algorithmic advantages for its analysis. For instance, the closeness centrality distribution in Figure 14c presents a bimodal behavior, which could be explained by the existence of a well-connected core usually present in heavy-tail degree distribution networks.

Treewidth. Treewidth is a graph parameter measuring the structural similarity between a graph and a tree. It is based on the construction of a tree decomposition which captures how subset of nodes can be grouped to form a tree structure that maintains the global structure of the former graph. For instance, graphs having treewidth equal to one are trees, cycles have treewidth two, and clique graphs have a treewidth equal to the number of nodes minus one. The computation of the treewidth is in NP, but several approximation strategies can be used[82]. The upper bound ($8,554$ in Table 5), computed on the undirected version of the KG, can be considered relatively small because it represents about 1.5% of the KG size. This result is consistent with a tree-like hierarchical structure of RNA-KG that has a small and well-connected core.

Isomorphic node groups. RNA-KG contains 829 *isomorphic node groups*, that is nodes with exactly the same neighbours, node and edge types. Nodes in such groups are topologically indistinguishable, that is, swapping their identifiers would not change the graph topology. These groups involve a total of 14.30K nodes (2.47%) and 398.32K edges (4.54%), with the largest one containing 1.04K nodes and 19.78K edges. This particular group has degree 19 and is composed of riboswitches, specifically putative Ile (GAU) T-box riboswitches, and contains sequences that are all located upstream of an isoleucine–tRNA ligase. Other isomorphic node groups involve other riboswitches, tRNAs, tsRNAs, and tRFs. The detected isomorphic group components involve sncRNAs all interacting with amino acids at a molecular level or that originate from tRNA with molecular interactions tied to specific amino acids. For example, these groups may include sequences such as `Aspartic acid-GTC` tRNA sequences or `tsRNA-Leucines`. All these isomorphic node groups deserve further investigation to check whether the involved molecules correspond to the same tRNA, riboswitch, tsRNA, or tRF and thus pruning them to improve the information quality of RNA-KG. Indeed, these groups derive from different RNA sources and contain molecules presenting proprietary identifiers that might collapse.

Usage Notes

While every effort has been made to provide complete, up-to-date and correct information, we make no warranty about the completeness and accuracy of the RNA-KG content. The use of the data contained in this database is limited to research-oriented and non-profit activities only (as requested by the data sources from which the data have been extracted).

Code Availability

The RNA-KG 's project website is at http://fievel.anacleto.di.unimi.it:9999. The code to reproduce results, together with documentation and tutorials, is available in RNA-KG 's GitHub repository at https://github.com/AnacletoLAB/RNA-KG. In addition, the repository contains information and Python scripts to build new versions of RNA-KG as the underlying primary resources get updated and new data become available. RNA-KG data resource is hosted on Zenodo under a persistent identifier https://doi.org/10.5281/zenodo.10078877. We have deposited the KG and all relevant intermediate files in this repository.

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Author contributions statement

M.M. and G.V. designed the study. Em.C. retrieved, processed, and harmonized datasets. T.J.C., M.M. defined the methodology for the construction of the KG. Em.C. and S.B. worked on the specification of the mapping alignment. Em.C. generated the KG that was analyzed by A.C. and M.S.G. S.B. and P.P. set up the SPARQL endpoint and developed the SPARQL queries on the generated KG. G.V., E.C., J.G., J.R., P.N.R. identified the possible applications of the KG in conducting knowledge discovery in life science. M.M., Em.C. and G.V. wrote the initial draft of the paper. All authors reviewed the final version of the manuscript and approved it.

Competing interests

The authors declare no competing interests.

Figures & Tables
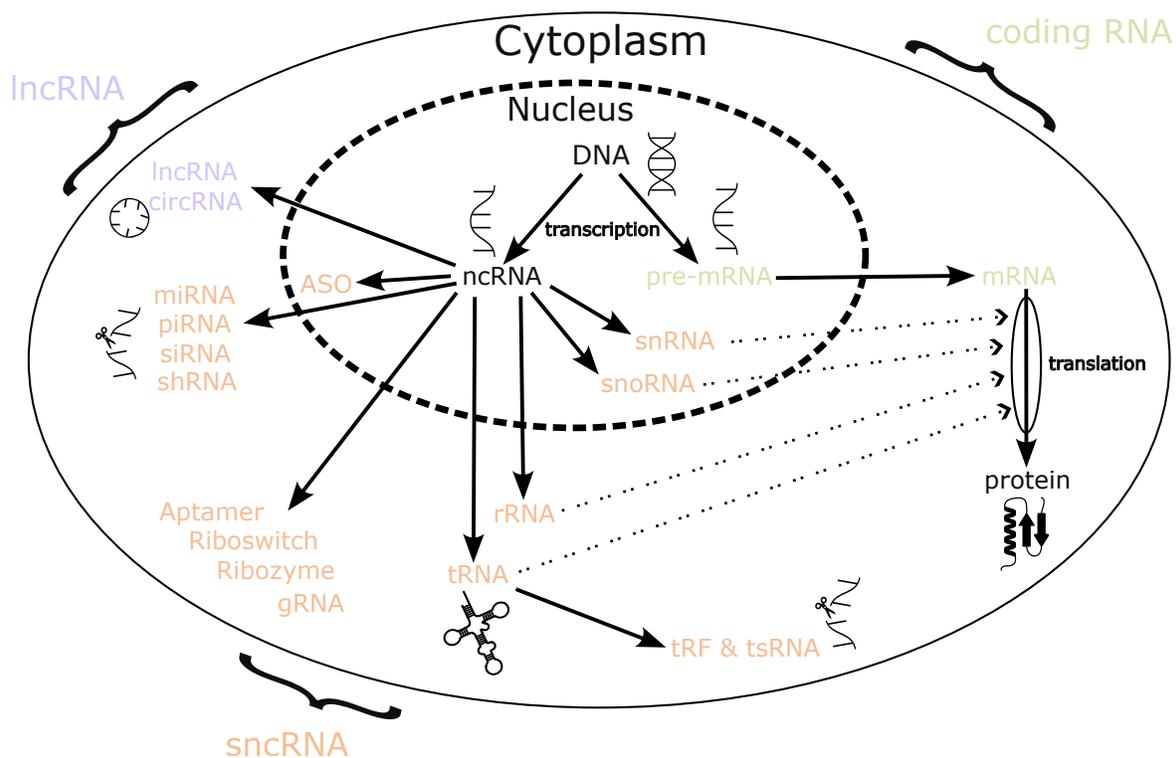
Figure 1. Schematic representation of the RNA network within a cell.
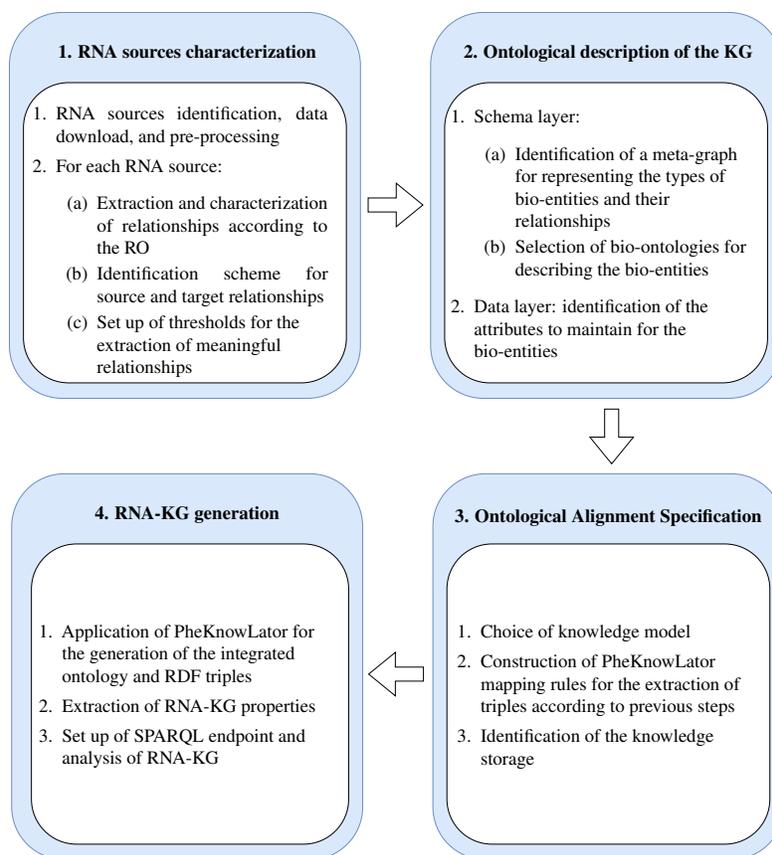
Figure 2. Workflow for the construction of RNA-KG.
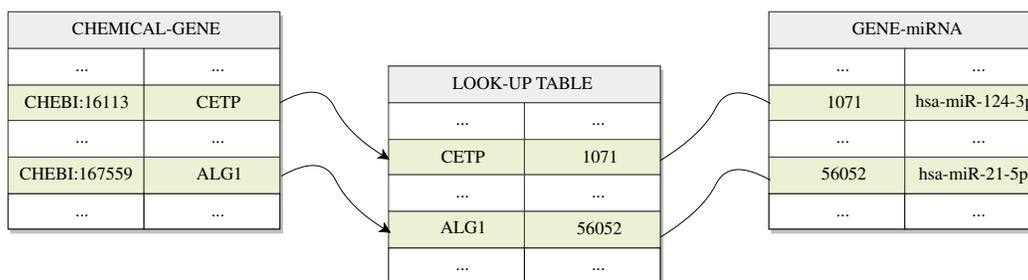
Figure 3. The relationship between chemicals and miRNA cannot be decoded directly because of the use of different identification schemes. However, by means of a look-up table the relationship can be highlighted.
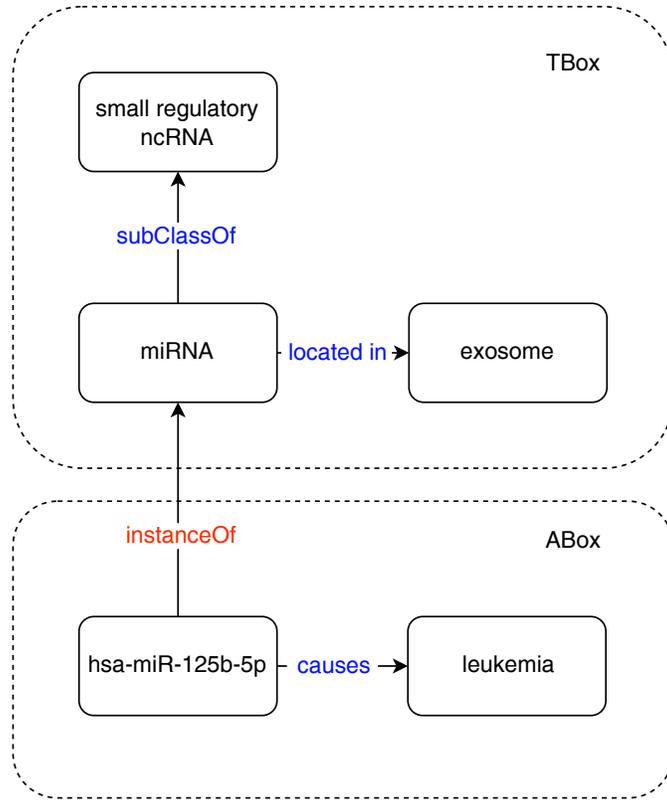
Figure 4. An example of the use of Description Logic (DL) for knowledge modeling. The TBox includes classes (i.e., `miRNA`, `small regulatory ncRNA`, and `exosome`), and the assertions between classes (i.e., "`miRNA subClassOf small regulatory ncRNA`" and "`miRNA is located in exosome`"). The ABox includes instances of classes (i.e., *hsa-miR-125b-5p*) represented in the TBox and assertions about those instances (i.e., "*hsa-miR-125b-5p* `instanceOf` miRNA" and "*hsa-miR-125b-5p* `causes` leukemia").
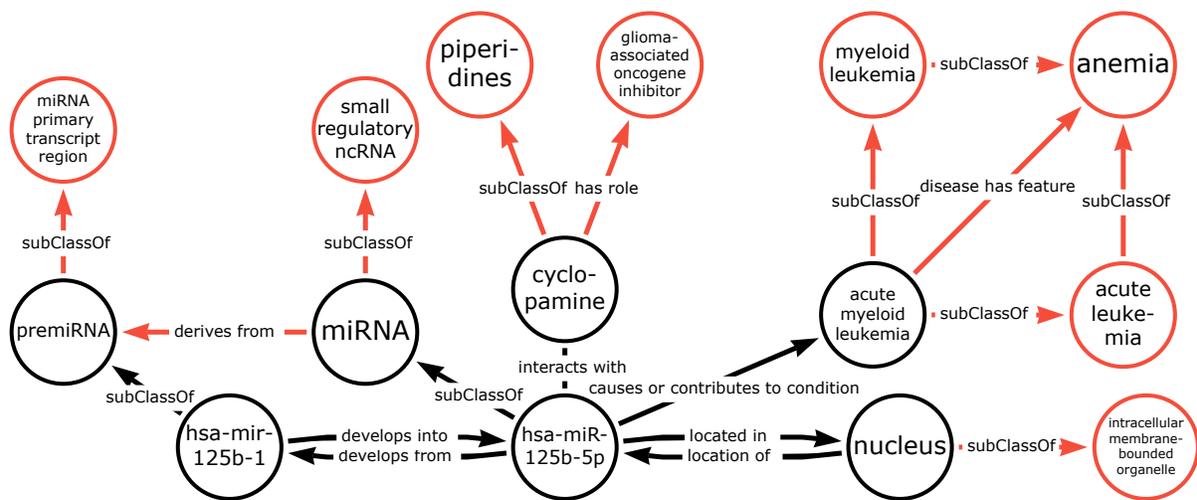
Figure 5. Example of a RNA-KG subgraph realized according to the instance-based, inverse relations, semantically abstracted (OWL-NETS without harmonization) parameters. Black nodes and edges come from the integration of RNA sources, whereas red ones from the integration of selected ontologies.
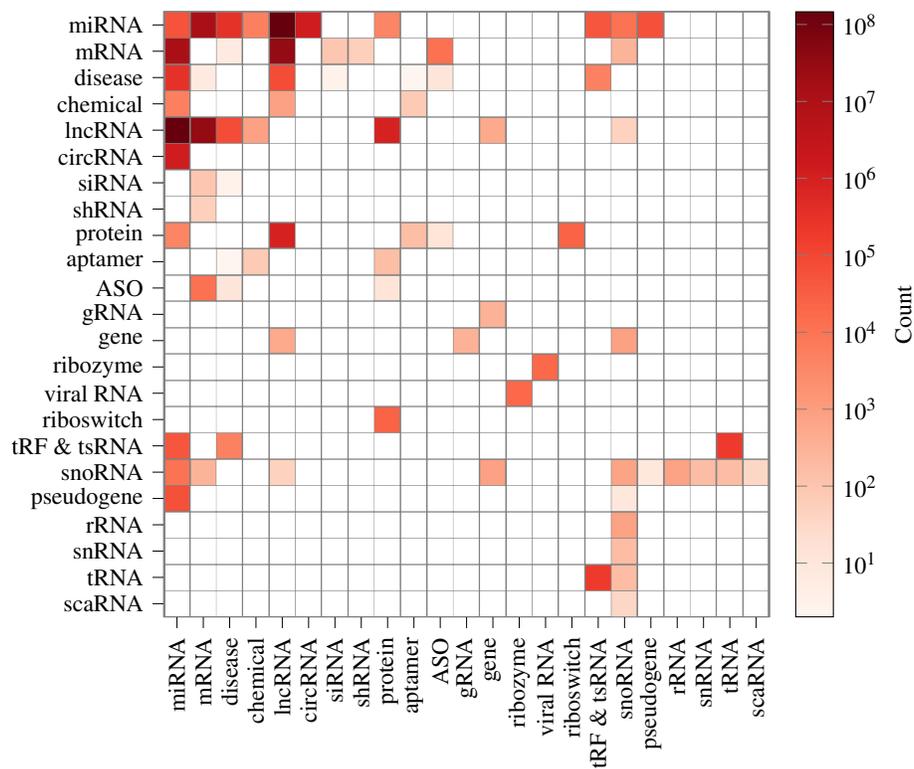
Figure 6. Number of relationships involving RNA molecules and relevant bio-entities (gene, protein, chemical, and disease) within the considered RNA sources. Colors represent the ranges of relationships in log scale, as reported in the legend.
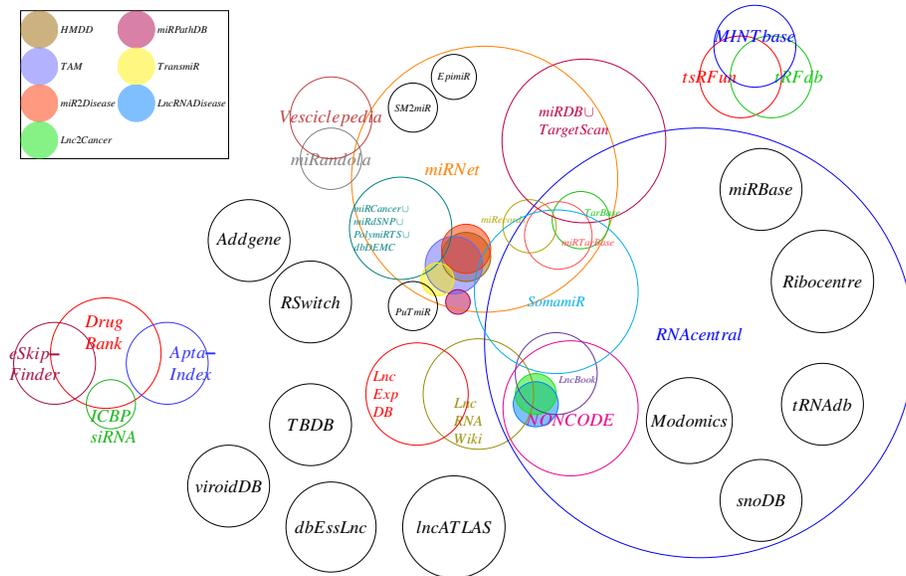
Figure 7. Bubbles represent the relationships made available from the considered data sources. Overlapping and inclusions of bubbles show the presence of common relationships among the considered data sources.
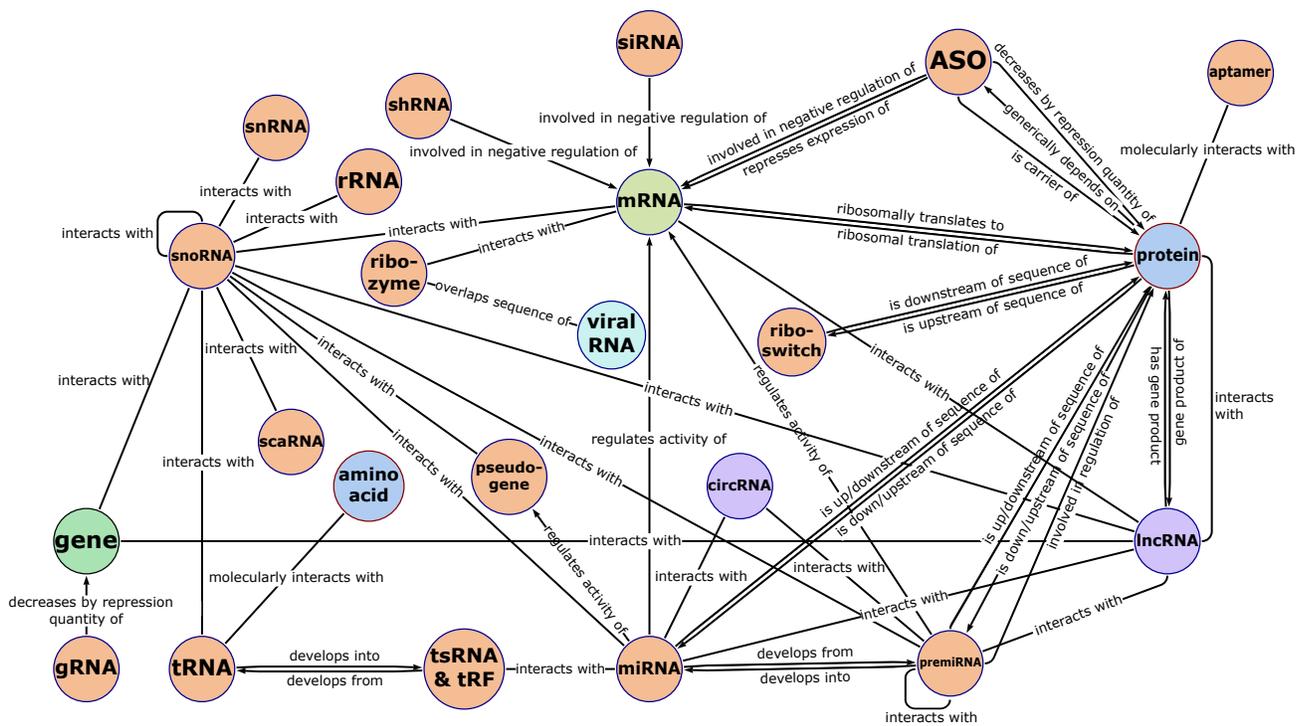
Figure 8. RNA-KG meta-graph. Most non-RNA entities are not represented to simplify the visualization.

Figure 9. The complete conceptual RNA-KG meta-graph.

(a) Distribution of nodes.

(b) Distribution of edges.
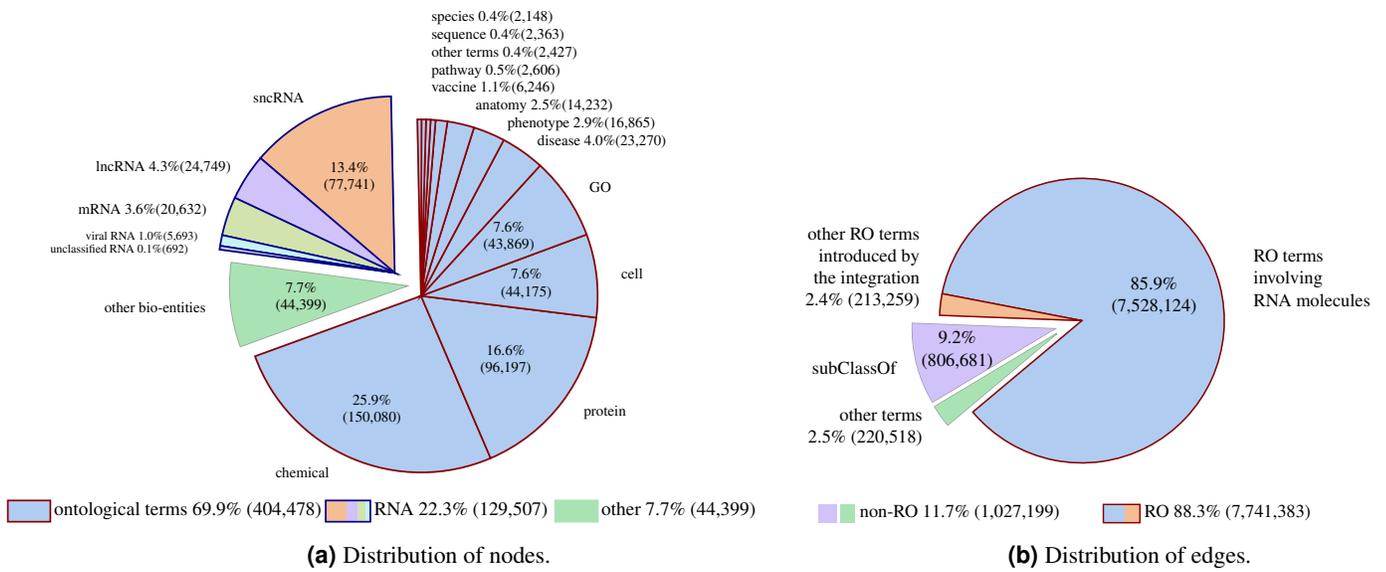
Figure 10. Pie-chart of: (a) node distribution according to node types. (b) edge distribution according to edge types.

(a) Distribution of RNA molecules.

(b) Distribution of other bio-entities.
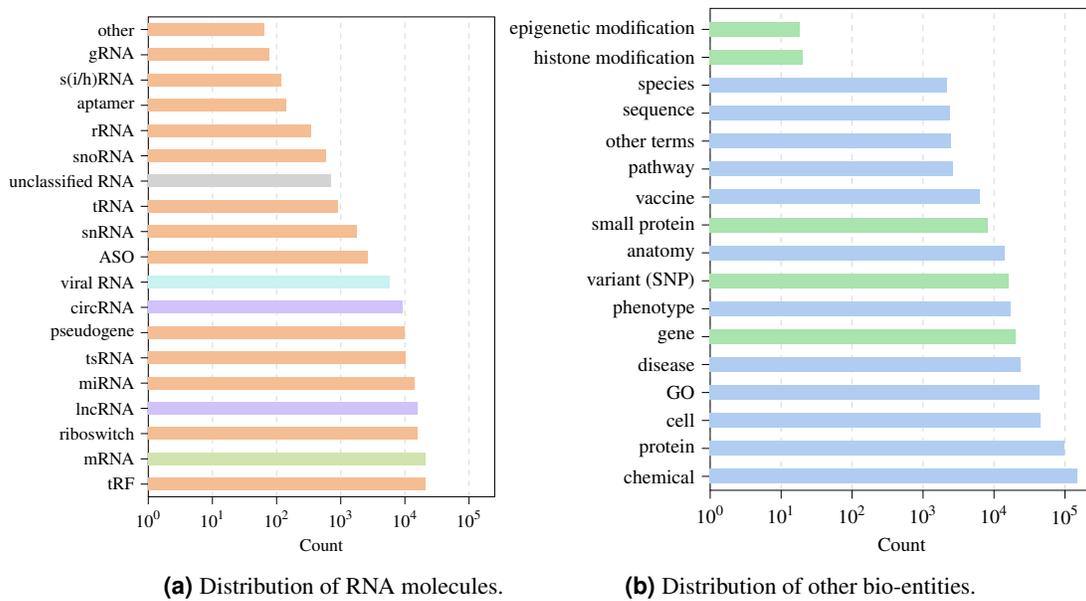
Figure 11. Node distribution according to node types.
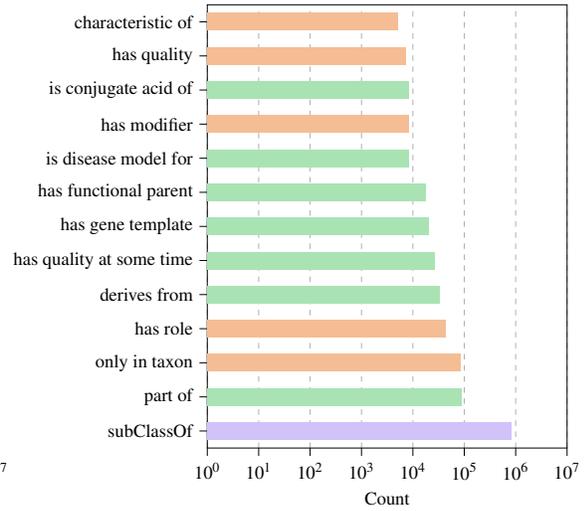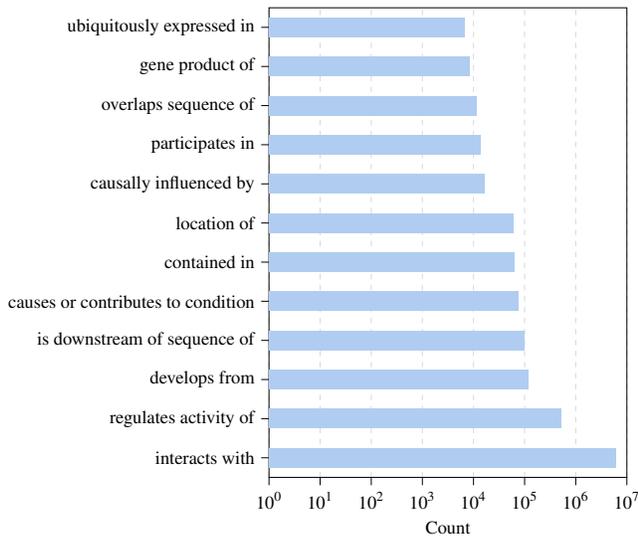
(a) Distribution of edges involving RNA molecules.

(b) Distribution of other edges in RNA-KG.

Figure 12. Edges distribution. Only direct edges with more than 5,000 occurrences are reported.
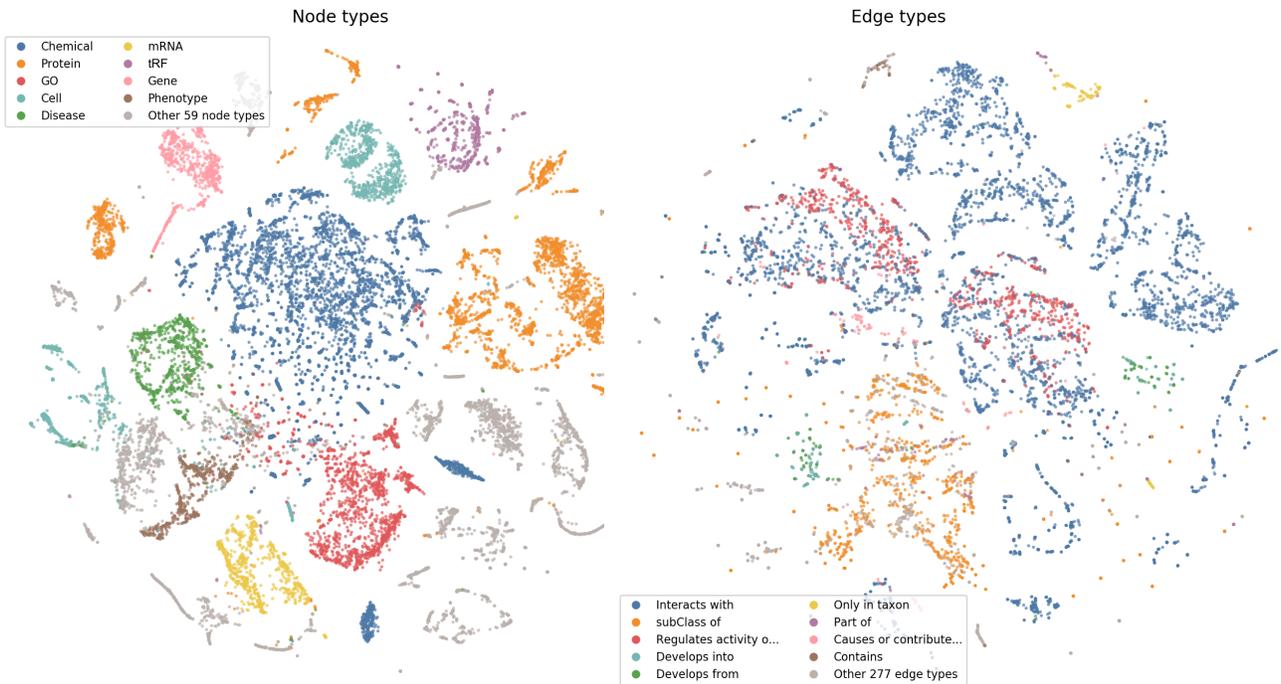
(a) Node types embedding.

(b) Edge types embedding.

Figure 13. Bidimensional view of RNA-KG embeddings.
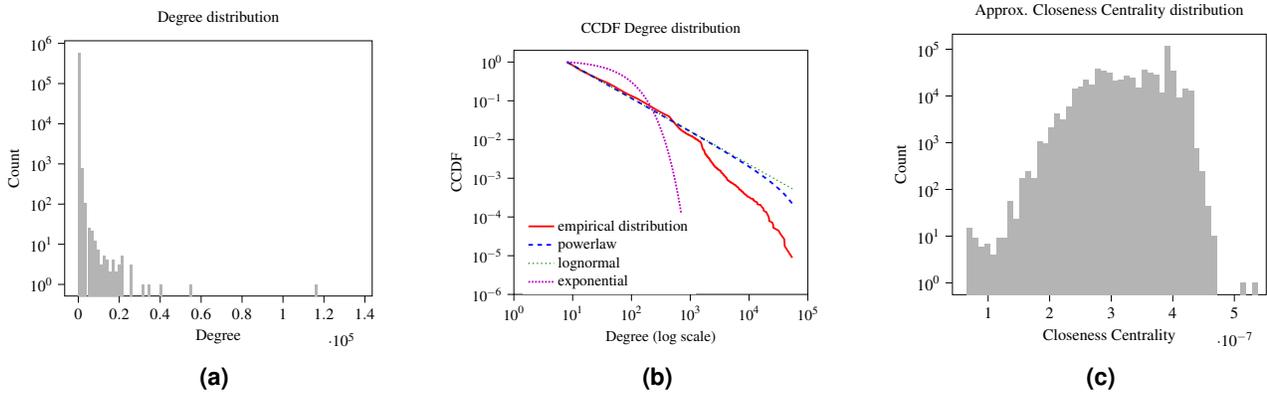
Figure 14. (a) Node degree distribution (semi-log). (b) Complementary cumulative distribution (CCDF) for the node degree. (c) Approximated closeness centrality distribution.

Name	Abbr.	Description
Human Phenotype Ontology[38]	HPO	Terms representing medically relevant phenotypes and disease-phenotype annotations.
Gene Ontology[34]	GO	Terms representing attributes of gene products in all organisms. Cellular component, molecular function, and biological process domains are covered.
Monarch Merged Disease Ontology[83]	Mondo	Terms representing human diseases.
Vaccine Ontology[84]	VO	Terms in the domain of vaccine and vaccination.
Chemical Entities of Biological Interest[85]	ChEBI	Structured classification of molecular entities of biological interest focusing on "small" chemical compounds.
Uber-anatomy Ontology[86]	Uberon	Terms representing body parts, organs and tissues in a variety of animal species, with a focus on vertebrates.
Cell Line Ontology[87]	CLO	Terms representing publicly available cell lines.
PRotein Ontology[88]*	PRO	Terms representing protein-related entities (including specific modified forms, orthologous isoforms, and protein complexes).
Sequence Ontology[89]	SO	Terms representing features and properties of nucleic acid used in biological sequence annotation.
Pathway Ontology[90]	PW	Terms for annotating gene products to pathways.
Relation Ontology[23]	RO	Terms and properties representing relationships used across a wide variety of biological ontologies.

Table 1. Main biomedical ontologies employed for RNA-KG construction (* modified to exclude all non-human proteins).

Type	Data source	Species	# RNAs	Format	API	Threshold	SI	Relation with	TI	# Relation
miRNA	miRBase[91]	271	87,474	rel/CSV	no		WR	premiRNA	WR	48,885
	miRDB[92]	5	7,086	CSV	no	$\sigma > 80$	WR	mRNA	WR	3,519,884
	miRNet[93]	10	7,928	rel/CSV	yes		WR	SNP	WR	67,532
								mRNA	WR	3,025,487
								snoRNA	WR	9,738
								chemical	M	4,935
								TF	M	3,311
								epi. mod.	M	1,955
								lncRNA	WR	31,345
								pseudogene	WR	59,417
								circRNA	WR	804,086
								disease	M	32,004
	miRecords[94]	9	384	CSV	no	validated	WR	mRNA	M	1,529
	HMDD[95]	HS	1,206	CSV	no		WR	disease	M	35,547
	EpimiR[96]	7	617	CSV	no		WR	epi. mod.	M	1,974
	miR2Disease[97]	HS	349	CSV	no		WR	disease	O	3,273
	TargetScan[98]	5	5,168	CSV	no	validated	WR	mRNA	WR	2,850,014
	SomamiR DB[99]	HS	1,078	CSV	no	validated	WR	mRNA	WR	2,313,416
								circRNA	WR	428,237
								lncRNA	WR	127,025
								disease	M	2,424
	TarBase[100]	18	2,156	rel/CSV	no		WR	mRNA	WR	665,843
	miRTarBase[101]	28	4,630	CSV	no		WR	mRNA	WR	2,200,449
	SM2miR[102]	21	1,658	CSV	no		WR	chemical	M	4,989
	TransmiR[103]	19	785	CSV	no	validated	WR	TF	M	3,730
	PolymiRTS[104]	HS	11,182	rel/CSV	no		WR	disease	M	83,516
	dbDEMC[105]	HS	3,268	CSV	no	p_{val}<0.01	WR	disease	M	160,800
	TAM[106]	HS	1,209	CSV	no		WR	mol. function	M	2,538
								miRNA	WR	1,218
								TF	M	165
								disease	M	12,516
								anatomy	M	58
	PuTmiR[107]	HS	1,296	CSV	no		WR	TF	M	12,097
	miRPathDB[108]	HS, MM	29,430	CSV	no	FDR<0.01	WR	mol. function	M	3,063
	miRCancer[109]	HS	57,984	CSV	no		WR	disease	M	9,080
	miRdSNP[110]	HS	249	CSV	no		WR	disease	WR	786
								SNP	M	758
	miRandola[111]	14	1,002	CSV	no		WR	extracell. form	M	3,262
								chemical	M	25
mRNA vaccine	DrugBank[112]		4	rel/RDF	yes^S		P	disease	M	7
s(i/h)RNA	ICBP siRNA[113]	HS, MM	147	HTML	no		P	mRNA	WR	147
	DrugBank[112]		4	rel	yes^S		P	mRNA	WR	3
								disease	M	3
RNA aptamer	Apta-Index[114]		230	rel	no		P	chemical	M	77
								protein	M	153
	DrugBank[112]		2	rel/RDF	yes^S		P	protein	M	2
								disease	M	2
ASO	eSkip-Finder[115]	4	2,196	rel	no		P	mRNA	WR	11,778
	DrugBank[112]		12	rel/RDF	yes^S		P	protein	M	12
								mRNA	WR	7
								disease	M	11
gRNA	Addgene[116]	29	296	HTML	no		P	gene	WR	321

Table 2. Main data sources (Part I). For each type of RNA molecule, the table reports the corresponding data sources. Moreover, for each data source, `Species` and `#RNAs` columns specify the number of species and distinct sequences (`HS` and `MM` tags refer to specific species *Homo sapiens* and *Mus musculus*); `Relation with` and `#Relation` columns specify the distinct relationships with bio-entities and their number; `Format` column refers to the data format (`CSV` for flatfiles, `rel` for relational tables, `RDF`, or `HTML` for web pages); `API` column reports the availability of API or SPARQL endpoints (the last one denoted with the superscript s) for data access; `Threshold` column provides identified quality threshold within the source. `SI` and `TI` columns contain the class of the identification schemes (`WR` – *Well-Reputed*, `O` – *Ontology-based*, `M` – *Mapping-based*, and `P` – *Proprietary*) adopted respectively by source and target(s) within a specific resource (the source is the RNA molecule specified in the `Type` column, whereas target(s) are specified in the `Relation with` column).

Type	Data source	Species	# RNAs	Format	API	Threshold	SI	Relation with	TI	# Relation
lncRNA	LncBook[117]	HS	323,950	rel/CSV	no		WR	miRNA	WR	146,092,274
								small protein	WR	772,745
								disease	M	34,536
								biological context	M	95,243
	LncRNADisease[118]	4	6,066	CSV	no		WR	disease	M	20,277
	LncExpDB[119]	HS	101,293	rel/CSV	no		WR	mRNA	WR	28,443,865
	dbEssLnc[120]	HS, MM	207	JSON	no		WR	biological role	P	207
								biological process	O	28
	lncATLAS[121]	HS	6,768	CSV	no		WR	cell. comp.	M	2,429,368
	NONCODE[122]	39	644,510	rel	no		WR	disease	O	32,226
	Lnc2Cancer[123]	HS	3,402	CSV	no		WR	disease	O	9,254
	LncRNAWiki[124]	HS	106,063	rel/CSV	no		WR	small protein	WR	9,387
								disease	M	7,634
								biological context	M	18,453
								cell. comp.	M	4,969
								gene	WR	509
								miRNA	WR	210
								TF	M	232
								biological process	M	10,806
								mol. function	M	1,800
								chemical	M	789
								pathway	M	571
Ribozyme	Ribocentre[125]	1,195	21,084	rel	no		P	biological process	M	34
Viral RNA	ViroidDB[126]	9	9,891	CSV	no		WR	ribozyme	P	17,460
Riboswitch	TBDB[127]	3,621	23,497	CSV	no		P	protein	M	23,535
	RSwitch[128]	50	215	rel/CSV	no		P	bact. strain	WR	215
tRF & tsRNA	tRFdb[129]	7	863	CSV	no		P	tRNA	P	792
	tsRFun[130]	HS	3,940	CSV	no	FDR<0.01	P	miRNA	WR	45,165
								tRNA	P	46,798
								disease	M	4,620
	MINTbase[131]	HS	28,824	CSV	no		P	tRNA	P	125,285
snoRNA	snoDB[132]	HS	751	CSV	no		WR	gene	WR	763
								mRNA	WR	276
								lncRNA	WR	45
								miRNA	WR	17
								pseudogene	WR	10
								rRNA	P	735
								snoRNA	WR	670
								snRNA	WR	164
								tRNA	P	164
								scaRNA	WR	34
tRNA	tRNAdb[133]	681	9,758	rel	no		P	amino acid	M	8,872
Inter RNA	RNAInter[134]	156	455,887	CSV	yes	$\sigma \geq 0.2886$	WR	chemical	M	10,890
								histone mod.	P	1,060,685
								RBP	M	5,200,067
								TF	M	9,323,690
								protein	M	22,543,829
								gene	WR	119,377
	RNALocate[135]	104	123,592	CSV	yes		WR	cell. comp.	M	213,429
	RNADisease[136]	117	91,245	CSV	yes	$\sigma \geq 0.95$	WR	disease	O	343,273
	ncRDeathDB[137]	12	648	CSV	yes		WR	prog. cell death	M	4,615
	cncRNADB[138]	21	2,002	CSV	yes		WR	anatomy	M	2,598
	ViRBase[139]	152	41,718	CSV	yes	$\sigma \geq 0.7$	WR	viral RNA	WR	719,214
								viral protein	M	195
	Vesiclepedia[140]	41	20,490	CSV	no		WR	extracell. form	M	388,154
	DirectRMDB[141]	25	19,702	CSV	no		WR	epi. mod.	WR	904,712
	Modomics[142]	32	225	rel/RDF	yes		WR	epi.mod.	WR	276

Table 3. Main data sources (Part II).

Relation ID	Name	Inverse Relation ID	Inverse Name
RO:0000056	participates in	RO:0000057	has participant
RO:0000079	function of	RO:0000085	has function
RO:0001015	location of	RO:0001025	located in
RO:0001018	contained in	RO:0001019	contains
RO:0002202	develops from	RO:0002203	develops into
RO:0002204	gene product of	RO:0002205	has gene product
RO:0002245	over-expressed in		
RO:0002260	has biological role		
RO:0002246	under-expressed in		
RO:0002291	ubiquitously expressed in	RO:0002293	ubiquitously expresses
RO:0002302	is treated by substance	RO:0002606	is substance that treats
RO:0002430	involved in regulation of		
RO:0002430	involved in negative regulation of		
RO:0002434	interacts with*		
RO:0002436	molecularly interacts with*		
RO:0002526	overlaps sequence of*		
RO:0002528	is upstream of sequence of	RO:0002529	is downstream of sequence of
RO:0002559	causally influenced by	RO:0002566	causally influences
RO:0003002	represses expression of		
RO:0003302	causes or contributes to condition		
RO:0010001	generically depends on	RO:0010002	is carrier of
RO:0011002	regulates activity of		
RO:0011007	decreases by repression quantity of		

Table 4. Main relations among bio-entities involving RNA with the RO identifier (* symmetric relationship).

Graph parameter	
Number of nodes	578,384
Number of directed edges	8,768,582
Max out degree	27,109
Max in degree	117,135
Number of edges*	5,583,802
Max degree*	117,142
Min degree*	1
Mean degree*	9.65
Diameter*	36
Upper bound Treewidth*	8,554
Mean closeness centrality*	3.38×10^{-7}

Table 5. Basic topological properties of RNA-KG (* calculated on the undirected version of the KG).

Supplementary material

Supplementary Table 1 specifies the bio-ontologies that can be exploited for representing concepts in RNA sources. RNA sources are categorized according to the main treated molecules of RNA (whose characteristics are reported in Tables 2-3).

Supplementary Tables 2-6 detail the interactions present in RNA-KG by showing the two interactors with their numerosity (`Subject` column refers to the numerosity of the first entity while `Object` column refers to the numerosity of the second entity in the `Edge` column), the RO relation we used to semantically describe the interaction (`Relation` column) with its cardinality (`Direct Relation(s)` column), and the sources that have been processed to include the interaction in RNA-KG (`Source(s)` column). We omit inverse relationships because they can be retrieved by means of Table 4. Supplementary Figure 1-2 show bio-entities present in RNA sources and the mapping on RO terms we used to represent relationships within the sources. Each source is annotated with a red spot if the bioentity or the RO term is present in the source. Confirming our previous analysis, lncRNA, miRNA, mRNA, and protein are among the most represented molecules, whereas `interacts with`, `regulates activity of`, and `causes or contributes to condition` are among the most represented RO terms. Supplementary Table 7 shows the primary node types and their corresponding identifiers with an instance sample. Finally, Supplementary Listings 1- 3 show three examples of queries on RNA-KG that can be executed through the SPARQL endpoint's query tab.
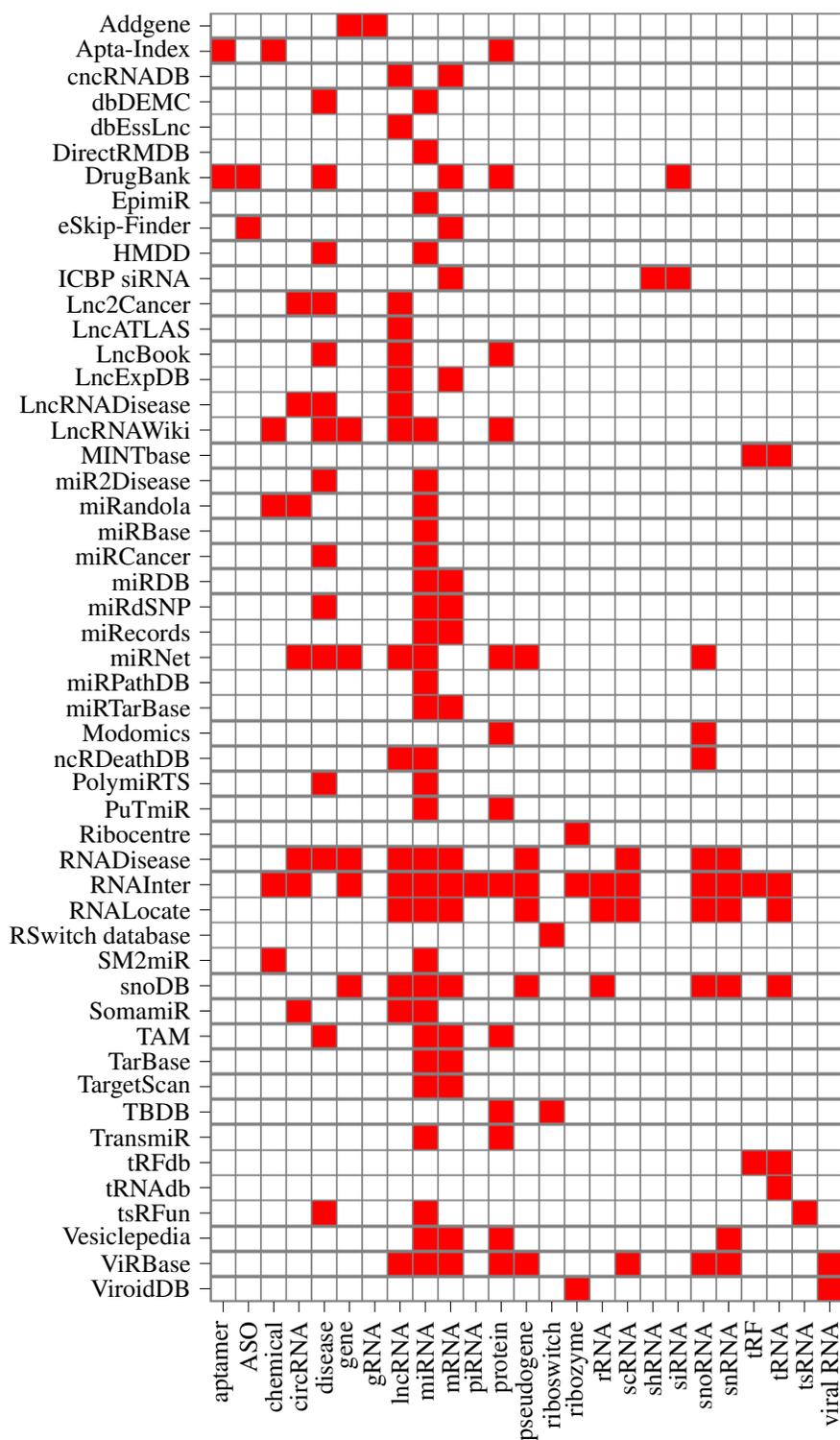
Supplementary Figure 1. Relevant bio-entities involved in RNA sources. Columns represent bio-entities involved in the RNA sources (rows) included in RNA-KG.
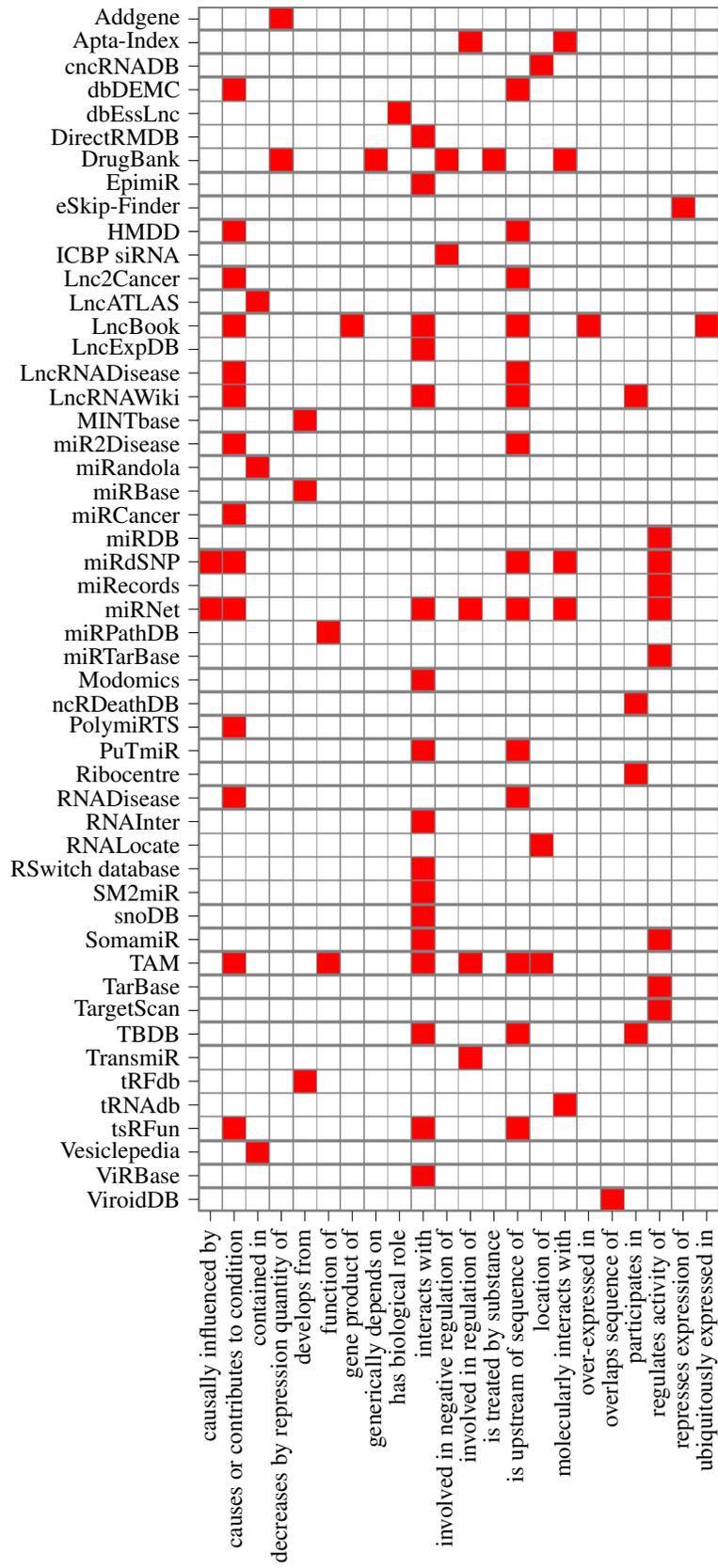
Supplementary Figure 2. Overlap of of RO terms in RNA sources. Columns represent the RO terms involved in the RNA sources (rows) included in RNA-KG.

Type	Data source	GO	Mondo/HPO	VO	ChEBI	Uberon	CLO	PRO	SO	PW
miRNA	miRBase								x	
	miRDB								x	
	miRNet	x	x		x			x	x	
	miRecords								x	
	EpimiR	x							x	
	HMDD		x						x	
	miR2Disease		x						x	
	TargetScan								x	
	SomamiR DB		x						x	
	TarBase								x	
	miRTarBase								x	
	SM2miR				x				x	
	TransmiR							x	x	
	PolymiRTS		x						x	
	dbDEMC		x						x	
	TAM	x	x			x		x	x	
	PuTmiR							x	x	
	miRPathDB	x							x	
	miRCancer		x						x	
	miRdSNP		x						x	
	miRandola	x			x				x	
mRNA vaccine	DrugBank		x	x						
siRNA	ICBP siRNA								x	
	DrugBank		x		x				x	
RNA aptamer	Apta-Index				x			x		
	DrugBank		x		x			x		
ASO	eSkip-Finder								x	
	DrugBank		x		x			x		
gRNA	Addgene								x	
lncRNA	LncBook	x	x			x	x		x	
	LncRNADisease		x						x	
	LncExpDB								x	
	dbEssLnc	x			x				x	
	lncATLAS	x							x	
	NONCODE		x						x	
	Lnc2Cancer		x						x	
	LncRNAWiki	x	x		x			x	x	x
Ribozyme	Ribocentre	x							x	
Viral RNA	ViroidDB								x	
Riboswitch	TBDB							x	x	
	RSwitch			x					x	
tRF	tRFdb								x	
	tsRFun		x						x	
	MINTbase								x	
snoRNA	snoDB								x	
tRNA	tRNAdb				x				x	
Inter RNA	RNAInter				x				x	
	RNALocate	x							x	
	RNADisease		x						x	
	ncRDeathDB	x							x	
	cncRNADB							x	x	
	ViRBase							x	x	
	Vesiclepedia	x							x	
	DirectRMDB								x	
	Modomics							x	x	

Supplementary Table 1. Bio-ontologies that can be exploited for the characterization of data sources.

Edge	Relation	Source(s)	Subjects	Objects	Direct Relation(s)
premiRNA-miRNA	develops into	miRBase	1,917	2,656	2,879
premiRNA-pseudogene	interacts with	RNAInter	1	1	1
miRNA-protein	interacts with	RNAInter	10	98	105
premiRNA-protein	interacts with	RNAInter	20	22	26
premiRNA-mRNA	regulates activity of	miRDB miRecords TarBase miRTarBase TargetScan SomamiR miRdSNP	11	107	117
miRNA-mRNA	regulates activity of	miRDB miRecords TarBase miRTarBase TargetScan SomamiR miRdSNP	2,761	19,125	1,373,343
miRNA-mRNA	interacts with	RNAInter	2,599	16,718	580,001
premiRNA-mRNA	interacts with	RNAInter	133	175	222
miRNA-miRNA	interacts with	RNAInter	4	4	4
miRNA-pseudogene	regulates activity of	miRNet	642	3,743	59,377
miRNA-pseudogene	interacts with	RNAInter	466	720	1,894
mRNA-pseudogene	interacts with	RNAInter	856	1,043	1,173
pseudogene-pseudogene	interacts with	RNAInter	79	77	85
rRNA-pseudogene	interacts with	RNAInter	5	3	5
miRNA-circRNA	interacts with	RNAInter	42	139	322
miRNA-othersRNA	interacts with	RNAInter	6	12	13
miRNA-epigenetic modification	interacts with	EpimiR RNAInter DirectRMDB	499	22	1,911
premiRNA-epigenetic modification	interacts with	EpimiR RNAInter DirectRMDB	421	27	773
protein-epigenetic modification	interacts with	Modomics	32	7	33
scaRNA-epigenetic modification	interacts with	Modomics	21	4	21
snoRNA-epigenetic modification	interacts with	Modomics	6	3	6
miRNA-disease	causes or contributes to condition	miR2Disease HMDD miRNet dbDEMC miRdSNP TAM RNADisease PolymiRTS miRCancer	2,627	611	38,258
premiRNA-disease	causes or contributes to condition	miR2Disease HMDD miRNet dbDEMC miRdSNP TAM RNADisease PolymiRTS miRCancer	608	193	5,034
miRNA-lncRNA	interacts with	miRNet LncRNAWiki SomamiR RNAInter	2,534	777	13,893
premiRNA-lncRNA	interacts with	miRNet LncRNAWiki SomamiR RNAInter	111	535	3,450

Supplementary Table 2. RNA-KG Descriptive statistics by primary edge type (Part I).

Edge	Relation	Source(s)	Subjects	Objects	Direct Relation(s)
variant-miRNA	causally influences	miRNet miRdSNP	300	164	343
variant-premiRNA	causally influences	miRNet miRdSNP	10,756	251	11,281
variant-gene	causally influences	miRNet	357,872	16,755	357,872
variant-disease	causally influences	miRdSNP	321	26	346
variant-TF	causally influences	miRNet	2,080,335	113	2,082,657
tsRNA-miRNA	interacts with	tsRFun	8,044	103	121,236
tsRNA-disease	causes or contributes to condition	tsRFun	449	31	26,602
tRF-tRNA	develops from	tRFdb MINTbase	20,628	882	114,851
tRF-mRNA	interacts with	RNAInter	269	11,150	26,314
tRF-lncRNA	interacts with	RNAInter	18	6	18
tRF-pseudogene	interacts with	RNAInter	20	13	26
piRNA-lncRNA	interacts with	RNAInter	1	1	1
piRNA-mRNA	interacts with	RNAInter	1	1	1
snoRNA-gene	interacts with	snoDB	373	249	379
snoRNA-premiRNA	interacts with	snoDB miRNet	1	1	1
snoRNA-miRNA	interacts with	snoDB miRNet RNAInter	249	509	1,385
snoRNA-snoRNA	interacts with	snoDB	74	86	344
snoRNA-lncRNA	interacts with	snoDB RNAInter	146	31	196
snoRNA-snRNA	interacts with	snoDB RNAInter	432	329	717
snoRNA-rRNA	interacts with	snoDB	427	318	672
snoRNA-mRNA	interacts with	snoDB RNAInter	99	142	180
snoRNA-tRNA	interacts with	snoDB	4	4	4
snoRNA-retained intron	interacts with	snoDB	25	8	33
snoRNA-scaRNA	interacts with	snoDB RNAInter	24	9	34
snoRNA-pseudogene	interacts with	snoDB RNAInter	8	8	9
lncRNA-gene	interacts with	LncRNAWiki RNAInter	185	620	1,138
othersRNA-gene	interacts with	RNAInter	1	2	2
mRNA-gene	interacts with	RNAInter	3	10	10
lncRNA-disease	causes or contributes to condition	LncRNADisease Lnc2Cancer LncRNAWiki LncBook RNADisease	1,331	347	6,557
circRNA-disease	causes or contributes to condition	LncRNADisease Lnc2Cancer RNADisease	14	8	15
snRNA-disease	causes or contributes to condition	RNADisease	7	13	14
pseudogene-disease	causes or contributes to condition	RNADisease	101	68	397
snoRNA-disease	causes or contributes to condition	RNADisease	14	6	14
scRNA-disease	causes or contributes to condition	RNADisease	1	3	3
mRNA-disease	causes or contributes to condition	RNADisease	412	93	502
lncRNA-chemical	interacts with	LncRNAWiki RNAInter	822	80	1,173
small protein-lncRNA	gene product of	LncBook	8,178	810	8,417
lncRNA-protein	interacts with	LncBook LncRNAWiki RNAInter	8,412	294	16,212
lncRNA-biological context	over-expressed in	LncBook	822	9	1,395
lncRNA-biological context	under-expressed in	LncBook	1,742	9	3,128

Supplementary Table 3. RNA-KG Descriptive statistics by primary edge type (Part II).

Edge	Relation	Source(s)	Subjects	Objects	Direct Relation(s)
lncRNA-biological role	has biological role	dbEssLnc	173	3	173
lncRNA-biological context	ubiquitously expressed in	LncBook	2,221	9	6,610
lncRNA-cellular component	contained in	LncATLAS	10,207	6	27,287
lncRNA-pathway	participates in	LncRNAWiki	30	11	43
lncRNA-biological process	participates in	LncRNAWiki	21	2	23
miRNA-TF	is upstream of sequence of	PuTmiR	4	17	19
miRNA-TF	is downstream of sequence of	PuTmiR	4	10	10
premiRNA-TF	is upstream of sequence of	PuTmiR	484	66	1,839
premiRNA-TF	is downstream of sequence of	PuTmiR	488	65	1,949
premiRNA-TF	involved in regulation of	miRNet TransmiR TAM	330	320	1,869
premiRNA-molecular function	has function	TAM miRPathDB	26	2	29
premiRNA-premiRNA	interacts with	TAM	320	646	820
premiRNA-anatomy	located in	TAM	57	7	70
lncRNA-anatomy	located in	cncRNADB	4	5	6
mRNA-anatomy	located in	cncRNADB	3	3	3
lncRNA-cell	located in	cncRNADB	49	7	52
mRNA-cell	located in	cncRNADB	41	23	70
mRNA-chemical	interacts with	RNAInter	92	12	97
TEC-chemical	interacts with	RNAInter	2	1	2
snoRNA-chemical	interacts with	RNAInter	15	2	15
pseudogene-chemical	interacts with	RNAInter	82	7	84
premiRNA-chemical	interacts with	SM2miR RNAInter miRNet miRandola	17	11	22
miRNA-chemical	interacts with	SM2miR RNAInter miRNet miRandola	724	147	3,067
ASO drug-disease	is substance that treats	DrugBank	10	8	12
ASO drug-protein	decreases by repression quantity of	DrugBank	5	11	11
ASO drug-protein	is carrier of	DrugBank	1	1	1
siRNA drug-mRNA	involved in negative regulation of	DrugBank	3	3	3
siRNA-mRNA	involved in negative regulation of	ICBP siRNA	77	54	79
shRNA-mRNA	involved in negative regulation of	ICBP siRNA	40	42	42
siRNA drug-disease	is substance that treats	DrugBank	4	4	6
aptamer-protein	molecularly interacts with	Apta-Index	33	76	85
aptamer-chemical	molecularly interacts with	Apta-Index	114	67	114
aptamer drug-protein	molecularly interacts with	DrugBank	2	4	4
aptamer drug-disease	is substance that treats	DrugBank	1	4	4
mRNA vaccine-disease	is substance that treats	DrugBank	8	1	8
lncRNA-mRNA	interacts with	RNAInter LncExpDB	2,214	18,228	2,429,654
lncRNA-lncRNA	interacts with	RNAInter	1,431	1,431	3,187
lncRNA-rRNA	interacts with	RNAInter	10	8	17
lncRNA-pseudogene	interacts with	RNAInter	136	2,239	2,577
lncRNA-ncRNA	interacts with	RNAInter	4	6	6
lncRNA-scaRNA	interacts with	RNAInter	7	8	11
lncRNA-TF	interacts with	RNAInter	4,833	370	173,842
lncRNA-ribozyme	interacts with	RNAInter	1	1	1
circRNA-protein	interacts with	RNAInter	1	2	2
ncRNA-protein	interacts with	RNAInter	12	2	12
othersRNA-protein	interacts with	RNAInter	12	2	12
pseudogene-protein	interacts with	RNAInter	44	17	54
ribozyme-protein	interacts with	RNAInter	1	2	2

Supplementary Table 4. RNA-KG Descriptive statistics by primary edge type (Part III).

Edge	Relation	Source(s)	Subjects	Objects	Direct Relation(s)
scRNA-protein	interacts with	RNAInter	1	5	5
snRNA-protein	interacts with	RNAInter	3	11	11
snoRNA-protein	interacts with	RNAInter	2	3	3
snoRNA-miscRNA	interacts with	snoDB	2	2	2
unknownRNA-protein	interacts with	RNAInter	1	1	1
vRNA-protein	interacts with	RNAInter	1	1	1
riboswitch-protein	is downstream of sequence of	TBDB	9,384	1,405	148,262
riboswitch-bacterial strain	interacts with	RSwitch database	215	77	215
riboswitch-biological process	participates in	TBDB	13,072	111	13,072
viralRNA-ribozyme	overlaps sequence of	ViroidDB	5,654	6	5,896
ribozyme-biological process	participates in	Ribocentre	2	6	11
miRNA-viralmRNA	interacts with	ViRBase	80	38	250
snRNA-viralmRNA	interacts with	ViRBase	1	1	1
lncRNA-viralmRNA	interacts with	ViRBase	3	8	8
pseudogene-viralmRNA	interacts with	ViRBase	1	3	3
snRNA-viralmiRNA	interacts with	ViRBase	2	1	2
pseudogene-viralmiRNA	interacts with	ViRBase	351	4	352
snoRNA-viralmiRNA	interacts with	ViRBase	8	1	8
premiRNA-viralmiRNA	interacts with	ViRBase	1	1	1
unknownRNA-viralmiRNA	interacts with	ViRBase	3	1	3
lncRNA-viralmiRNA	interacts with	ViRBase	263	1	263
othersRNA-viralmiRNA	interacts with	ViRBase	1	1	1
scRNA-viralmiRNA	interacts with	ViRBase	1	1	1
protein-viralmiRNA	interacts with	ViRBase	11	18	21
mRNA-viralmiRNA	interacts with	ViRBase	17,564	63	17,923
miRNA-viralmiRNA	interacts with	ViRBase	1	1	1
lncRNA-viral protein	interacts with	ViRBase	1	1	1
miRNA-viral protein	interacts with	ViRBase	51	15	59
miRNA-ribozyme	interacts with	RNAInter	1	1	1
miRNA-unknownRNA	interacts with	RNAInter	14	4	14
miRNA-scRNA	interacts with	RNAInter	1	1	1
othersRNA-mRNA	interacts with	RNAInter	58	68	70
othersRNA-lncRNA	interacts with	RNAInter	41	16	49
othersRNA-pseudogene	interacts with	RNAInter	8	8	8
othersRNA-rRNA	interacts with	RNAInter	1	1	1
snRNA-snRNA	interacts with	RNAInter	21	21	33
snRNA-lncRNA	interacts with	RNAInter	34	14	52
snRNA-mRNA	interacts with	RNAInter	39	96	100
snRNA-pseudogene	interacts with	RNAInter	9	11	15
eRNA-mRNA	interacts with	RNAInter	2	2	4
scRNA-mRNA	interacts with	RNAInter	1	23	23
mRNA-mRNA	interacts with	RNAInter	4,459	4,459	7,035
mRNA-rRNA	interacts with	RNAInter	120	4	133
mRNA-ncRNA	interacts with	RNAInter	7	5	7
mRNA-scaRNA	interacts with	RNAInter	4	2	4
mRNA-protein	interacts with	RNAInter	179	130	227
rRNA-rRNA	interacts with	RNAInter	2	3	3
circRNA-RBP	interacts with	RNAInter	1,027	31	1,105
mRNA-RBP	interacts with	RNAInter	8,856	130	17,754
ribozyme-RBP	interacts with	RNAInter	1	13	13
scaRNA-RBP	interacts with	RNAInter	11	17	35
scRNA-RBP	interacts with	RNAInter	1	5	5
othersRNA-RBP	interacts with	RNAInter	19	26	54
snRNA-RBP	interacts with	RNAInter	44	42	158
lncRNA-RBP	interacts with	RNAInter	1,011	140	6,136
snoRNA-RBP	interacts with	RNAInter	200	70	753
ncRNA-RBP	interacts with	RNAInter	5	45	48
rRNA-RBP	interacts with	RNAInter	19	9	30
pseudogene-RBP	interacts with	RNAInter	1,014	92	1,907

Supplementary Table 5. RNA-KG Descriptive statistics by primary edge type (Part IV).

Edge	Relation	Source(s)	Subjects	Objects	Direct Relation(s)
premiRNA-RBP	interacts with	RNAInter	32	18	37
unknownRNA-TF	interacts with	RNAInter	1	74	74
circRNA-TF	interacts with	RNAInter	33	6	33
ribozyme-TF	interacts with	RNAInter	3	64	94
scaRNA-TF	interacts with	RNAInter	17	83	429
othersRNA-TF	interacts with	RNAInter	541	152	11,851
snRNA-TF	interacts with	RNAInter	1,124	109	24,489
snoRNA-TF	interacts with	RNAInter	419	108	11,932
scRNA-TF	interacts with	RNAInter	1	74	74
tRNA-TF	interacts with	RNAInter	8	10	77
ncRNA-TF	interacts with	RNAInter	22	110	716
rRNA-TF	interacts with	RNAInter	26	55	713
pseudogene-TF	interacts with	RNAInter	9,524	245	188,443
mRNA-TF	interacts with	RNAInter	5,019	222	8,629
premiRNA-TF	interacts with	RNAInter	1,839	140	71,662
miRNA-TF	interacts with	RNAInter	1,522	272	4,038
circRNA-extracellular vesicle	contained in	miRandola	6	1	6
lipid-extracellular vesicle	contained in	Vesiclepedia	35	3	47
mRNA-extracellular vesicle	contained in	Vesiclepedia	13,907	2	14,116
snRNA-extracellular vesicle	contained in	Vesiclepedia	1	1	1
protein-extracellular vesicle	contained in	Vesiclepedia	11,924	5	20,081
miRNA-extracellular vesicle	contained in	Vesiclepedia	435	2	554
premiRNA-extracellular vesicle	contained in	Vesiclepedia	26	2	29
circRNA-miRNA	interacts with	SomamiR miRNet	4,309	2,590	302,197
circRNA-premiRNA	interacts with	SomamiR miRNet	8,755	110	129,990
unknownRNA-histone modification	interacts with	RNAInter	1	18	18
mRNA-histone modification	interacts with	RNAInter	42	20	486
othersRNA-histone modification	interacts with	RNAInter	20	20	263
lncRNA-histone modification	interacts with	RNAInter	4,816	20	51,375
ncRNA-histone modification	interacts with	RNAInter	12	20	130
pseudogene-histone modification	interacts with	RNAInter	43	20	460
premiRNA-histone modification	interacts with	RNAInter	1,842	20	20,754
premiRNA-subcellular location	located in	RNALocate	578	7	926
miRNA-subcellular location	located in	RNALocate	2,572	15	3,496
snRNA-subcellular location	located in	RNALocate	1,719	4	1,719
ncRNA-subcellular location	located in	RNALocate	85	9	107
pseudogene-subcellular location	located in	RNALocate	218	6	230
snoRNA-subcellular location	located in	RNALocate	570	7	763
scaRNA-subcellular location	located in	RNALocate	1	1	1
rRNA-subcellular location	located in	RNALocate	2	2	3
lncRNA-subcellular location	located in	RNALocate	1,047	11	2,313
lincRNA-subcellular location	located in	RNALocate	22	5	28
othersRNA-subcellular location	located in	RNALocate	3	1	3
tRNA-subcellular location	located in	RNALocate	1	1	1
circRNA-subcellular location	located in	RNALocate	1	1	1
Y RNA-subcellular location	located in	RNALocate	4	1	4
scRNA-subcellular location	located in	RNALocate	2	1	2
mRNA-subcellular location	located in	RNALocate	13,646	19	50,903
vRNA-subcellular location	located in	RNALocate	3	2	6
mtRNA-subcellular location	located in	RNALocate	10	2	19
miRNA-programmed death	participates in	ncRDeathDB	581	3	792
lncRNA-programmed death	participates in	ncRDeathDB	99	2	99
snoRNA-programmed death	participates in	ncRDeathDB	1	1	1
gRNA-gene	decreases by repression quantity of	Addgene	77	43	77
ASO-mRNA	represses expression of	eSkip-Finder	2,633	16	2,678
ASO drug-mRNA	involved in negative regulation of	DrugBank	6	4	6
tRNA-mRNA	interacts with	RNAInter	4	4	4
tRNA-amino acid	molecularly interacts with	tRNAdb	549	19	549
tRNA-lncRNA	interacts with	RNAInter	8	4	9

Supplementary Table 6. RNA-KG Descriptive statistics by primary edge type (Part V).

Node type	Full name	Identifier(s)
Anatomy	-	Uberon (http://purl.obolibrary.org/obo/**UBERON_0005253**)
Amino acid	-	ChEBI (http://purl.obolibrary.org/obo/**CHEBI_25017**)
ASO	AntiSense Oligonucleotide	Oligo name in literature (https://eskip-finder.org?**H45_1-13_18-30**)
ASO drug	AntiSense Oligonucleotide drug	DrugBank (https://go.drugbank.com/drugs/**DB05528**)
Aptamer	RNA aptamer	Apta-Index (https://www.aptagen.com/**aptamer-details/?id=608**)
Aptamer drug	RNA aptamer drug	DrugBank (https://go.drugbank.com/drugs/**DB04932**)
Bacterial strain	-	NCBI Taxonomy Browser (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/**wwwtax.cgi?id=485**)
Biological context	-	Uberon (http://purl.obolibrary.org/obo/**UBERON_0000479**) GO (http://purl.obolibrary.org/obo/**GO_0070062**) CLO (http://purl.obolibrary.org/obo/**CLO_0009828**) Mondo (http://purl.obolibrary.org/obo/**MONDO_0005108**)
Biological process	-	GO (http://purl.obolibrary.org/obo/**GO_0044848**)
Biological role	-	NIH Talking Glossary of Genetic Terms (https://www.genome.gov/genetics-glossary/**Oncogene**)
Cell	-	CLO (http://purl.obolibrary.org/obo/**CLO_0009828**)
Cellular component	-	GO (http://purl.obolibrary.org/obo/**GO_0110165**)
Chemical	-	ChEBI (http://purl.obolibrary.org/obo/**CHEBI_77062**)
circRNA	Circular RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**6575?circRNA**)
Disease	-	Mondo (http://purl.obolibrary.org/obo/**MONDO_0004971**)
Epigenetic modification	-	GO (http://purl.obolibrary.org/obo/**GO_0006306**) ENCODE (https://www.encodeproject.org/targets/**H3K4me2**)
eRNA	RNA enhancer	Human enhancer RNA Atlas (HeRA) (https://hanlab.uth.edu/HeRA?**IL1beta-RBT46**)
Extracellular vesicle	-	GO (http://purl.obolibrary.org/obo/**GO_1990742**)
Gene	-	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**1954**)
Genomic sequence	-	SO (http://purl.obolibrary.org/obo/**SO_0000704**)
gRNA	Guide RNA	Addgene (https://**www.addgene.org/41818**)
Histone modification	-	dbEM (http://crdd.osdd.net/raghava/dbem?**H3K9me2**)
lincRNA	Long intergenic RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**100287569?lincRNA**)
Lipid	-	ChEBI (http://purl.obolibrary.org/obo/**CHEBI_136143**)
lncRNA	Long non-coding RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**100506207?lncRNA**)
miscRNA	Miscellaneous RNA	NCBI Entrez gene (www.ncbi.nlm.nih.gov/gene/**6029?misc_RNA**)
mRNA	Messenger RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**1756?mRNA**)
mRNA vaccine	-	DrugBank (https://go.drugbank.com/drugs/**DB15654**)
miRNA	Mature microRNA	miRBase (https://www.mirbase.org/cgi-bin/mature.pl?mature_acc=**MIMAT0022711**)
mtRNA	Mitochondrial RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**4549?mtRNA**)
ncRNA	Non-coding RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**102723629?ncRNA**)
Other (not classified yet) RNA	-	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**3537?other**)
Pathway	-	PW (http://purl.obolibrary.org/obo/**PW_0000632**)
Phenotype	-	HPO (http://purl.obolibrary.org/obo/**HP_0005506**)
piRNA	Piwi-interacting RNA	piRBase (http://bigdata.ibp.ac.cn/piRBase?**piR-39980**)
premiRNA	Hairpin microRNA	miRBase (https://www.mirbase.org/cgi-bin/mirna_entry.pl?acc=**MI0000067**)
Programmed cell death	-	GO (http://purl.obolibrary.org/obo/**GO_0097300**)
Protein	-	PRO (http://purl.obolibrary.org/obo/**PR_Q92506**)
Pseudogene	-	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**442240?pseudo**)
Retained intron	-	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**23642?retained_intron**)
RBP	RNA-Binding Protein	PRO (http://purl.obolibrary.org/obo/**PR_Q92506**)
Riboswitch	-	TBDB (https://tbdb.io/tboxes/**UQCD7JYG.html**)
Ribozyme	RIBOnucleic acid enZYME	Rfam (http://rfamlive.xfam.org/family/**RF02682**)
rRNA	Ribosomal RNA	snoDB (http://scottgroup.med.usherbrooke.ca/snoDB/**28S-3616?snoDBrRNA**)
scRNA	Small conditional RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**618?scRNA**)
scaRNA	Small Cajal body-specific RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**677767?scaRNA**)
shRNA	Short/small hairpin RNA	ICBP siRNA (http://web.mit.edu/sirna/sequences/results-**1107.html**)
siRNA	Short interfering RNA	ICBP siRNA (http://web.mit.edu/sirna/sequences/results-**1053.html**)
siRNA drug	Short interfering RNA drug	DrugBank (https://go.drugbank.com/drugs/**DB15935**)
Small protein	-	SmProt (http://bigdata.ibp.ac.cn/SmProt/SmProt.php?ID=**SPROHSA53815**)
snRNA	Small nuclear RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**26824?snRNA**)
snoRNA	Small nucleolar RNA	NCBI Entrez gene (http://www.ncbi.nlm.nih.gov/gene/**727676?snoRNA**)
Subcellular location	-	GO (http://purl.obolibrary.org/obo/**GO_0005840**)
TEC	To be Experimentally Confirmed RNA	NCBI Entrez gene (https://www.ncbi.nlm.nih.gov/gene/**8123?TEC**)
TF	Transcription Factor	PRO (http://purl.obolibrary.org/obo/**PR_000007035**)
tRF	tRNA-derived fragment	tRFdb (http://genome.bioch.virginia.edu/trfdb?**tRF-3018b**) MINTbase (https://cm.jefferson.edu/MINTbase/InputController?v=f&g=GRCh37&e=1&search=submit&t=All&am=All&an=All&da=&tn=&fs=&fn=**tRF-16-4YDRFUE**)
tRNA	Transfer RNA	GtRNAdb (http://gtrnadb.ucsc.edu/genomes/eukaryota/Hsapi19/genes/**tRNA-Gln-CTG-1-3.html**) tRFdb (http://genome.bioch.virginia.edu/trfdb?**chr8.trna4-TyrGTA**) NCBI Entrez gene (https://www.ncbi.nlm.nih.gov/gene/**4567?tRNA**)
tsRNA	tRNA-derived small RNA	tsRFun (https://rna.sysu.edu.cn/tsRFun/searchDetail-tsRNA.php?tsRNAid=**tsRNA-Gly-i-0605**)
Unknown RNA	-	NCBI Entrez gene (https://www.ncbi.nlm.nih.gov/gene/**100128998?unknown**)
Vaccine	-	VO (http://purl.obolibrary.org/obo/**VO_0000186**)
Variant (SNP)	-	NCBI dbSNP (https://www.ncbi.nlm.nih.gov/snp/**rs71354105**)
Viral miRNA	-	miRBase (https://www.mirbase.org/cgi-bin/mature.pl?mature_acc=**MIMAT0001581**)
Viral mRNA	-	NCBI Entrez gene (https://www.ncbi.nlm.nih.gov/gene/**43740578?viral_mRNA**)
Viral protein	-	PRO (http://purl.obolibrary.org/obo/**PR_000036828**)
Viral RNA	-	NCBI Nucleotide database (https://www.ncbi.nlm.nih.gov/nuccore/**KF869252.1**)
vRNA	Vault RNA	NCBI Entrez gene (https://www.ncbi.nlm.nih.gov/gene/**56664?vRNA**)
Y RNA	-	NCBI Entrez gene (https://www.ncbi.nlm.nih.gov/gene/**6090?Y_RNA**)

Supplementary Table 7. RNA-KG primary node types and their corresponding identifiers with an instance sample.

Supplementary Listing 1. SPARQL query to retrieve all miRNA molecules that causes or contributes to the development of leukemia.

```
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>
PREFIX obo: <http://purl.obolibrary.org/obo/>


SELECT ?miRNA
WHERE {
  ?miRNA rdfs:subClassOf obo:SO_0000276. # SO_0000276 ->label-> miRNA
  ?miRNA obo:RO_0003302 obo:MONDO_0005059.
    # RO_0003302 ->label-> causes or contributes to condition;
    # MONDO_0005059 ->label-> leukemia
}
```

Supplementary Listing 2. SPARQL query to retrieve all premiRNA molecules that develop into mature miRNAs known to be located in an apoptotic body and cause or contribute to the development of a cancer.

```
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>
PREFIX obo: <http://purl.obolibrary.org/obo/>


SELECT ?premiRNA ?disease
WHERE {
  ?premiRNA rdfs:subClassOf obo:SO_0000647; # SO_0000647 ->label-> premiRNA
            obo:RO_0002203 ?miRNA. # RO_0002203 ->label-> develops into
  ?miRNA rdfs:subClassOf obo:SO_0000276;
         obo:RO_0003302 ?disease.
  ?miRNA obo:RO_0001025 obo:GO_0097189.
    # RO_0001025 ->label-> located in; GO_0097189 ->label-> apoptotic body
  ?disease rdfs:subClassOf obo:MONDO_0004992. # MONDO_0004992 ->label-> cancer
}
```

Supplementary Listing 3. SPARQL query to retrieve all lncRNA molecules that are over-expressed in a viral infectious disease and are known to cause or contribute to a disease treated by at least one RNA drug.

```
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>
PREFIX obo: <http://purl.obolibrary.org/obo/>
PREFIX disease: <http://purl.obolibrary.org/obo/MONDO_>
PREFIX RNAdrug: <https://go.drugbank.com/drugs/>

SELECT ?lncRNA ?disease ?RNAdrug (COUNT(DISTINCT ?RNAdrug) as ?numRNAdrugs)
WHERE {
    ?lncRNA rdfs:subClassOf obo:SO_0001877; # SO_0001877 ->label-> lncRNA
       obo:RO_0002245 obo:MONDO_0005108;
          # MONDO_0005108 ->label-> viral infectious disease
       obo:RO_0003302 ?disease.
    ?disease obo:RO_0002302 ?RNAdrug.
      # RO_0002302 ->label-> is treated by substance

    FILTER(STRSTARTS(STR(?disease), STR(disease:)))
    FILTER(STRSTARTS(STR(?RNAdrug), STR(RNAdrug:)))
}
GROUP BY ?lncRNA ?disease ?RNAdrug
HAVING (COUNT(DISTINCT ?RNAdrug) >= 1)
```