NAR Genomics and Bioinformatics, 2026, **8**, lqag089
https://doi.org/10.1093/nargab/lqag089
Methods Article

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InteRRact: a web server for the interactive exploration and comparison of transcriptome-wide RNA–RNA interactions

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Abstract

RNA–RNA interactions (RRI) can now be probed on a transcriptome-wide scale using proximity ligation methods such as SPLASH, PARIS, LIGR-seq, RIC-seq, and others. While individual pipelines for computationally processing the corresponding raw duplex reads exist, there is currently no method for comparing and exploring RRI networks across experimental protocols and cellular conditions. It thus remains difficult to discover biologically relevant interactions, to assess reproducibility, and to evaluate protocol-specific differences. Here, we present InteRRact - a web server for interactively exploring human RRI datasets derived from published duplex probing experiments. One key feature is that all available datasets have been processed uniformly. InteRRact visualizes intermolecular RRIs as gene-level networks and intramolecular interactions as linear, locus-specific genomic tracks. All RRIs are annotated with multiple quantitative metrics and evaluated statistically, allowing the user to readily filter interactions by strength of evidence and confidence. Moreover, any two datasets can be compared to identify shared and dataset-specific interactions across cell types, conditions, and experimental protocols. InteRRact thereby enables the discovery of biologically relevant interactions. InteRRact is available at https://e-rna.org/interract.

Introduction

Investigating RNA–RNA interactions (RRIs) in living cells remains a challenging yet rewarding task. Any RNA transcript can potentially exert a part of its biological functionality via intramolecular RNA interactions (*cis* RRIs) or intermolecular RRIs (trans RRIs). These two types of interactions may depend on the details of the cellular conditions—including potential binding partners—as well as the spatial and temporal localization of the transcript within the cell. Moreover, processes such as splicing and RNA editing may alter the chemical identity of the transcript during its life within the cell. Unless a *cis* or trans RRI has been evolutionarily conserved to some extent, any computational prediction method that bases its predictions solely on the sequence of the transcript cannot be expected to reliably identify all functionally relevant *cis* and trans RRIs [1, 2]. Experimental evidence is thus essential for identifying *cis* and trans RRIs in specific conditions *in vivo*.

In addition to RNA structure-probing approaches such as SHAPE and DMS-MaPseq—which only provide indirect evidence for *cis* RNA structure features—RNA duplex-probing methods provide more direct evidence for *cis* and trans RRIs. Pioneering methods—SPLASH [3], LIGR-seq [4], and PARIS [5]—provide information on subsequences that are directly interacting in the form of chimeric reads. These experimental protocols can detect *cis* and trans RRIs on a transcriptome-wide scale but remain inefficient and produce sparse and noisy raw duplex data where typically only a single-digit percentage fraction corresponds to captured RNA duplexes. As a result, the downstream interpretation of raw duplex data strongly depends on how they are computationally processed, filtered, and interpreted.

There already exist several computational pipelines for processing raw duplex data. Each pipeline outputs the detected RRIs in terms of the so-called duplex groups, which are defined as aggregated sets of overlapping chimeric reads mapped to separate loci that support the corresponding *cis* or trans RRI. Coordinates of duplex groups are accompanied by features such as the predicted hybridization energy or the estimated statistical confidence, which are used to assess the reliability of the corresponding *cis* or trans interaction. Given the high uncertainty inherent in duplex data, as well as their dependence on different potential criteria for filtering, it becomes highly desirable to be able to investigate RRIs visually and intuitively, yet in a still quantitative and principled manner.

Most of the existing computational pipelines offer some visualization capabilities, or at least output data in a format that can be displayed in the integrated genome viewer (IGV) [6]

Received: April 14, 2026. **Revised:** June 3, 2026. **Accepted:** July 13, 2026

or other genome browsers. While the linear representation is adequate for inspecting *cis* interactions, it is not well suited for the analysis of trans RRIs, as it cannot depict the underlying global transcriptome-wide organization and connectivity patterns. Capturing these properties requires a network-based representation, which remains largely unavailable for RNA duplex probing data. Except for ChimericFragments [7], which provides a graph-based visualizer that must be set up locally by the user, and ChiRA [8], which features a dashboard hosted on the Galaxy Project [9, 10], the possibilities for interactively exploring RRI network data derived from duplex probing experiments remain limited.

In addition to the computational pipelines for processing raw duplex probing data, several public databases provide access to published RRI datasets [11–14]. A comparison of their key features, data processing strategies, and visualization capabilities is provided in Table 1. Although these resources are valuable for data access and a gene-specific inspection of experimental evidence, they share several limitations. One key limitation is that the datasets have not been processed in a uniform and principled manner. Furthermore, information on the coverage of published duplex probing datasets remains incomplete and uneven across protocols, some entries lack key information such as genomic coordinates, and interaction-level features may be collapsed to a single confidence score. In addition, visualization is typically restricted to tabular searches, gene-specific views, and linear genomic tracks. As a result, none of the existing resources support transcriptome-wide RRI networks or a direct comparison of datasets.

To summarize, there is an increasing gap between the growing availability of RNA duplex probing datasets and the limited means for their meaningful exploration. While existing data processing pipelines support raw data processing and online databases provide access to some published interaction datasets, there is currently no tool that applies consistent data processing and allows for the inspection of the resulting RRI networks and a comparison across conditions. To fill this gap, we present InteRRact, a web-based tool for the analysis of human *cis* and trans RRIs derived from published RNA duplex probing experiments. InteRRact supports the exploration of these datasets both through their genomic positions and through their relationships within the global interactome, while allowing data filtering via multiple reliability criteria.

Methods

Implementation

InteRRact is technically implemented via an R/Shiny framework. The network visualization is provided with the visNetworkR wrapper for the vis-network.js JavaScript library [15]. The interactive linear genome tracks are displayed with igvShiny [16] widgets based on igv.js [17].

The server functionality is organized into four modules, each residing on a separate tab: visualization of a single preprocessed dataset, comparison of two datasets, comparison of multiple datasets, and visualization of user-uploaded data. Figure 1 summarizes the structure of the main inputs and outputs of InteRRact. Its panels display the representative outputs of these modules, including the single-dataset network view, the pairwise comparison network, the linear genomic view, and the multiple-dataset comparison.

The main page provides a brief description of each module together with a symbolic illustration of typical use cases. In addition, it provides information on the preprocessing of the original RNA duplex probing samples and the key RRI features that can be used for filtering and exploration.

Datasets preprocessing

A full list of the pre-processed samples from RNA duplex probing experiments is provided in Supplementary Table S1. Duplex groups within each sample were identified with our own DuplexDiscovereR [18] pipeline in a single pipeline call, see Supplementary Table S2 for details on the applied parameters.

In addition to the binomial test implemented in DuplexDiscovereR, we applied the odds-ratio test used in several pipelines for the RBP-dependent RNA duplex or RNA contacts probing. This test may be more appropriate for RIC-seq [19] data, although its relative performance has not been assessed to date, given the limited number of available datasets and validated interactions.

To assess the replicate support and to represent the data in a more convenient, compact form, duplex groups detected in individual replicates within the same condition and protocol were aggregated and clustered into duplex groups per condition. Hybridization energies for per-condition duplex groups were predicted with RNAhybrid from ViennaRNA [20]. For duplex groups replicated across multiple samples, their per-sample features, such as their loci coverage and gene expression, are summarized by their mean, and *P*-values are summarized by their maximum, i.e. the most conservative *P*-value.

Additionally, we used UCSC RepeatMasker [21] and the ENCODE Blacklist annotations [22] to label and filter out duplex groups mapping to repeats or otherwise problematic genome regions. Thereby, duplex groups mapping to DNA "Simple repeat," "low_complexity," and "High Mapping Signal" were excluded from the datasets, as these are likely to represent mapping artefacts rather than RNA duplexes from actual transcripts. Duplex groups mapping to non-transcribed pseudogenes were also removed from the processed datasets. Comprehensive information on the number of recovered duplex groups in each dataset is available on the InteRRact server and included in the Supplementary Materials as Supplementary Table S3.

Visualization of a single dataset

The single-dataset visualization module takes as input the user-defined filtering parameters, including thresholds for coverage, replicate support, *P*-value, and hybridization energy, and optional restriction to selected genes or genomic loci. The filtered data are represented in two complementary ways: as a gene-level interaction network for trans RRIs (Fig. 1A) and as linear genomic tracks for both *cis* and trans RRIs (Fig. 1C). In the interaction network, nodes correspond to genes, and edges represent sets of duplex groups connecting the respective gene pairs. Changes in data filters are applied interactively to the selected dataset and update both the network and the genomic view.

The genomic view is displayed via two independent widgets that allow for the simultaneous inspection of two potentially disjoint genomic loci involved in a trans RRI. In all genomic views, *cis* and trans interactions are rendered as pairs of region boxes connected by a line. This representation is gener-

Table 1. Comparison of RRI databases that are based on experimental data and their key features

Database	RASP2	RNAInter 4.0	CRIS	InteRRact
Experimental methods for probing RNA–RNA interactions	SPLASH PARIS PARIS2 LIGR-seq RIC-seq	SPLASH PARIS LIGR-seq	PARIS, PARIS2 SHARC-seq	SPLASH PARIS LIGR-seq RIC-seq
Species	24 species	156 species	Human, mouse	Human
Unified data post-processing	No	No	Yes, CRSSANT	Yes, DuplexDiscovereR
Information on each trans RNA–RNA interaction	Coordinates of interacting region, number of RNA–RNA interactions for each gene pair	Confidence score for each gene pair based on citation metadata	Coordinates of interacting regions, read coverage	Coordinates of interacting regions, hybridization energy of interaction, read coverage, *P*-value
Information on experimental replication	No	No	No	Yes
Visualization of *cis* interactions	Linear, genomic (IGV)		No	Linear, genomic (IGV)
Visualization of trans interactions	Static image for a single gene		No	Network of all trans RNA–RNA interactions, detailed information for each node and edge within network
Ability to compare two datasets	No	No	No	Yes, both for *cis* and trans interactions
Ability to upload and analyse user-specified duplex dataset	No	No	Yes	Yes

ated by us with a custom backend script adapted to the igv.js widget and allows for the vertical separation of displayed interactions, avoiding the single-line cluttered stacking typical of commonly used interaction track arc when multiple interactions share the same locus.

For the interactions selected by the user, the module displays the associated feature values, including hybridization energy, replicate support, coverage, and *P*-value, together with a schematic representation of the predicted RNA hybrid within the duplex group arms. Additionally, the node information showing the gene ID, biotype, and the interaction partners are also provided.

A Louvain community detection algorithm from the R igraph [23] package is applied automatically to identify network communities, which can be used either as the network colouring rule or as input for a Gene Ontology analysis. The Gene Ontology over-representation analysis is implemented with the clusterProfiler R [24] package and can be launched by the user for up to 10 communities at once for biological process, molecular function, and cellular component terms.

Comparing two datasets

The comparison module takes as input two pre-processed datasets together with user-defined filtering parameters. The selected data are then used to identify matching interactions between the two datasets and are represented as a combined interaction network and linear genomic tracks containing interactions from both datasets (Fig. 1B).

To identify overlapping interactions, duplex groups from both datasets are pooled and clustered, yielding a union set of overlapping interaction regions. Based on this overlap, each duplex group is labelled as either matched between both datasets or specific to one of them. A combined gene-level interaction network is then constructed from all genes detected in either dataset. Nodes are classified according to whether the corresponding gene participates in interactions in both datasets or only one of them. Edges in the combined interaction network are classified into four categories: edges supported by matching duplex groups in both datasets, edges formed by interactions specific to either the first or second dataset only, and an "unmatched" category in which interactions between the same genes exist in both datasets but do not match. Two duplex groups are labelled as matched if their corresponding arms are identical in strand, chromosome, and their start and end coordinates are shifted by no >30 nt.

The comparison module applies the same data filters as the single dataset module. Filters by read count, coverage, replicate support, *P*-value, or hybridization energy are applied to either datasets before comparison. Changing these thresholds triggers the re-computation of the comparison, because the set of retained interactions in each dataset may change. In contrast, changes applied to an already constructed comparison network are displayed instantly, similarly to the single-dataset module.

Comparing multiple datasets

The module for multiple comparison takes as input a list of selected dataset names and presents as output as an interactive UpSet plot with the option to browse and download interactions for each dataset-overlap category (Fig. 1D). Optionally, a user-uploaded dataset can be included in the multiple comparison, allowing the user to compare the custom set of new RRIs against already featured datasets.

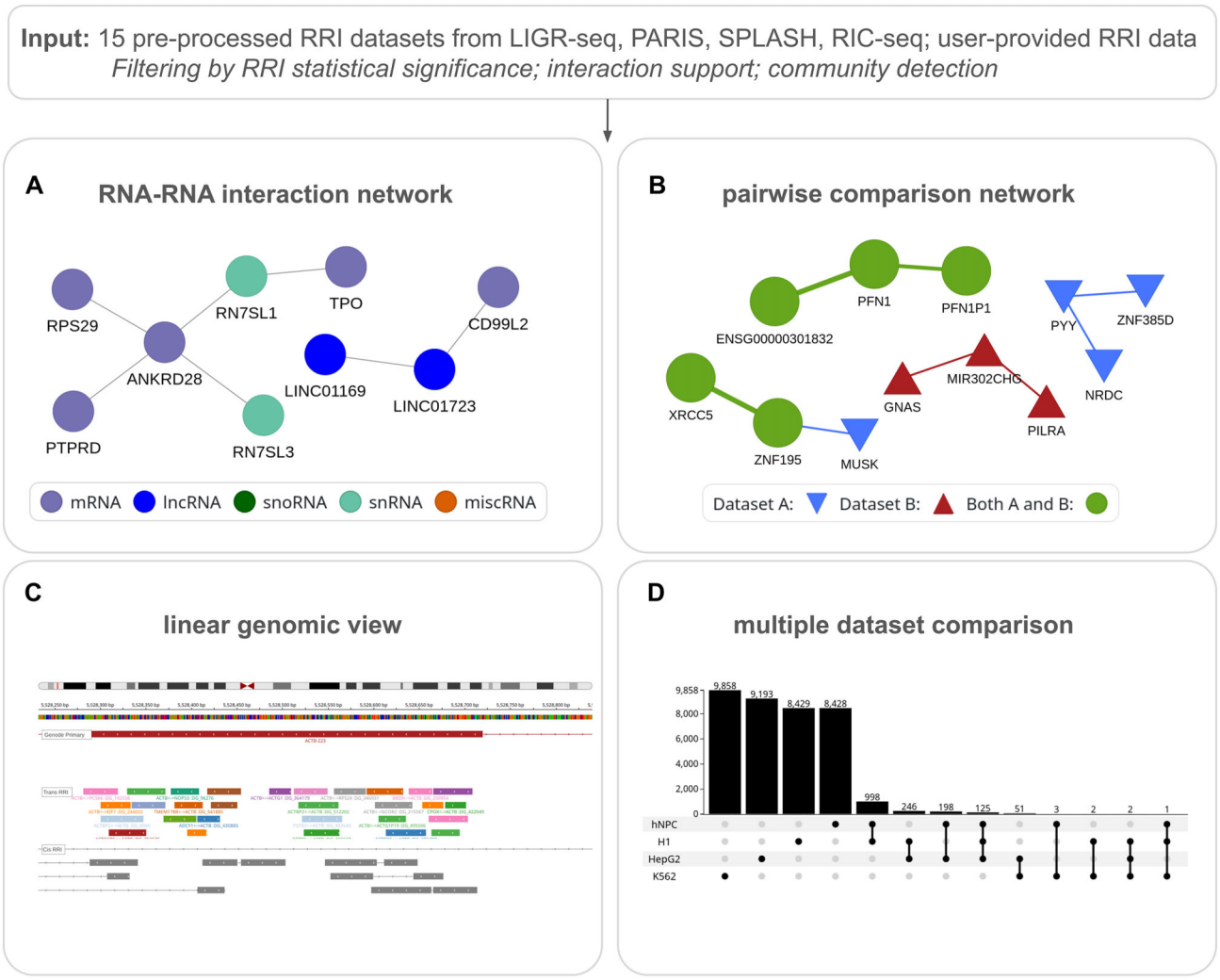

Figure 1. Overview of InteRRact inputs and representative outputs. The provided datasets of pre-processed RRI or a user-provided dataset are analysed by interaction-level measures and confidence-based filtering. (**A**) A single datasets specific to one cell line and one condition can be explored as gene-level RRI networks. (**B**) A pairwise comparison is built for two RRI datasets. Shape and colours of nodes and edges identify matched, unmatched, and dataset-specific interactions in a combined network representation. (**C**) *Cis* and trans interactions can be inspected in a traditional linear genomic view. (**D**) A multiple-dataset comparison summarizes interactions shared across selected datasets as an UpSet plot.

Importantly, InteRRact does not compare two datasets through a naive direct intersection of genomic regions. Such intersections are ambiguous and challenging to interpret, as the comparison of overlapping regions produces a non-symmetric result where a single interaction in either dataset can have multiple matching hits in another. InteRRact avoids these problematic many-to-many relationships by providing a more coherent basis for pairwise and multiple comparisons. Comparisons between multiple datasets are based on assembling the superset of RRIs hosted on InteRRact that contain non-redundant interactions. This superset is used to find RRIs shared across two or more datasets. This methodology is described in more detail in [18].

No confidence filters are applied to the datasets prior to building the superset of RRIs, as datasets available on InteRRact derive from different experimental protocols and vary in ranges and availability of RRI confidence features. For example, binomial random ligation test *P*-values are not valid for RIC-seq data, and only a single replicate is available for both conditions in the PARIS HEK cell line dataset. Confidence filters may be applied for each dataset overlap category after the UpSet plot is generated.

Analysing data provided by the user

The user input module accepts custom RRI data in BEDPE format following the same conventions as specified by bedtools [25]. In addition to the standard BEDPE fields, the input provided by the user may contain optional nameA and nameB columns specifying the identifiers of the two interactors. When provided, these identifiers are used directly as graph node labels and for classification of *cis* and trans interactions. If they are not provided, interaction loci are annotated automatically with the basic subset of GENCODE v48 gene annotations, and node identities are inferred from overlapping gene coordinates. In this case, the input data are expected to be mapped to the hg38 human genome assembly.

As the BEDPE specification allows unlimited multiple metadata fields to be included, the user may also provide several numeric-type features with the fixed names that InteRRact will infer:n_reads, deltaG, and *P*-value, while also supporting the generic format specified score and two additional optional metadata fields *score1* and *score2*. The up-to-date requirements for the input format are specified in the server tutorial.

After import, the user-provided data are represented in the same way as the datasets provided by InteRRact. The output consists of a gene-level network for trans RRIs and linear genomic tracks for inspection of *cis* and trans interactions. Loci that cannot be assigned to known genes are excluded from the trans RRI network.

Results

InteRRact is a web-based tool for the interactive exploration and comparison of *cis*- and trans-RRIs in human cells. An overview of its inputs and outputs is shown in Fig. 1. We next use representative examples to show how the server supports single-dataset exploration and how pairwise comparison of interaction landscapes allows a broader survey of interaction patterns across datasets. Together, these examples illustrate how InteRRact can recover known RRIs in conjunction with supporting duplex evidence and place them into a wider context of the transcriptome-wide RNA–RNA interactome.

Example single dataset: snoRNA-host interaction

To illustrate the single-dataset mode, we examine the snoRNA-host interaction SNORD2–EIF4A2, which was analysed in detail in [26]. In that study, SNORD2 was proposed to interact with the intronic sequence of its host gene EIF4A2 near exon 4 and to affect host splicing by sequestering the branch point. The interaction is supported by duplexes detected in PARIS and LIGR-seq datasets and was followed up experimentally as a model of snoRNA-dependent regulation of the host transcript.

We used the LIGR-seq dataset in InteRRact, as it provides the strongest representation of small RNA interactions, including snoRNAs. Querying the network for SNORD2 and restricting the display to its immediate graph neighbours readily recovers the SNORD2–EIF4A2 interaction. The corresponding network component, the selected-edge view showing the supporting duplex groups, and the linear genomic view are shown in Fig. 2.

In the trans RRI network, RRIs are represented as edges connecting genes. Clicking on the corresponding edge reveals the supporting duplex groups together with the predicted RNA hybrid. Selecting this duplex group allows the user to move from the network representation of the trans interaction to its genomic loci in the linear view. For SNORD2–EIF4A2, the linear genomic view places both duplex-group arms on the EIF4A2 locus, consistent with the known host-gene context of this interaction. For this example, the supporting duplex group extends beyond the annotated genomic boundaries of SNORD2, indicating that the underlying chimeric reads map outside the SNORD2 coordinates. This supports the interpretation proposed by Bergeron *et al.* [26] that the interaction may act in *cis* through the formation of intramolecular RNA structure with SNORD2 rather than as a mature snoRNA acting in trans.

The workflow for the above example of SNORD2–EIF4A2 can be applied to other interacting genes beyond this validated interaction. Interaction hubs can be readily identified in the network, coloured either by community structure or gene type, and followed up through the same sequence of views: local network neighbourhood, edge-level inspection of duplex support, and the corresponding linear genomic context.

Both the linear and network views can be queried by specifying multiple gene names or a range of genomic coordinates, thereby allowing for a greater flexibility in exploration in case the specific locus or group of genes are of more interest than a particular gene. Since the linear view is based on the commonly used igv.js framework, users can also extend it with custom tracks according to their own analysis goals. Thus, InteRRact can be used both to recover published interactions and to survey additional interactions, such as the snoRNA–target in the same LIGR-seq dataset as candidates for further exploration.

Example two datasets: pairwise comparison of H1 and hNPC RIC-seq data

To demonstrate the use of the comparison mode, we examine two RIC-seq datasets generated from H1 and hNPC cells, the transition from pluripotency to neural differentiation. We used the embedded InteRRact filter to investigate whether there are dataset-specific subnetworks and if these comprise genes that are consistent with the corresponding cellular state. In addition to many mixed communities containing both shared and condition-specific interactions, we indeed observe dataset-specific communities that contain marker of pluripotency in H1 (LIN28A) and genes associated with differentiation into neuronal and glial lineages in hNPC (MAPK10, APP, and QKI) (Fig. 3).

Generally, we can expect overall differences in the gene expression levels between the two cell lines. Strongly expressed marker RNAs of stem cells such as LIN28A may thus have an overall higher chance of randomly interacting with highly expressed genes. To account for this, we use an adjusted *P*-value filter in this comparison, which helps to control for such random observations.

The pairwise comparison module in InteRRact is thus a useful instrument for a qualitative comparison of two RRI landscapes. First, it provides a direct visual summary of the hub genes and individual interactions that are shared or dataset-specific. Second, it allows interaction communities to be analysed in the context of known biological conditions, allowing researchers to identify interactions involving genes associated with the underlying cellular state and to pinpoint their interaction partners that do not yet have clear functional annotation for further study.

Using InteRRact to analyse user data

InteRRact provides a module for the visualization and analysis of a user-supplied dataset based on a light version of the single-dataset comparison module. This module does not include the full set of interaction confidence measures available for the pre-processed datasets but offers the flexibility to utilize several features for interactive filtering and browsing the data. Users can provide three numeric scores: hybridization energies, number of reads, and *P*-values. We chose to support

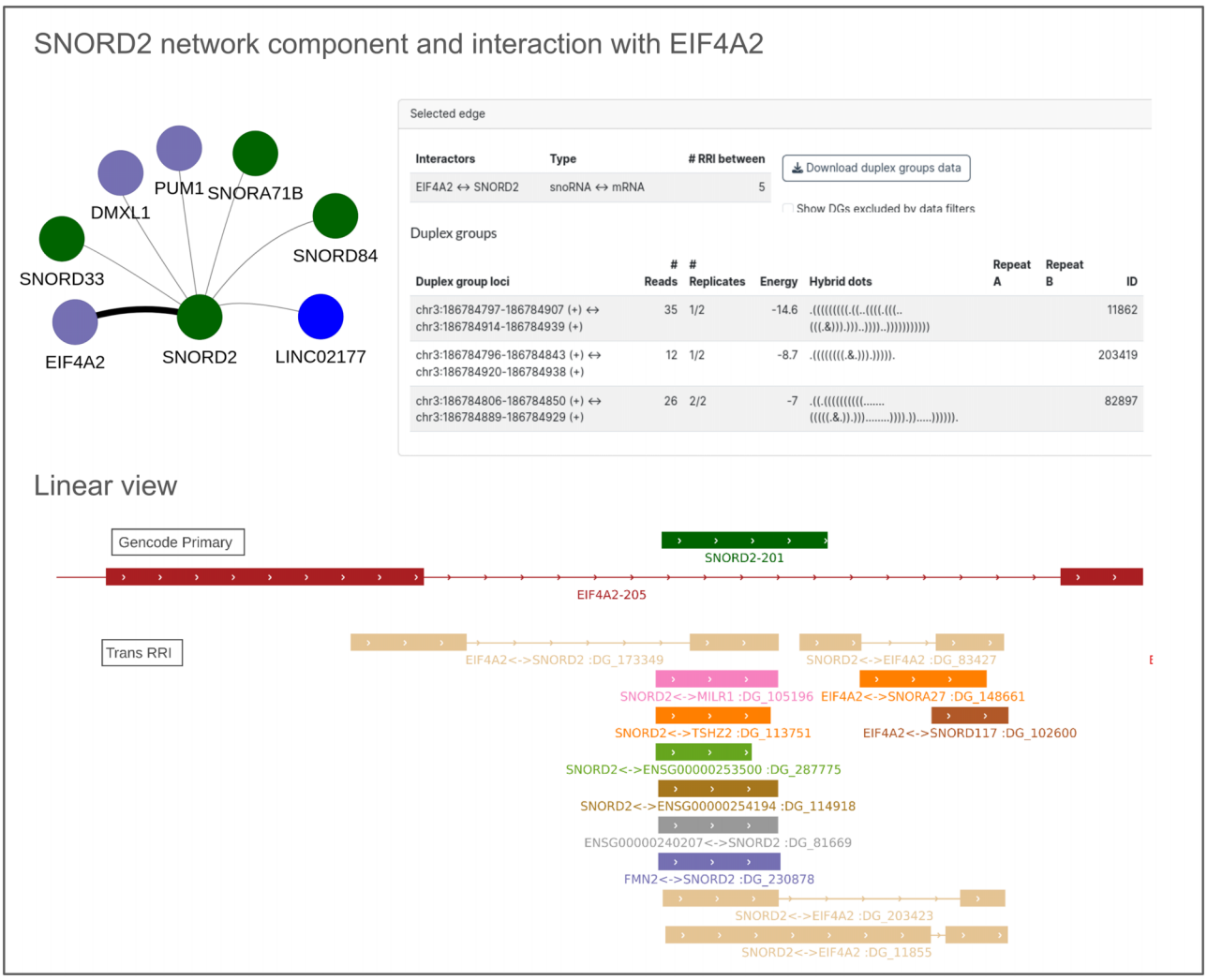

Figure 2. Single-dataset exploration of the validated SNORD2–EIF4A2 interaction in InteRRact. The upper left panel shows the SNORD2-centred network component from the LIGR-seq dataset, with the SNORD2–EIF4A2 interaction highlighted. The upper right panel displays the user interface for the selected edge, showing the duplex groups supporting this interaction and their associated confidence measures. The lower panel shows the linear genomic view at the EIF4A2 locus, where the selected interaction can be browsed together with nearby RRIs (only the trans interaction track is shown).

BEDPE as an intuitive interaction input format that is compatible with many software and packages for bioinformatics and to which other interaction formats can be converted. Once successfully imported, user-provided interactions may also be used in the multiple comparison module, providing broader utility than exploring the single dataset.

On the InteRRact web page, we provide example input files that are subsets of the SPLASH HeLa dataset. These examples use the same general format but contain different metadata, reflecting the option to use different procedures for assigning node names before drawing the interaction network. The examples can be downloaded and re-uploaded into InteRRact and are accompanied by a short tutorial and interface guidance. User-uploaded data are stored only for the duration of the browser session.

Multiple comparison module

The multiple comparison module allows users to browse and export duplex groups matched between several datasets. Additionally, users can add a custom uploaded dataset to the comparison. This feature is particularly useful as it allows users to query RRI data hosted on InteRRact by providing a number of paired loci at once and assessing the number of duplex groups matching them. We provide a short tutorial example online for this module as well.

Discussion

InteRRact addresses a widening gap in the analysis of RRI probing data. RNA–RNA proximity ligation methods offer a promising way to probe *cis* and trans RRIs on a transcriptome-wide scale. In order to investigate the corresponding network of *cis* and trans RRIs, it is first necessary to carefully process the raw data, which is computationally and conceptually not a trivial task. InteRRact provides human duplex datasets that have already been uniformly processed. Duplex data from one or more datasets can be visually explored in terms of gene-level networks and genomic tracks, as well as a range of filters that quantify the strength of evidence. It is thereby possible to intuitively explore ideas, form hypotheses, and discover evidence for new biol-

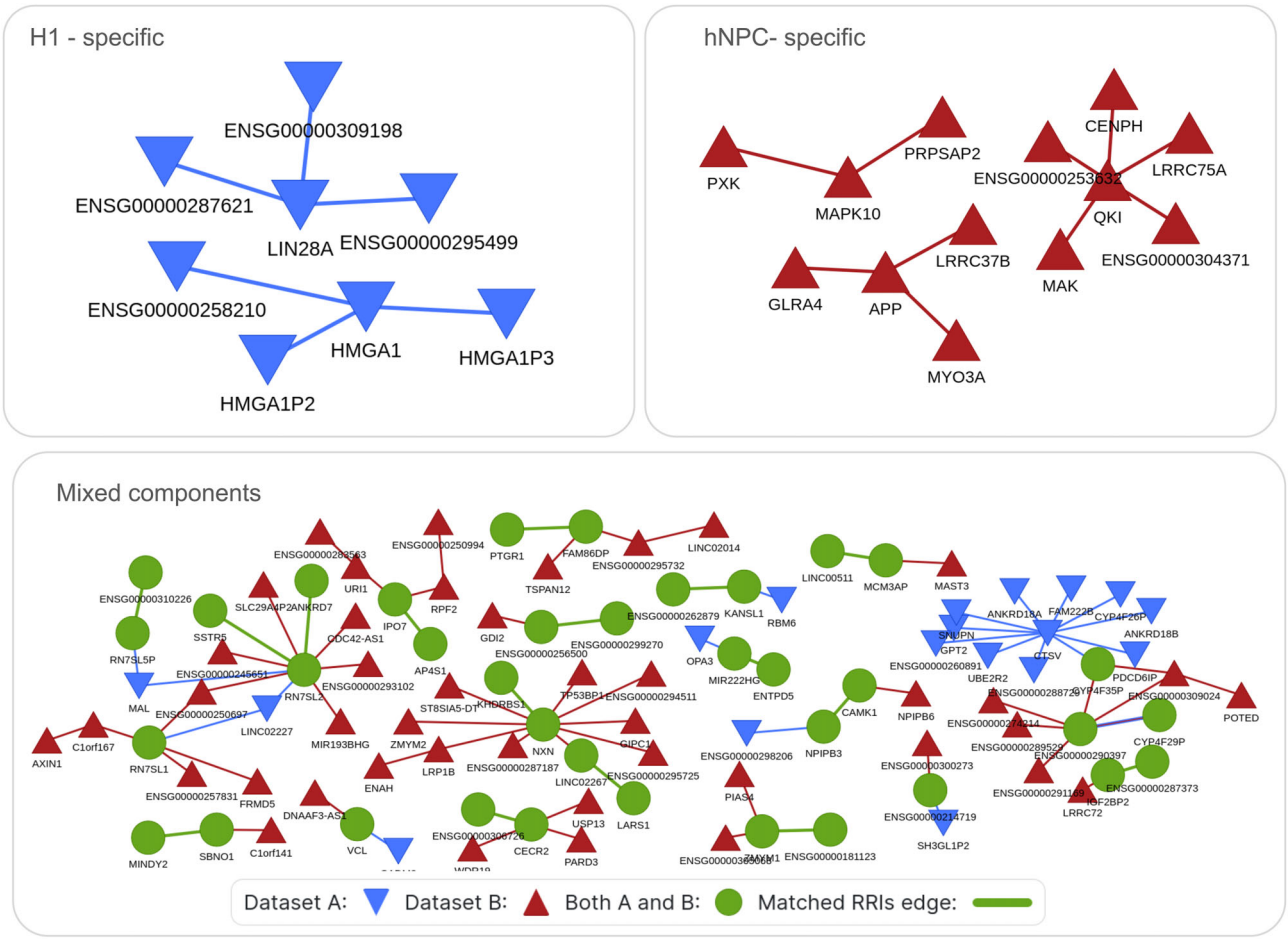

Figure 3. Pairwise comparison of H1 and hNPC RIC-seq datasets in InteRRact. Top left, H1-specific subnetworks, including a component containing the pluripotency-associated marker LIN28A. Top right, an hNPC-specific subnetwork containing genes associated with neuronal differentiation. Bottom, a trans interaction with components in which shared nodes and matched edges are mixed together with dataset-specific nodes and unmatched edges. Selected dataset A corresponds to H1 and dataset B to hNPC.

ogy, which can thereby be prioritized for targeted follow-up experiments.

To our knowledge, there are currently no publicly available instruments that provide analogous capabilities for qualitative comparison of RNA duplex probing datasets. While other recent tools, such as [27] and [28], focus on visualization and comparison of RNA structures for single transcripts, they do not address the RRIs in trans.

RNA duplex probing protocols offer a substantial advantage over methods that can only target specific RNA molecules [29, 30], as they yield transcriptome-wide information that reflects a snapshot of the cellular complexity *in vivo*. These advantages come together with analytical challenges arising from data sparsity, variability across experiments, and uncertainty in interaction support, which complicate downstream interpretation. InteRRact addresses several challenges originating from the current state of RNA duplex probing methods by providing clear and unified criteria for assessing the reliability of all datasets in terms of *P*-values, replicates, and hybridization energies. This enables users to easily identify and explore trustworthy *cis* and trans interactions without having to perform any of the underlying calculations and statistics themselves.

Future work on InteRRact is likely to focus on the incorporation of additional and possibly non-human datasets and on improving the annotation heuristics to enable the transfer from gene-level to more accurate transcript-level graph representations. Another future improvement may be the integration with other modalities that probe for the physical proximity of the genomic loci, as the genome-wide chromatin interaction maps. This requires, however, a dedicated approximation procedure to overlay sparse *cis* and trans RRI datasets, which typically have a resolution on the order of tens of nucleotides, with chromatin maps that typically have a resolution in kilobases [31].

We expect the relevance of InteRRact and its featured methodology to increase as more datasets become available and as new experimental protocols emerge. Recent proximity-ligation methods such as KARR-seq [32] or CAR-SPLASH [33] extend the range of available datasets, and RIC-seq has already expanded in coverage across the datasets [34]. While the significant efficiency bottlenecks of the underlying duplex probing methods still provide significant challenges that need to be overcome with improved protocols, these bottlenecks also imply that the vast fraction of the *cis* and trans RNA–RNA interactome remains largely undiscovered.

We thus hope that InteRRact will significantly facilitate the exploration of RRI networks and the discovery of new regulatory functions and their underlying molecular mechanisms.

Acknowledgements

Author contributions: Egor Semenchenko (Conceptualization [equal], Data curation [lead], Formal analysis [lead], Methodology [lead], Software [lead], Supervision [equal], Visualization [lead], Writing – original draft [lead], Writing – review & editing [equal]), Jingwen Luo (Data curation [equal], Software [equal], Writing – review & editing [supporting]), Volodymyr Tsybulsky (Data curation [equal], Software [equal], Writing – review & editing [supporting]), Charlie William Rettig (Software [supporting], Writing – review & editing [supporting]), and Irmtraud M. Meyer (Conceptualization [equal], Funding acquisition [lead], Supervision [equal], Writing – review & editing [equal])

Supplementary data

Supplementary data is available at NAR Genomics & Bioinformatics online.

Conflict of interest

None declared.

Funding

Helmholtz-Gemeinschaft. Funding to pay the Open Access publication charges for this article was provided by Helmholtz Association, Germany.

Data availability

InteRRact is available at https://e-rna.org/interract.

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Received: April 14, 2026. **Revised:** June 3, 2026. **Accepted:** July 13, 2026