Data-Driven Information Extraction and Enrichment of Molecular Profiling Data for Cancer Cell Lines

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Abstract

Motivation: With the proliferation of research means and computational methodologies, published biomedical literature is growing exponentially in numbers and volume (Lubowitz et al., 2021). As a consequence, in the fields of biological, medical and clinical research, domain experts have to sift through massive amounts of scientific text to find relevant information. However, this process is extremely tedious and slow to be performed by humans. Hence, novel computational information extraction and correlation mechanisms are required to boost meaningful knowledge extraction. **Results**: In this work, we present the design, implementation and application of a novel data extraction and exploration system. This system extracts deep semantic relations between textual entities from scientific literature to enrich existing structured clinical data in the domain of cancer cell lines. We introduce a new public data exploration portal, which enables automatic linking of genomic copy number variants plots with ranked, related entities such as affected genes. Each relation is accompanied by literature-derived evidences, allowing for deep, yet rapid, literature search, using existing structured data as a springboard. **Availability and Implementation**: Our system is publicly available on the web at `https://cancercelllines.org`. **Contact**: The authors can be contacted at ellery.smith@zhaw.ch or rahel.paloots@uzh.ch.

Key words: Cancer cell lines, copy number variants, natural language processing, information extraction

Introduction

Cancer research is one of the most challenging and promising biomedical areas as reflected in the amount of attention it receives (Elmore et al., 2021, Cabral et al., 2018, Siegel et al., 2022). Cancer cell lines are important models for the study of cancer-related pathophysiological mechanisms as well as for pharmacological development and testing procedures. Cell lines are obtained from patient-derived malignant tissue and are cultivated *in vitro*, potentially in an "immortal" way. Cancer cell lines are supposed to retain most of the genetic properties of the originating cancer (Mirabelli et al., 2019), including genomic modifications that are characteristic for the respective disease's pathology and are absent in normal tissues.

A class of mutations ubiquitous in primary tumors and derived cell lines are genomic *copy number variants* (CNVs) which represent structural genome variations in which genomic segments of varying sizes have been duplicated or deleted from one or both alleles. The set of CNVs observed in a given tumor ("CNV profile") frequently includes one or multiple changes characteristic for a given tumor type. For instance, while many colorectal carcinomas display duplications of chromosome 13 (Lassmann et al., 2007, Baudis, 2007), neuroepithelial tumors frequently show small, often bi-allelic deletions involving the CDKN2A gene locus on the short arm of chromosome 9 (Bostrom et al., 2001, Hoischen et al., 2008, Rao et al., 2010). Recurring CNV events are supposed to be driven by their selective advantage for cancer cells, *i.e.* recurrently duplicated regions predominately will affect genes favorable for a clonal expansion ("oncogenes") and, conversely, deleted regions will frequently contain growth-limiting ("tumor-suppressor") genes (Vogelstein et al., 2013).

The collection and comparative analysis of cancer and cancer cell line CNV data is important for the understanding of disease mechanisms as well as the discovery of potential therapeutics. Progenetix (Baudis and Cleary, 2001, Huang et al., 2021) is a knowledge resource for oncogenomic variants, mainly focusing on representing cancer CNVs. A recent spin-off from the Progenetix resource is *cancercelllines.org* - a database dedicated to genomic variations in cancer cell lines. In addition to CNVs, *cancercelllines.org* also includes information about sequence variations such as single nucleotide variants (SNVs), assembled from the aggregation of genomic analysis data of cell line instances. Currently over 16,000 cell lines from over 400 different cancer diagnoses are represented in this resource.

Natural language processing (NLP) has proven to be a game-changer in the field of clinical information processing for attaining pivotal knowledge in the healthcare domain (Landolsi et al., 2022). In fact, numerous studies have been undertaken in exploring indirect relations between drugs, diseases, proteins and genes from unstructured text provided in literature resources. One among many is (Subramanian et al., 2020), where the authors systematically design an NLP pipeline for drug re-purposing via evidence extraction from PubMed abstracts. Even though such studies exhibit some promising performance, neither ground truth is considered for further relevance evaluation of discovered drug-cancer

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therapeutic associations, nor visualization of results is provided. Additionally, SimText (Macnee et al., 2021), a text mining toolset built for visualization of similarities among biomedical entities, manages to extract and display knowledge interconnections from user-selected literature text. However, no quantitative metrics were presented for evaluating the efficiency of the utilized NLP methods.

In this paper we study how to use state-of-the-art information extraction algorithms such as LILLIE (Smith et al., 2022) to identify known mutated genes and find out which genes are most likely affected in certain CNV regions. As a result, **we introduce a novel data exploration system, allowing for the dynamic visualization and exploration of previously orthogonal data models by extracting and enriching information from both structured and unstructured data**. The user will be able to visualize gene information extracted by our algorithm on the CNV profiles of cancer cell lines. The source code for our system is available to the public on GitHub[1].

Methods and Materials

Proposed Method

In this paper we propose a novel end-to-end methodology that combines information extracted from unstructured text (i.e., publication abstracts from PubMed) with structured knowledge resources (i.e., Progenetix and cancercelllines.org) in order to construct an interface for exploratory analysis of positionally mapped genomic variations based on literature evidence. Our work mainly consists of two parts: i. fine-tuning LILLIE (Smith et al., 2022), a state-of-the-art information extraction tool, in the cancer cell lines context and ii. development of a portal that serves as the interface for linking various genomic CNV findings with evidence extracted from literature text.

More specifically, we use cell lines as a jumping-off point to provide our literature extraction results. For each cell line, we visualize a corresponding CNV plot, which is annotated by selected extracted genes, and a categorized, ranked list of related entities, as shown in Figure 1 and on the results page of our system[2]. We provide the most relevant evidence for the given result alongside the title of each paper, allowing the user to easily check the validity of the result, and a toggle to expand each result, revealing the full annotated abstract text, as shown in Figure 2.

Information Extraction from Unstructured Text

While there are many existing systems which focus on either the topic of biomedical text extraction (Landolsi et al., 2022) or the creation of knowledge graphs from text (Franklin et al., 2021, Xu et al., 2020, Qu and Cui, 2021), the *main challenge of our approach was to merge these two concepts* with an existing structured database, such that both can be explored in parallel, and provide complementary information in a streamlined fashion.

Rather than using a known benchmarking dataset for either information extraction or knowledge graph creation, as for example explored in Mohamed et al., 2019, we designed our system using an existing live knowledge base, with a focus

Fig. 1. A sample of the results available for the cell line *HOS*, including: (1) associated genomic locations mapped on the copy number variation profile plot (gain CNVs yellow, loss CNVs in blue); (2) evidences for each result; (3) and the relevant abstracts from which the results were derived. The results columns are, from left to right: Gene, Cytoband, or other entity label; Primary evidence for each abstract (the relevant cell line/entity annotations are marked in bold); Abstract title, and a link to the corresponding PubMed article; Expand/Collapse controls to view detailed information (shown in Figure 2).

on pragmatic data exploration of real-world data, rather than test-set performance.

In biomedical text extraction, particularly when the domain is narrow, rule-based and dictionary-based approaches for entity-relation extraction have been shown to give comparable performance to learning-based methods (Landolsi et al., 2022). As such, we use an enhanced version of the LILLIE triple extractor (Smith et al., 2022), where the learning-based component has been removed, and the rules have been fine-tuned for this specific use case. The result is an automatic information extractor with high precision and significant performance increase over equivalent methods (see Section 3).

Triple Extraction

Rather than other recent work, which focuses on recognizing a predecided set of relations (Patrick et al., 2011, Luo et al., 2022) we use the open information extraction paradigm (Liu et al., 2016) to extract any potential relationship between entities in the text, namely, as natural language subject-predicate-object triples. The use of this model allows a researcher to explore richer and more descriptive relations between entities than if they were mapped to discrete categories, and takes into account the fact that relationships in oncogenomics are often complex and subtle. Thus, open information extraction methods, coupled with domain expertise, was determined to be optimal for this use case. The format of these triples is described in detail in Smith et al., 2022.

We firstly run the LILLIE system on the abstracts of all research articles in the Progenetix corpus, then we use dictionary-based methods (Quimbaya et al., 2016) to match the subject and object with their corresponding entities in a custom

[1] https://github.com/progenetix/cancercelllines-web

[2] https://cancercelllines.org/cellline/?id=cellosaurus:CVCL_0312

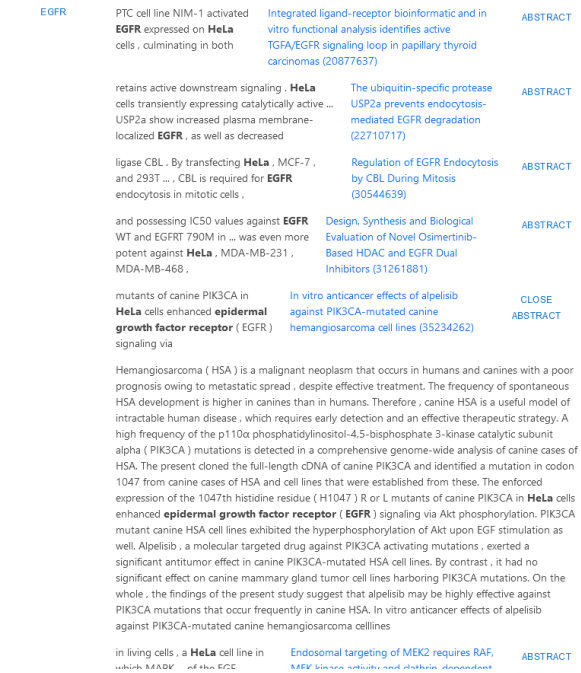

Fig. 2. Section of the results demonstrating a relationship between the cell line *HeLa* and the gene *EGFR*, showing the paper title, primary evidence for the result, and, when expanded, the full annotated abstract text.

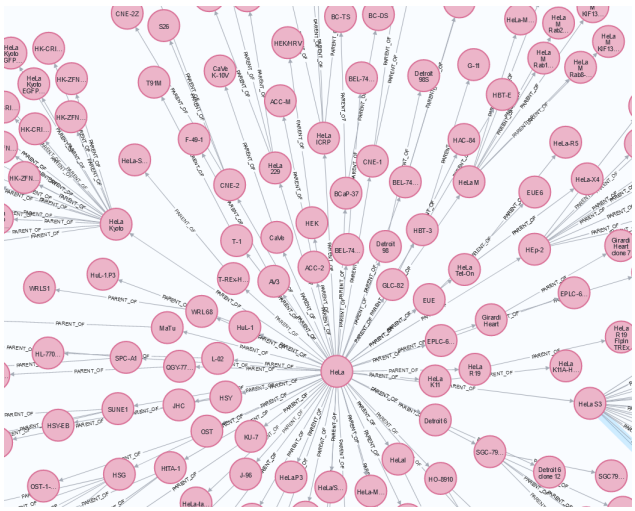

Fig. 3. Portion of the cell line hierarchy for *HeLa*, showing the entity itself, and its daughter cell lines. Nodes in the graph are derived from the ontologies (in this case, Cellosaurus), and the edges indicate a '*parent-of*' relationship.

ontology. An sample of this ontology is shown in Figure 3, which depicts a portion of the resultant subgraph for the cell line *HeLa*, derived from Cellosaurus.

We used the following data sources to construct the graph ontology (graph metrics are shown in Section 3):

- The cancer section of the NCIt thesaurus (Sioutos et al., 2007)
- The UBERON anatomical ontology (Mungall et al., 2012)
- The Cellosaurus cell-line index (Bairoch, 2018)

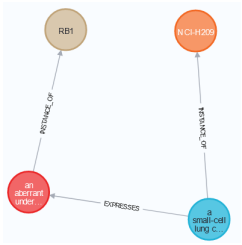

Fig. 4. Graph representation of the relationships in the text "*a small-cell lung cancer cell line (NCI-H209) expresses an aberrant underphosphorylated form of the retinoblastoma protein RB1*", deriving an EXPRESSES relationship between the cell line *NCI-H209* and the gene *RB1*.

- Cytogenetic mapping information from Progenetix (Huang et al., 2021)
- The HUGO gene nomenclature (Tweedie et al., 2021)

We then place these triples in a graph database, as shown in Figure 4. Unlike in other works on biomedical knowledge graph building (Mohamed et al., 2019), we do not infer any relations using the graph itself. Only relations directly implied by the text are present in the graph, as shown in Figure 4. By contrast, Mohamed et al., 2019 attempt to synthesize whether a relationship exists in between two nodes based on existing relationships using a knowledge graph embeddings approach. Our aim here is to provide a link between existing evidences (between natural language and structured data), rather than synthesize new knowledge using machine learning methods.

Pair Extraction

While triple extraction can expose deep semantic relations between entities, this approach does not necessarily provide a complete representation of all relationships within the text, as it only extracts predicates that are directly expressed as singular verb phrases. An example of a strong sentential relationship extracted by triples is shown in the abstract in Figure 2, whereas long-distance relationships as shown in Figure 5 are not currently reliably extractable using similar methods. This is a known shortcoming of current information extraction techniques, and recent efforts such as BioRED (Luo et al., 2022) have attempted to mitigate this deficiency by providing a corpus of long-distance relations that may span an entire document. However, the BioRED corpus is limited in both the number of relationship annotations and the fact that no specific annotations for cell lines are provided.

A such, we *augment our high precision triples with an additional high-recall method to capture long-distance relations*, using simple information retrieval techniques such as term distance. This method can perform well on small text documents such as abstracts, as shown in Figure 5, where a complex relationship between *Detroit 562* and *TP53* is extracted using simple term-distance metrics, but would have a lower weighting than a triple-based relationship due to it being a weaker inference. This is similar to a question-answering task on small text documents, and metrics such as this have been shown (Smith et al., 2015) to give comparable or superior performance to more complex semantic analysis methods, even on more involved relationships.

Naturally, if two entities are present in the same textual snippet, they are likely related in some manner, though this is not easily represented in the standard subject-predicate-object model. As such, we augment our triple extraction with what

Fig. 5. Section of the results demonstrating a relationship between the cell line *HeLa* and the gene *EGFR*, showing the paper title, primary evidence for the result, and, when expanded, the full annotated abstract text.

we term as *pair extraction*, where we extract subject-object pairs, but leave the relation expressed as a simple numerical quantity. We combine these pair extractions with triples with a simple linear weighting system to produce a more representative ranking in the final output. Examples of the different extraction methods can be seen by comparing Figures 2 and 5, where the cell line *HeLa* is explicitly linked with *EGFR* through a triple relation in Figure 2, showing a strong evidence. A weaker long-distance relationship exists in Figure 5 between *Detroit 562* and *TP53*. State-of-the-art information extraction techniques are not capable of finding such a link; but, by highlighting a potential relationship to the user, through an interface, a researcher can be allowed to make a judgement on it, or use it as a jumping-off point for discovering potentially new information.

Results

In this section we will fist apply our information extraction system for analyzing various cancer types. Afterwards we will evaluate the performance of our automatic information extraction pipelines. In particular, we want to address the following two research questions:

- *Research question 1: How well does our information extraction pipeline work for studying cancer cell lines and for exploring potentially new information?*
- *Research question 2: What is the performance of our automatic information extraction algorithm for combining structured and unstructured data, i.e. from a database for cancer cell lines and research abstracts from PubMed?*

Example Use Cases

To validate the efficacy of our approach, we analyzed the results of our novel information extraction pipeline and how the extracted data corresponds to cell line CNV profiles. We will now illustrate how to analyze two different cancer types using our approach with the help of two example use cases.

Head and Neck Squamous Cell Carcinomas - Cell Line Detroit 562

Figure 6 depicts the CNV profile for Detroit 562 - a pharyngeal squamous cell carcinoma cell line (NCIT code C102872). Pharyngeal squamous cell carcinoma is a part of head and neck squamous cell carcinomas, often related to smokers. The results of our information extraction pipeline for genes AURKA and WEE1 claim that these genes are highly expressed and down-regulated[3] respectively in cancers, see (Lee et al., 2019). This information is confirmed on the CNV profile where AURKA is duplicated and WEE1 is deleted. Similarly, MYC gene is brought forward as a possible target due to high expression and the region is duplicated on the CNV profile as well.

Figure 6 also indicates TP53, a tumor-supressor gene involved in the control of cell division located on the short arm of chromosome 17. Due to its inhibitory role on cellular expansion, it is a frequent target of genomic deletions in a variety of cancers. However, TP53 can also acquire gain-of-function mutations that contribute e.g. to radio-resistance, thus explaining the duplication in this region in the case of a mutant allele (Ganci et al., 2020). Conversely, NGF - a gene that is reported to be expressed in Detroit 562, exhibits alleleic deletion in our CNV data (Dudás et al., 2018), points towards alternative mechanisms responsible for its transcriptional activation.

Breast Carcinomas - Cell Line MDA-MB-453

Breast cancer is the most common cancer type in women, affecting more than 250,000 women in the US alone, see (Siegel et al., 2017). In breast cancer several clinico-pathological parameters have been recognized. One of the rare but clinically especially aggressive variants is the "triple-negative" subtype, *i.e.* where the tumor cells do not express 3 receptors commonly targeted in hormonal and immunotherapy: estrogen receptor, progesterone receptor and ERBB2 (HER2) receptor. Cell line MDA-MB-453 is a breast cancer cell commonly used to represent the triple-negative expression profile[4]. However, using our information extraction pipeline we could match this cell line to a publication that claimed its expression of ERBB2[5], see (Santra et al., 2017). Indeed, in our CNV data from 16 instances of MDA-MB-453 we can observe genomic duplications involving the ERBB2 locus on 17q (see Figure 7).

While another paper claims PTEN to be expressed in MDA-MB-453 (Singh et al., 2011) the CNV profile does not indicate a genomic duplication event as causative and therefore indicating transcriptional de-regulation. We also matched this cell line to 2 papers where mutation in KRAS was confirmed by our SNV data. Moreover, the expression of PIK3CA was confirmed by the duplication on the CNV profile as well as the mutation of the same gene was detected in the SNV data, see (Patra et al., 2017).

Thus, to answer *Research Question 1*: We show here that our novel information extraction feature facilitates further research into cancer cell lines. We were able to prove some known gene expression levels for cell lines Detroit 562 and for MDA-MB-453. Moreover, we could discover some new or conflicting information about some other genes.

[3] These results can be reconstructed here: `https://cancercelllines.org/cellline/?id=cellosaurus:CVCL_1171`

[4] `https://www.cellosaurus.org/CVCL_0418`

[5] These results can be reconstructed here: `https://cancercelllines.org/cellline/?id=cellosaurus:CVCL_0419`

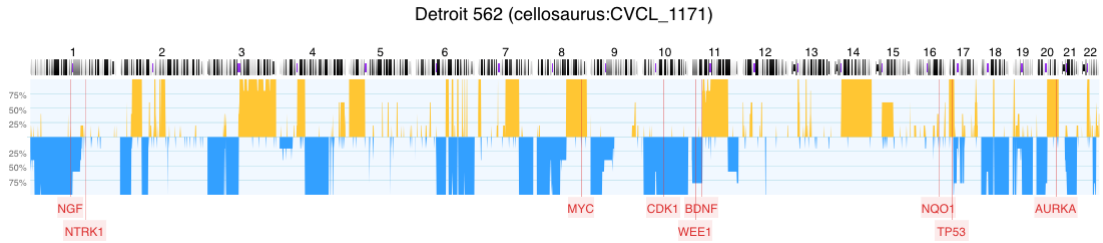

Fig. 6. CNV frequency profile of 5 instances of the cancer cell line Detroit 562 annotated with enriched gene information from our information extraction pipeline. Copy number gains are shown in yellow and deletions in blue. Of note, a few of the regional CNVs deviate from the 100% expected for stable clonal propagation due to some genomic instability and possible variation in the fidelity of individual profiling experiments. Mapping positions of genes of interest are shown in red.

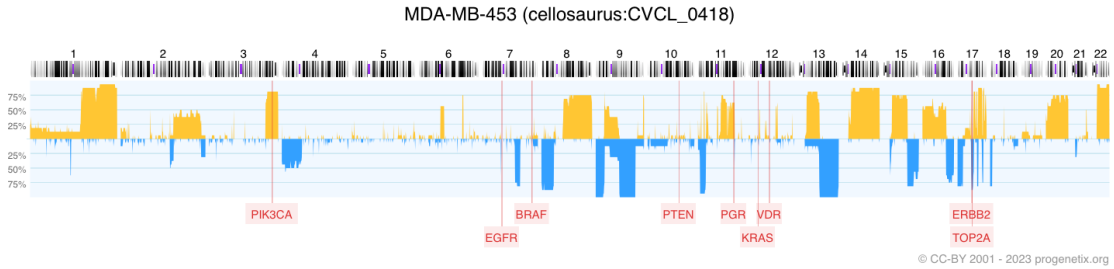

Fig. 7. CNV frequency profile of 16 breast cancer cell line MDA-MB-453 samples, annotated with enriched gene information from our information extraction pipeline. Copy number gains are shown in yellow and deletions in blue. Mapping positions of genes of interest are shown in red.

More insights about how to reconstruct the exploration of these use cases with our system can be found at `https://docs.cancercelllines.org/literature-data/`.

Information Extraction

After applying our information extraction pipeline for studying various cancer types, we will now evaluate the performance in terms of accuracy and processing time of our system.

Data Exploration

The Progenetix and cancercelllines.org resources provide PubMed identifiers for articles with a direct relation to genomic analyses in cancer cell lines. Crawling the PubMed database from these identifiers resulted in a corpus of 52,412 textual abstracts, which were used by our system to generate our graph database. As shown in Table 1, we find 770,230 total entity matches, leading to a total of 12,139 distinct nodes in our graph.

Table 1. Number of input abstracts, the number of matched entities found by our system, along with the number of cell lines extracted, and the number of unique relations per cell line.

Number of Abstracts	52,412
Total Entity Matches	770,230
Unique Entity Matches	12,139
Unique Cell Lines	1,411
Abstracts per Cell Line	6.09
Linked Entities per Cell Line	53.609

Information Extraction Performance

We evaluated our system on the BioRED NER benchmark (Luo et al., 2022) to gain an approximate idea of the performance of our system. While the BioRED evaluation metrics differ somewhat to the task we are performing (since we do not include entity types such as *species* or *chemical*, and our entity spans differ to their model), we were able to evaluate the match accuracy on a per-paper level. In this case, our system achieves an accuracy of 91.8% on the test set when identifying whether genes and cell lines are relevant to a paper, which is comparable to 93.5% for PubMedBERT, as reported by Luo et al., 2022. However, PubMedBERT was trained specifically on the BioRED corpus, unlike ours. Currently, no exact benchmark exists for extracting and weighting relations between genes and cell lines; however, we provide instead a qualitative analysis in Section 3, demonstrating the usage of our system on real-world data to discover new knowledge.

For this work, we used an enhanced version of the LILLIE triple extractor system, tailored for merging natural language and structured data. The primary improvement was in customizing the parameters and modifying the rule table of the rule-based component to suit the linguistic patterns used to describe cell lines, genes and cytobands, and in trimming down our system to only the *high-precision rule-based component*. As shown in Smith et al., 2022, this increases the precision of the extracted triples, and removes the need for additional training data and reduces the human effort in developing a custom validation set.

By leveraging the flexibility of our rule-based component, we could adjust the precision-recall balance directly, based on qualitative output, to produce the desired results, without the need for costly and open-domain deep-learning approaches. These modifications demonstrate the strength and flexibility of the LILLIE extraction approach, where the output could

be adjusted easily on-the-fly based on the current use-case requirements.

The average end-to-end time taken to add new abstracts to our database is 3.56 seconds per paper, measured on a system with the following specifications: Intel Xeon W-11855M CPU @ 3.20GHz, 64GB RAM, NVIDIA RTX A4000 GPU. Our system includes a mechanism for adding new entries to the database from a provided list of PubMed IDs, and this time includes: crawling, information extraction, pair indexing and database construction (as described in Section 4). We believe that these result, in combination with Table 1 and our performance analysis on the BioRED benchmark, answers *Research Question 2* posed at the beginning of this section.

Discussion

Starting from a domain specific resource for curated genomic and associated data in cancer cell lines we extended its "classical" online database paradigm towards a knowledge exploration resource through the implementation of our novel literature information extraction algorithms. This change enables researchers to use the existing data - such as annotated genomic variations, visual indication of structural variation events and disease-related annotations - to gain context specific insights into molecular mechanisms through exploration of the added literature-derived information either directly or to prioritize follow-up analyses. We could show that the extracted results can easily be related to the resource's hallmark CNV profiles and this combination opens possibilities for knowledge expansion, including the critical evaluation of pre-existing annotations which may be affected by the fast-mutating nature of cancer cell lines. In our information extraction implementation we have shown that an interactive bimodal exploration model can be achieved in a streamlined manner, even if one data source comprises unstructured information.

Ubiquitous application of high-throughput molecular analyses as well as their interpretation in an ever increasing amount of publications drive a "data deluge" in biomedical research. Our work demonstrates an application of information extraction techniques to add a knowledge exploration dimension to a genomic data resource. By doing so, we provide a tool to increase the speed and depth of scientific research using computational linguistic methods.

For this work, we provide an evaluation on a subset of the BioRED corpus (and benchmarking of our information extractor is provided in Smith et al., 2022); however, there is no currently existing benchmark for extracting relations specifically between genes and cell lines. Instead, we provide a qualitative analysis in Section 3, demonstrating that our system can be applied on real-world data to discover new knowledge. We envision our system as a tool to dynamically discover novel data in tandem with a domain expert, rather than a traditional approach that can be directly evaluated using an existing benchmark.

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Conflict of Interest: None declared.

Data Availablity

The data underlying this article are available at `https://github.com/progenetix/cancercelllines-web` and `https://pubmed.ncbi.nlm.nih.gov/`.

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