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Applications Note

Data and text mining

HiPub: translating PubMed and PMC texts to networks for knowledge discovery

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Abstract

Summary: We introduce HiPub, a seamless Chrome browser plug-in that automatically recognizes, annotates and translates biomedical entities from texts into networks for knowledge discovery. Using a combination of two different named-entity recognition resources, HiPub can recognize genes, proteins, diseases, drugs, mutations and cell lines in texts, and achieve high precision and recall. HiPub extracts biomedical entity-relationships from texts to construct context-specific networks, and integrates existing network data from external databases for knowledge discovery. It allows users to add additional entities from related articles, as well as user-defined entities for discovering new and unexpected entity-relationships. HiPub provides functional enrichment analysis on the biomedical entity network, and link-outs to external resources to assist users in learning new entities and relations.

Availability and Implementation: HiPub and detailed user guide are available at http://hipub.korea.ac.kr.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Many of the biomedical research papers are about the interactions between genes, proteins or drugs in a specific biological context. New hypotheses could be formulated by mining these papers and designing new sets of experiments to validate (or refute) hypotheses in the knowledge discovery process. However, the volume and rate of current biomedical publications are far larger and more rapid than our ability to extract and use them in this knowledge discovery cycle. For example, PubMed and PubMed Central (PMC) currently have more than 26 million abstracts and 4 million full-text articles, respectively, in their collections, and PubMed receives more than 3000 new abstracts per day. Hence, it is impossible for researchers to manually go through all the records to extract relevant information for their research.

To address these challenges, we developed HiPub, a Chrome browser plug-in that automatically highlights, annotates and translates biomedical entities (e.g. genes, proteins, drugs and diseases) from texts into networks for knowledge discovery. Compared with related tools, HiPub has the following unique features and advantages (Supplementary Table S1):

- HiPub works as a seamless Chrome extension in PubMed/PMC websites for knowledge discovery and network exploration.
- HiPub recognizes, highlights and annotates an array of biomedical entities such as genes, diseases, drugs, cell lines and mutations in PubMed (abstracts) and PMC (abstracts and full texts).
- HiPub integrates two complementary named-entity recognition (NER) methods to achieve high precision and recall: PubTator

(Wei *et al.*, 2013) and BEST entity extractor (BEST EE) (Lee,S. *et al.*, 2016)

- HiPub visualizes texts as interactive biomedical entity networks using information from texts and external resources.
- HiPub integrates biomedical entities in similar articles into the biomedical entity network.
- HiPub provides an interactive User Interface for network exploration, enrichment analyses and link-outs to external databases.

2 HiPub description

The HiPub system consists of two components: the Chrome browser extension and the Biomedical NER server. HiPub is designed for PubMed (abstracts) and PMC (abstracts and full texts), and supports several journal websites. After HiPub is invoked, it recognizes the URL, and the document ID (such as PMID or PMCID) is submitted to the HiPub server for processing the document on the fly.

2.1 HiPub chrome extension

2.1.1 Biomedical entity recognition and annotation function

HiPub recognizes and highlights the following biomedical entities from texts: genes, proteins, drugs, diseases, cell lines and mutations. When a highlighted entity is selected and clicked, a pop-up window will appear with basic information about the entity and with links to various external databases for additional information. Basic information about entities was collected from NCBI Gene, MeSH and Cellosaurus (http://web.expasy.org/cellosaurus). All other detailed information about articles and functions is accessible in a HiPub window which automatically appears on the bottom right corner of the web browser.

2.1.2 Biomedical entity network

HiPub generates biomedical entity networks based on two approaches: (1) using the co-occurrence of entities in an opened article; and (2) utilizing the evidence of entity-relationships from external databases. For the co-occurrence approach, HiPub extracts the relations between entities in a text as these relations represents novel results reported in the publication. To add known relations to the publication-specific entity network, HiPub utilizes BEReX (Jeon *et al.*, 2014) which consolidates entity-relationships from multiple data sources. By doing so, HiPub summarizes biomedical entities and their relationships within a specific context (from publication) and existing knowledge (from external databases).

2.1.3 Augmenting biomedical entity network with entities from similar articles

To explore the relationships between biomedical entities in related articles, HiPub utilizes the PubMed API to retrieve 10 articles that are the most similar to a specific paper. Using the ‘Add Similar Articles’ tab in the HiPub window, users can read and add entities to the biomedical entity network. This function allows users to expand the biomedical entity network, and use other related studies for discovering new or unexpected interactions between entities.

2.1.4 Augmenting biomedical entity network with user-defined entities

Similarly, user-defined entities can be easily added to the entity network utilizing BEReX. When a new user-defined entity is added, the shortest paths between existing entities in the network and the newly added entity will be automatically displayed, and users can also further explore the network by linking-out to the BEReX web service.

2.1.5 Detailed query for external databases

Users can send a detailed query about the entities recognized by HiPub to several external databases. HiPub provides three categories for querying a set of entities in external databases: literature (PubMed and Google Scholar), enrichment (BEST and g:Profiler) (Reimand *et al.*, 2007) and network (KEGG, STRING and BEReX).

2.1.6 Functional enrichment analysis of entities

For genes and proteins recognized in a text, HiPub performs enrichment analysis to find the most related KEGG pathway and Gene Ontology using NCBI Biosystems (Geer *et al.*, 2010).

2.2 Biomedical named entity recognition server

To achieve high precision and recall for named entity recognition (NER), HiPub integrates two complementary NER tools: PubTator (Wei *et al.*, 2013) and BEST entity extractor (BEST EE) (Lee,S. *et al.*, 2016). PubTator is a machine learning-based NER tool that achieves high recall whereas BEST EE is a dictionary-based NER tool that is fast and highly precise. Both NER tools support protein/gene, drug and disease name recognition. PubTator recognizes mutation and species information, and BEST EE recognizes cell line names. Integrating the results of both tools enables HiPub to recognize a broad range of entities. We used BEST EE for HiPub NER and combined the result with PubTator data that was obtained using PubTator’s RESTful API (Wei *et al.*, 2016) (Supplementary Figure S1). Since PubTator provides NER data of only PubMed abstracts, it is unable to recognize entities in only non-abstract parts; however, BEST EE can recognize such entities.

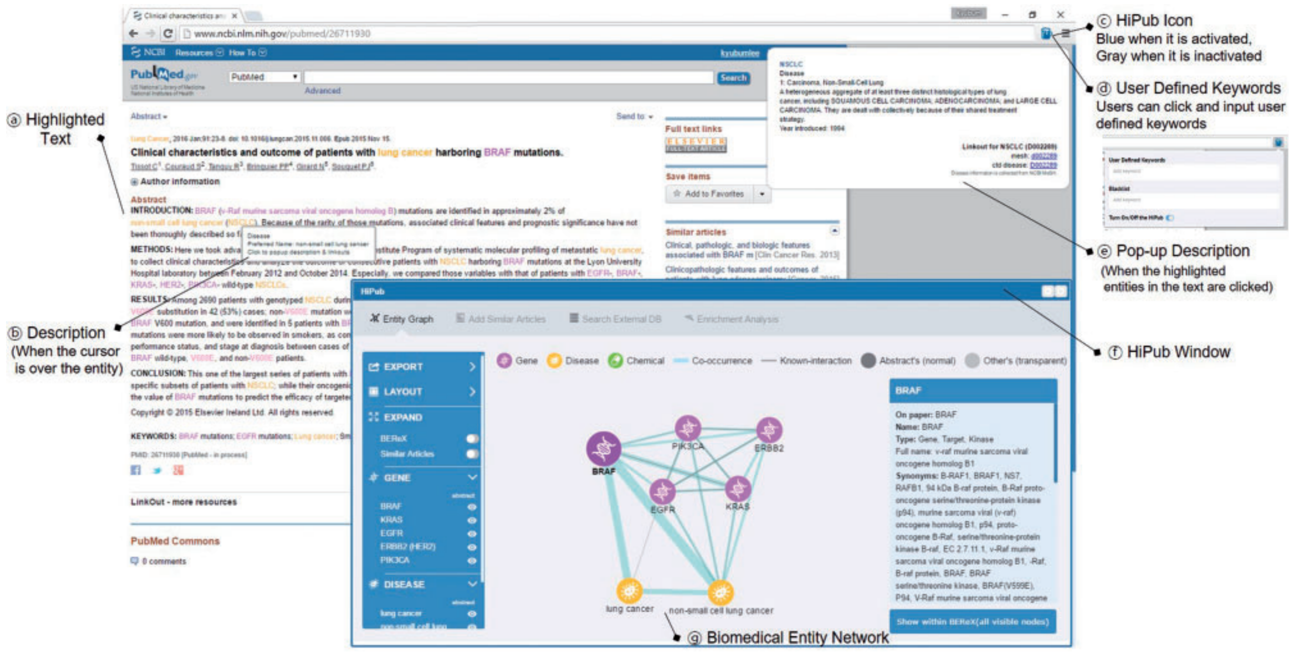
To evaluate the performance of HiPub NER, we tested it on the manually curated abstracts from BRONCO (Lee,K. *et al.*, 2016), and compared it with PubTator and TPX-plus (Joseph *et al.*, 2015). The evaluation results of the NER methods are shown in Supplementary Table S2. HiPub achieves high precision, recall and F1-score as compared to PubTator and TPX-plus in this corpus. More details are available in Supplementary Data (Supplementary Figure S2). See Supplementary Results for details.

2.3 Implementation and installation

HiPub is implemented as a Chrome extension with JavaScript and is available at the Chrome Web Store. Cytoscape.js is used for network visualization and exploration. The HiPub server is implemented using Java and SPRING I/O. It stores all the PubMed abstracts in local storage for rapid and efficient text processing, with daily updates for newly published articles The HiPub project page contains the user manual, installation link and other related information (http://hipub.korea.ac.kr). Figure 1 illustrates a screen shot of HiPub with some features highlighted on an abstract. See User Manual for more details.

3 Use case

The research article PMID 23684607 (Andrysik *et al.*, 2013) describes a functional genetic screen that identifies key genes and regulators in driving cells toward p53-dependent apoptosis (via *BBC3* gene/PUMA protein) and cell cycle arrest (via *CDKN1A* gene/p21 protein). From the screen, the following two new genes that are also key were identified: (1) *TCF3* which is a transcription factor that drives *CDKN1A* expression and suppresses *BBC3* expression across multiple cancer cell types; (2) *TRIAP1* which is a specific repressor of *CDKN1A*. Five genes (*TP53*, *BBC3*, *CDKN1A*, *TCF3* and *TRIAP1*) were mentioned in the abstract, and these were correctly recognized, annotated and highlighted by HiPub (Supplementary Figure S3). However, in the result of



Clinical characteristics and outcome of patients with lung cancer harboring BRAF mutations.

INTRODUCTION: BRAF (v-Raf murine sarcoma viral oncogene homolog B) mutations are identified in approximately 2% of non-small cell lung cancer (NSCLC). Because of the rarity of those mutations, associated clinical features and prognostic significance have not been thoroughly described so f

Disease
Preferred Name: non-small cell lung cancer
Click to popup description & linkouts

NSCLC
Disease
1: Carcinoma, Non-Small-Cell Lung
A heterogeneous aggregate of at least three distinct histological types of lung cancer, including SQUAMOUS CELL CARCINOMA; ADENOCARCINOMA; and LARGE CELL CARCINOMA. They are dealt with collectively because of their shared treatment strategy.
Year introduced: 1994

Linkout for NSCLC (D002289)
mesh: d002289
ctd disease: D002289

BRAF
On paper: BRAF
Name: BRAF
Type: Gene, Target, Kinase
Full name: v-raf murine sarcoma viral oncogene homolog B1
Synonyms: B-RAF1, BRAF1, NS7, RAFB1, 94 kDa B-raf protein, B-Raf proto-oncogene serine/threonine-protein kinase (p94), murine sarcoma viral (v-raf) oncogene homolog B1, p94, proto-oncogene B-Raf, serine/threonine-protein kinase B-raf, EC 2.7.11.1, v-Raf murine sarcoma viral oncogene homolog B1, -Raf, B-raf protein, BRAF, BRAF serine/threonine kinase, BRAF(V599E), P94, V-Raf murine sarcoma viral oncogene

Show within BEReX(all visible nodes)

Fig. 1. Overview of the HiPub application. (**a**) HiPub annotates and highlights biomedical entities in texts. (**b**) HiPub will display basic information of a highlighted entity when the cursor moves over it. (**c**) HiPub icon for turning on/off this application in the Chrome browser. (**d**) Users can click the icon to highlight and add user-defined entities to the biomedical entity network. (**e**) HiPub will display detailed information of a highlighted entity in a pop-up window when the entity is clicked. (**f**) HiPub window visualizes recognized entities in texts as a network, allows users to add entities from similar articles, provides search query links for external databases, and performs enrichment analysis for GO terms/KEGG pathways. (**g**) The biomedical entity network visualizes the relations between entities in a text. The network integrates context-specific entity-relationships extracted from the text and known relationships from external databases for discovering knowledge. Light blue and grey edges represent context-specific and known entity-relationships, respectively. Width of light blue edges represents the frequency of co-occurrence between two entities in the text. The darker grey edge represents the number of evidences supported by external sources

PubTator, some of the genes were wrongly annotated (e.g. PUMA is annotated as a species, not a protein) (Supplementary Figure S4). Next, HiPub visualized the interactions of these genes as a network by integrating co-occurrence relationships (light blue edges, extracted from the abstract) and existing knowledge (grey edges, obtained from external databases). The novel interactions between *TCF3* and *CDKN1A*, *TCF3* and *BBC3*, *TRIAP1* and *CDKN1A* were identified from the study. The entity network, which is the basic summary of the abstract (context-specific), faithfully captures these interactions (Supplementary Figure S5). In contrast, the existing databases (e.g. STRING) do not contain all the interactions (Supplementary Figure S6). Therefore, HiPub can be used as a tool to assist users in extracting important entity relationships from both texts and external databases, and integrating relations from related articles for knowledge discovery. See Supplementary Data for details and additional use case examples.

In summary, we have developed HiPub, a novel web browser plug-in that automatic recognizes, annotates and translates PubMed abstracts and PMC full-text articles into biomedical entity networks for knowledge discovery.

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Conflict of Interest: none declared.

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