

# Development and Application of an Interaction Network Ontology (INO) for Literature Mining of Vaccine-associated Gene-Gene Interactions

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**Abstract** — Literature mining of gene-gene interactions has been enhanced by ontology-based name classifications. However, in biomedical literature mining, interaction keywords have not been carefully studied and used beyond a collection of keywords. In this study, we report the development of a new Interaction Network Ontology (INO) that classifies >800 interaction keywords and incorporates interaction terms from the PSI Molecular Interaction (PSI-MI) and Gene Ontology (GO). Using INO-based literature mining results, a modified Fisher’s exact test was established to analyze significantly over- and under-represented enriched gene-gene interaction types within a specific area. Such a strategy was applied to study the vaccine-mediated gene-gene interactions using all PubMed abstracts. The Vaccine Ontology (VO) and INO were used to support the retrieval of vaccine terms and interaction keywords from the literature. In total 14 over-represented and 17 under-represented interaction types were identified. The analysis of these interaction types and their associated gene-gene pairs uncovered many scientific insights.

**Keywords**—ontology; vaccine; Interaction Network Ontology; INO; literature mining; enrichment analysis

## I. INTRODUCTION

Two common strategies of literature retrieval of reported gene-gene interactions include gene-gene co-occurrence and interaction keywords-based literature mining. In this paper, the gene-gene interaction represents a broad interactive relation between two genes or gene products [1]. Such a relation does not have to be direct physical interaction. The co-occurrence strategy identifies two related genes both listed in the same literature, or more specifically in the same title, abstract, or sentence. An example of such a strategy is the PubGene system that extracts gene relationships based on co-occurrence of gene symbols in MEDLINE titles and abstracts [2]. The other strategy relies on the identification of two genes together with an interaction keyword in the same sentence. Such a method may still generate many false-positive results. To improve the interaction keyword-based approach machine learning algorithms (e.g., support vector machine (SVM) [3]) with features extracted from syntactic analysis of sentences (e.g., dependency parse trees) can be used [4].

Ontologies can be applied to enhance literature mining performance. For example, in our previous work, a vaccine-specific sub-network was built by considering only the interactions that were extracted from sentences that contain the “vaccine” term (or its variants like “vaccines”,

“vaccination”, and “vaccinated”). This strategy does not retrieve the sentences where more specific vaccine names such as BCG (a commercial tuberculosis vaccine) are mentioned. Such vaccine names and their hierarchical relations are represented in Vaccine Ontology (VO) [5]. We found that the application of VO has significantly improved the analysis of the vaccine-specific sub-network [6].

An ontology that logically represents various interaction keywords/types and their semantic relations would help address the challenge of retrieving and classifying the types of gene-gene interactions in the interaction keyword-based literature mining. The GENIA ontology provides a semantically annotated corpus for biological literature mining [7]. However, this ontology does not specify various types of interactions between genes or proteins. Initiated from the classification of >800 interaction keywords [6], we have developed the Interaction Network Ontology (INO) that ontologically represents various interaction types and their relations, and collects and assigns interaction keywords to these different interaction types. The detail about the ontology will for the first time be provided in this manuscript.

In addition to supporting the literature mining of gene-gene interactions, INO can be used for interaction type enrichment analysis. Gene Ontology (GO)-based gene set enrichment analyses have been widely used to determine over- or under-represented biological functions in a set of genes obtained from high-throughput Omics studies. GO provides controlled vocabulary of standard terms for describing gene product characteristics in a hierarchical structure. The input for the GO term enrichment analysis is a list of genes. Such a method does not classify enriched gene-gene interactions. Since INO classifies different interaction types into a structured ontology, it becomes possible to perform gene-gene interaction enrichment study by comparing the INO-based literature mined data of gene-gene interactions in some specific domain over the data from the broad background literature mining.

In this manuscript, we will first introduce the INO development with a focus on its representation of interaction types and keywords for literature mining. An INO-based gene interaction enrichment method based on a modified Fisher’s exact test will then be introduced. Such a method has been applied to analyze the vaccine-mediated gene-gene

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interactions. The results of over- and under-represented gene-gene interaction types and gene-gene interactions will also be described in detail.

## II. METHODS

### A. *INO development*

INO was developed by following the Open Biological Ontology (OBO) Foundry ontology development principles, including openness and collaboration [8]. Its development is aligned and integrated with existing OBO Foundry library ontologies. INO imports existing terms by using OntoFox [9]. New terms generated in INO use the “INO\_” prefix. INO uses the format of W3C standard Web Ontology Language (OWL2) (<http://www.w3.org/TR/owl-guide/>). For efficient editing of INO, the Protégé 4.3 OWL ontology editor (<http://protege.stanford.edu/>) was used.

The INO source is open freely under a Creative Commons (CC) license for public and commercial usage. INO has been deposited at the INO SourceForge project page (<http://sourceforge.net/projects/ino/>). It is available in the ontology repositories of NCBO BioPortal (<http://purl.bioontology.org/ontology/INO>) and Ontobee [10] (<http://www.ontobee.org/browser/index.php?o=INO>).

### B. *INO-based literature mining of gene-gene interaction pairs and interaction types*

The sentences from the complete PubMed abstracts (published up to 12/31/2013) were obtained from the BioNLP database in the National Center for Integrative Biomedical Informatics (NCIBI; <http://ncibi.org/>). VO-SciMiner [11] was used to identify gene names/symbols, VO and INO terms from these sentences. Sentences with two gene names and INO terms (e.g., interacts, binds, activates) were selected. We obtained the dependency parse trees of the sentences using the Stanford Parser [12] and extracted the shortest dependency path between each pair of genes in a sentence. We defined an edit distance-based kernel function among these dependency paths and used SVM [3] to classify if a path describes an interaction between a gene pair [6]. A confidence score calculated based on SVM was used to measure the confidence of association between two genes in a sentence in the literature. Positively-scored sentences were kept, and the gene pairs together with the interaction keywords from these sentences were extracted. The extracted interaction keywords were mapped to INO to define the interaction types.

### C. *Development of INO-based statistical enrichment analysis of literature mined gene-gene interaction data*

A modified Fisher’s exact test has gained popularity over the last decade in high-throughput gene expression studies as a preferred method for identifying enriched biological functions among given gene sets [13, 14]. We implemented the modified Fisher’s exact test in Perl using the Ngram Statistics Package [15] to identify enriched gene-gene interaction types, in terms of INO terms, within a concept-specific sub-network. For each INO term, a 2x2 contingency table is obtained on

which the Fisher’s test runs, as shown in Table 1. Both under-represented and over-represented terms are selected as a significantly enriched INO term with a p-value < 0.05 after Benjamini-Hochberg (BH) multiple testing corrections. In the current study, vaccine-associated gene-gene interaction network was defined based on the gene-gene interactions obtained from the PubMed abstracts, including those retrieved by a PubMed search of ‘vaccine’ and those identified by SciMiner-VO using 186 specific vaccine terms extracted from the VO ‘vaccine’ branch. These 186 vaccine terms (e.g., tuberculosis vaccine BCG) are easily identified by natural language processing programs. This vaccine-associated network was compared against the complete gene-gene interaction network.

Table 1. 2x2 contingency table.

# of gene-gene Interaction pairs	Concept-specific sub-network	Whole Network
With the INO term	30 – 1	500
Without the INO term	150	30000

The sub-network has 30 gene pairs associated with this INO term out of a total of 180 gene pairs. A modified Fisher’s exact test, with the “- 1” modification made to the typical Fisher’s exact test to make the statistical test more conservative, was employed to identify significantly over-represented terms (p-value of 6.9E-20).

## III. RESULTS

### A. *The Interaction Network Ontology (INO)*

#### (1) *INO overall design and hierarchy*

INO is a biomedical ontology in the domain of molecular interactions and interaction networks. INO is aligned with the upper level Basic Formal Ontology (BFO) [16] (Figure 1). BFO contains two branches, continuant and occurrent. The continuant branch represents time-independent entity such as material entity, and the occurrent branch represents time-related entity such as process. BFO has currently been used by over 100 domain ontologies, including many (e.g., GO) within the framework of the OBO Foundry [8]. By aligning different domain ontologies under the two branches of BFO, INO is able to efficiently use the terms from other ontologies in representing signaling pathway elements.

Three key INO terms are interaction, network, and pathway. In INO, an interaction is defined as a processual entity that has two or more participants (i.e., interactors) that have an effect upon one another under a particular condition. An interactor (or called interactant) is defined as a material entity that plays the role of “interactor role”. With different roles, an interactor can be an ‘input interactor’, ‘output interactor’, ‘catalyst’, ‘positive regulator’, or ‘negative regulator’. An interaction consumes its input interactors (but not the catalysts or regulators) and generates its output interactors. A network is a process that includes at least two connected interactions. A network does not have to include a predefined start or end entity. A pathway is a type of network that has specified distinct start(s) and end(s). Each of the three INO key terms includes many subclasses.



[17] and the Ontology of Genes and Genomes (OGG) [18]. Provenance and source ontology IDs are kept in our term importing [9].

In total, INO includes 355 terms under the branch of INO *interaction*. These INO interaction terms and their associated literature mining keywords can be used for efficient literature text tagging and retrieval of sentences containing these keywords. The usage of these terms and keywords in our literature mining study is described below.

## B. INO-based literature mining of gene-gene interactions

### (1) Workflow and system design

The workflow of the ontology-based gene pair enrichment analysis is illustrated in Figure 3.

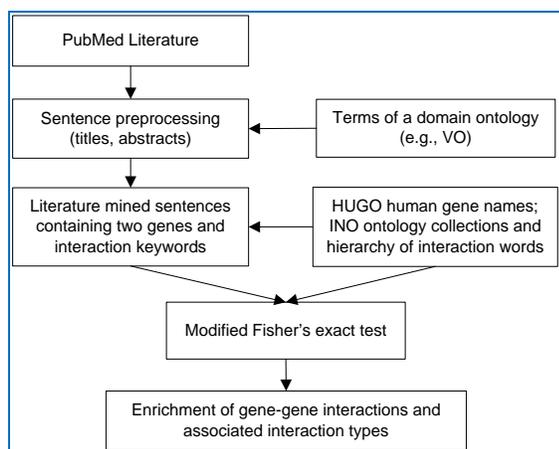


Figure 3. The workflow of INO-based gene-gene interaction enrichment analysis. The detail about the workflow is described in the text.

Specifically, all publications from PubMed were first downloaded. The sentences of article titles and abstracts were parsed and pre-processed. Human gene names and interaction keywords were tagged. To tag human gene names, the HUGO human gene nomenclature assignments (<http://www.genenames.org/>) were used. These human gene names are also available in the OGG [18]. The INO interaction types and associated keywords were used for tagging interaction keywords. As detailed in the Methods section, an INO-based modified Fisher's exact test was developed to identify enriched statistically significantly gene-gene interaction types and associated gene-gene pairs (Figure 3).

The INO-based workflow for literature mining of gene-gene interactions is applicable for different use case studies. Below we introduce the application of such a strategy for studying the gene-gene interactions in the vaccine domain.

### (2) INO-based literature enrichment analysis of vaccine-associated gene-gene interaction data

Our literature mining analysis used all PubMed documents published as of 12/31/2013. A total of 23,481,042 PubMed documents were used as the background data set for the analysis. Using this data set, SciMiner identified 314,152 gene pairs, each of which was associated with at least one INO term.

We applied our study to the vaccine domain. A PubMed search for vaccine-related documents resulted in 237,061 hits (as of 12/31/2013). VO-SciMiner additionally identified 28,908 documents using VO terms, resulting in a total of 265,969 documents to define the vaccine-associated document sets. The gene-gene interactions (*i.e.*, gene pairs) with positive SVM scores and at least one INO term at the same sentence level were compiled from these 265,969 PubMed abstracts. A total of 6,116 gene pairs were associated with at least one INO term.

Out of 78 INO interaction terms associated with at least five gene-pairs of the vaccine-associated sub-network, 14 terms were significantly over-represented (BH p-value < 0.05 and a minimal enrichment fold of 2) (Table 2). The results indicate that these 14 interaction types are more extensively studied in the vaccine context among the research of all the gene-gene interaction types published in PubMed.

Table 2. Significantly over-represented INO terms among the gene-gene interaction pairs of vaccine-associated sub-network

INO_ID	Reference Term	Enrichment Fold	BH * P-value	Most Frequent Gene-pair (#)
INO_0000140	neutralization	6.6	0	IFNG_IL12A (5)**
INO_0000096	induction of production	6.2	0	TNF_IFNG (2)
INO_0000106	gene fusion	5.6	0	CD40LG_CD40 (3)
INO_0000103	accessory regulation	3.9	0	CD8A_CD4 (55)
INO_0000062	costimulation	3.7	0	CD40_CD8A (4)
INO_0000169	synergization	3.0	0	CD8A_CD40 (5)
INO_0000089	co-regulation	2.9	0	CD8A_CD40 (5)
MI_0559	glycosylation reaction	2.9	0	IL17A_MUC6 (1)
MI_0195	covalent binding	2.5	0	CSF2_ACP2 (2)
MI_0208	genetic interaction	4.9	1.82E-10	CD40LG_CD40 (3)
MI_0571	mRNA cleavage	23.2	2.58E-07	CFI_SUPT5H (1)
MI_0902	RNA cleavage	16.2	2.21E-06	CFI_SUPT5H (1)
MI_0910	nucleic acid cleavage	6.4	6.11E-04	CFI_SUPT5H (1)
GO_0018377	protein myristoylation	2.3	2.68E-03	CD4_S100B (2)

Notes: \* BH: Benjamini-Hochberg; \*\* IFNG\_IL12A (5): represents the IFNG and IL12A gene pair shown in five papers.

Furthermore, our gene-gene interaction enrichment analysis was able to retrieve all the gene pairs associated with each interaction type (last column in Table 2). For example, as indicated in five publications (PubMed IDs: 19915058, 8557339, 15557182, 17517055, and 7525727), the cytokines interferon-gamma (IFNG) and interleukin-12A (IL12A) have been found to be closely related, and the neutralization of one cytokine often leads to decreased production of another one [19, 20]. Such *neutralization*-related research has been typically found in the field of vaccinology. In another example, associated with the interaction type “induction of production”, the production of one cytokine TNF (or IFNG) was found to be induced by another cytokine IFNG (or TNF) [21]. A close examination of all the gene pairs recorded in Table 2 shows that they are all related to the vaccine and immunology research. These results also confirm the specificity of our INO-based enrichment analysis.

In addition, our study found 17 significantly under-represented INO terms with a maximum enrichment fold of 0.5 (equivalent to 2 fold in over-representation) and BH P-value < 0.05 (Table 3). Compared to the general gene-gene interaction research, these interaction types are likely less

studied in the vaccinology research field. The reasons of these under-represented interaction types may vary. It is likely that some of these under-represented interactions represent new research opportunities in the vaccinology.

Table 3. Significantly under-represented INO terms among the gene-gene interaction pairs of vaccine-associated sub-network.

INO_ID	Reference Term	Enrichment Fold	BH P-value
MI_0203	dephosphorylation reaction	0.06	0
INO_0000178	tyrosine-phosphorylation	0.09	0
INO_0000044	gene expression regulation	0.26	0
INO_0000172	transactivation	0.26	0
INO_0000060	coprecipitation	0.28	0
GO_0016310	phosphorylation	0.36	0
MI_0403	colocalization	0.36	0
MI_0414	enzymatic reaction	0.42	0
MI_0194	cleavage reaction	0.49	0
MI_0213	methylation reaction	0.37	6.84E-16
INO_0000092	dissociation	0.28	6.27E-15
INO_0000048	coimmunoprecipitation	0.35	1.00E-13
INO_0000115	hyperphosphorylation	0.27	2.54E-08
INO_0000084	Destabilization	0.28	1.49E-05
GO_0006461	protein complex assembly	0.24	1.97E-05
INO_0000088	protein dimerization	0.26	6.41E-05
INO_0000171	Termination	0.42	3.98E-03

One advantage of INO based study is that we can rely on the INO hierarchy to identify the relations among enriched interaction types. Such a strategy is used to generate the hierarchies of enriched 14 over-represented and 17 under-represented INO interaction types (Figure 4). This study clearly shows the relations between many different interaction terms. For example, among the three over-represented terms ‘mRNA cleavage’, ‘RNA cleavage’, and ‘nucleic acid cleavage’, there are two parent-child relations as clearly shown in Figure 4. Interestingly, the term ‘cleavage reaction’ is one of the 17 under-represented terms (Table 3).

Both sets of over-represented and under-represented interaction terms share some common top-level terms including ‘regulation’, ‘direction interaction’, ‘association’, and ‘interaction’. Otherwise, specific profiles of the two sets are in general distinct at the bottom levels (Figure 4).

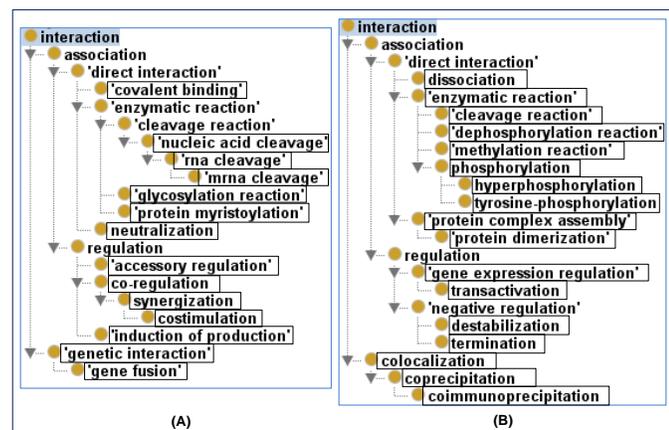


Figure 4. The hierarchies of over- and under-represented INO interaction terms. (A) The hierarchy of 14 over-represented INO interaction terms. (B) The hierarchy of 17 under-represented INO interaction terms. The results were generated using OntoFox [9] with the OntoFox setting “includeComputedIntermediates”, and visualized using the Protege-OWL

editor (<http://protege.stanford.edu/>). The box-enclosed terms are over- or under-represented interaction types directly identified in our program (see Tables 2 and 3). Other terms not enclosed in boxes are terms retrieved by OntoFox to ensure the completeness of the hierarchies.

#### IV. DISCUSSION

This paper introduces two major contributions in the area of ontology-based literature mining research. First, we have for the first time systematically introduced the development of the INO ontology targeting for robust literature mining of gene-gene interaction types. It is noted that in addition to literature mining, INO is also being developed to model various interactions and networks among different molecules [22]. However, the INO development was initiated from meeting our literature mining need [6]. Second, we have proposed and implemented a novel INO-based gene-gene interaction enrichment strategy. The INO-based gene pair enrichment analysis is novel in that the input of such analysis is the literature mined gene-gene interaction types and gene pairs. It differs from a typical GO enrichment analysis where a list of genes is the input. Such a strategy was further used to study the enriched gene-gene interaction types and gene pairs in the domain of vaccinology. Our results demonstrate that the INO offers a repository of hierarchical interaction keywords and platform for allowing systematical retrieval of interaction types from the literature. The INO-based gene-gene interaction enrichment method further provides a strategy for analyzing the retrieved gene-gene interaction literature results.

Our INO-based literature mining study found that while it is relatively easy to describe the relation between two genes when only one interaction keyword exists in the sentence containing these two genes, it is much difficult to describe the relation between the two genes if multiple keywords exist. For example, in our IFNG-IL12A neutralization-related interaction type, we can know these two genes participate in a neutralization-related interaction(s). However, it does not mean that IFNG neutralizes IL-12A, or vice versa. We can only say that these two genes interact somehow in a neutralization-related pattern. It is likely that multiple interaction-related keywords co-exist in one sentence. For example, an IFNG-IL12A neutralization-related sentence is “*In vitro IL-12 neutralization dramatically impaired the IFN-gamma response to S. typhimurium but not to ConA*” [23]. This sentence contains two interaction-related keywords “neutralization” and “impaired”. This is a complex relation where a neutralization of one gene impairs another gene expression. It hints that one gene positively regulates another. In this case, the *neutralization* is really an experimental condition. Our literature mining program retrieved both keywords independently without considering them together. It would be more advanced if we could process these two keywords simultaneously and assign a unique interaction type, such as ‘impairment after neutralization’, which would be a subclass (or child term) of the existing INO term ‘positively regulation’. While this example demonstrates a new direction of future research, such analysis does not undermine the contributions of

the new INO-based literature mining strategy first reported in this manuscript. Indeed, our strategy provides a new start point and platform for further addressing these challenges.

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Authors' contributions: JH developed the INO-based gene interaction enrichment assay and generated data with the vaccine domain use case. AO developed the SVM-based literature mining pipeline. ZX generated the script to execute the literature mining pipeline. YH developed the INO and was the primary writer of the manuscript. YH, JH, and AO all participated in the project design, result interpretation, and manuscript writing. All authors agreed on the manuscript publication.

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