On the Impact of Granularity in Extracting Knowledge from Bioinformatics Data

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Abstract: With the rapidly increasing amount of various types of biological data currently available to researchers, the focus of the biomedical research community has been shifting from pure data generation towards the development of new methodologies for data analytics. Although many researchers continue to focus on approaches developed for analyzing single types of biological data, recent attempts have been made to utilize the availability of heterogeneous data sets that contain various types of data and try to establish tools for data integration and analysis in many bioinformatics applications. Such attempts are expected to increase significantly in this coming decade. While this can be viewed as a positive step towards advancing big data analytics in bioinformatics, it is critical that these integration methodologies are meticulously studied to ensure high quality of the knowledge extracted from the integrated data. In this work, we employ data integration methods to analyze biological data obtained from protein interaction networks and gene expression data. We conduct a study to show that potential problems can arise from integrating or fusing data obtained at different granularity levels and highlight the importance of developing advanced data fusing techniques to integrate various types of biological data for analytical purposes. Further, we explore the impact of granularity from a more formulized approach and the granularity levels significantly impact the quality of knowledge extracted from the integrated data.

1 INTRODUCTION

The bioinformatics perspective of data integration is the uncovering of biological data and the extraction of useful biological information (Rhee et al., 2008). With the subsequent push towards data aggregation and integration (Chatr-aryamontri et al., 2013; Salwinski et al., 2004), comes a series of challenges, highlighted by rapidly changing bioinformatics data standards (Prasad et al., 2009; Kerrien et al. 2011). Many of these bioinformatics data standards are suitable for aggregation by targeting data reporting and storage, such as the Minimum Information about a high-throughput SEQuencing Experiment for microarrays (Ceol et al. 2009), standards of data-use are influenced by research outcomes and must be more flexible to handle the swift evolution of community ordained workflows. Particularly, standards must handle the sensitivities of data sources within these evolving workflows.

Data fusion is a special case of data integration where two or more pieces of data are combined to create a new parameter with its own novel meaning. Although the term data fusion is relatively new to bioinformatics, long associated with a military connotation, its utilization is becoming increasingly popular, with 21 PubMed publications in 2005 using the term "data fusion", and 95 publications in 2015.

Data fusion is a multi-step process, cascading from the primary step of data source selection (Taneera et al., 2012; Hanisch et al. 2002). The high complexity of bioinformatics data sources creates a special challenge (Bossi and Lehner, 2009). Not only does this complexity enhance the central characteristics of big data, such as variety and veracity, but it accentuates the problem of granularity.

Granularity refers to the shifts in scale where membership is defined through mereology (Bittner and Smith, 2003) or indiscernibility (Hobbs, 1995). These two granularity dimensions were originally specified as abstraction, shifts in specificity, and aggregation, shifts in part-whole relations (McCalla et al. 1992). Later the aggregation dimension was adapted to into granularity parthood, molecules in a cell, and determinate parthood, functioning members

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of the cell (Bittner et al., 2004). These scales have not seen a lot of change in recent publications, and the term granularity usually attributed to specificity. However, increased differentiation of granularity scales have been specified for ontology purposes (Rector et al., 2006; Vogt et al., 2012). In the biomedical domain, data sources contain members from a population of available data-producing sensors, we refer to the determinate parthood scale in this study. Further, we use the terms *abstraction* and *aggregation* in reference to their associated dimensions of granularity, instead of their traditional data processing definitions.

When examining biomedical data sources within the *abstraction dimension*, two overarching categories arise, isolated and integrated data sources. Isolated data sources are typically specific, representing results from single experiments. Integrated data sources, if single-modal, may exist at a similar abstraction level as isolated data sources. However, if multi-modal, due to multiple technologies being implemented, the data will exist at a higher abstraction and consequently lower granularity level.

We use microarray data as an example of low abstraction, high granularity data, since each series usually represents just a few experimental conditions across a limited number of tissues. The variability of cellular function within these tissues necessitates that microarray data is not the epitome of high granularity data, rather it exists at a granularity level where differences between cellular conditions can be extracted. To combat high false-positive and false-negative rates, microarray is often enriched through low-granular domain knowledge. A key component to microarray data analysis is to differentiate between cellular conditions. One data fusion methodology is to put these differences in the context of domain knowledge as a component of network creation (Agarwal et al., 2008), through enrichment (Xu et al., 2011), or examining expression differences within the protein-protein interaction (PPI) network (Medintz et al., 2007).

Protein-protein interaction databases may contain high abstraction, low granularity data. Some recent PPI databases are cell-specific or even molecule specific (Veres et al., 2014; Liu et al., 2011). Additionally, many integrated PPI databases, such as the Search Tool for the Retrieval of INteracting Genes/Protein (STRING), compile a list of potential relationships, not taking unique cellular conditions into account. STRING scores the interaction between proteins across a set of data sources in a union-like fashion (Bindea et al. 2009). Here, we use PPI data sources that are non-integrated and not condition specific, in order to bias the data towards a low granularity. These non-integrated PPI databases use manual curation methods to extract PPI information from scientific literature. So, even non-integrated PPI data sources are examples of multi-modal systems. Yet, since the manual curation methodologies employed to create PPI databases may innately increase the granularity of the data, the diversity in the curation methods may lead to the lower-abstraction levels. In this work, we examine the structural and biological attributes of several popular PPI databases in order to characterize their unique contributions towards data integration. We further examine their pathway enrichment of each database to determine any specificity or unique bias towards similar groupings of biological functionality, which would indicate increased levels of granularity.

Although the differences may be explicit between cellular conditions from the expression data and since PPI data comes from high abstraction data sources, integrating microarray data with PPI data that is not tissue or cellular condition specific does not model the true protein-protein interaction network within the experimental cellular condition. Therefore, the consequences of alternate expression and PPI network structure changes may not depict true biological reality. If the variability in granularity levels between PPI databases and microarray data biases the data away from high-granularity, potentially questionable biological information will be extracted after the data fusion implementation. To test this critical point, we can fuse the PPI and the microarray data and compare the information extraction between the original experimental microarray data and the fused datasets. In this study, we test to see the effect of fusing low abstraction, microarray data with high abstraction, PPI data on extraction of Type II Diabetes specific pathways.

Granularity along the *aggregation dimension* requires a more formulized definition, which is specified within the methods section. This formulization includes three suggestions for aggregation definition. First, using a rough set theory definition of granularity, data fusion of specific data sources lies on an abstraction granularity level dependent on a set of attributes governing the differentiation between data sources. Alternate abstraction levels along scales defined by a set of relevant attributes, impact the results of biological information extraction by biasing the fusion towards those chosen attributes. Second, when separating these data sources according to attributes we create a set of fusion networks for each attribute set used. The segmentation of the original data sources can also be used to define level of aggregation. Finally, the number of original data sources can be used to define aggregation within each fused network separately.

We use these three definitions of aggregation to test the relationship between information extraction and aggregation. So, in summary, we have three hypothesis:

> *H1: The different curation methods of non-integrated PPI databases do not offer unique bias towards specific biological functionality.*
>
> *H2: Fusion of low-abstraction and high-abstraction data will decrease experimental-specific information extraction.*
>
> *H3: There exists a definition of aggregation such that a relationship between granularity and information extraction can be seen.*

Section 2 describes the methods for this study, including the formulizations for the definition of granularity in the aggregation dimension. Section 3 depicts the results. Section 4 discusses the outcome of the study and its impact on the hypotheses. The paper concludes with section 5.

2 METHODS

Throughout the study, protein-protein interaction data and microarray data are modeled as networks, where the nodes represent the biological elements and the edges connect elements that are related by interaction or high correlation. In the first part, we attempt to find unique biological themes or functionalities associated with the PPI databases queried in order to answer hypothesis H1. We use structural similarity between the PPI networks and the quality of the clusters obtained from the networks using standard pathway, disease, and ontology enrichments. In this manner, we identify the biological functionality associated with each protein-protein interaction network and enriched clusters are mapped to human pathway hierarchies to search for significant patterns.

In the second part, we address hypothesis H2. To test the hypothesized relationship between abstraction and data extraction, we use a case study with a Type II Diabetes microarray series. We create the integrated network using PPI and microarray data. We then enrich obtained network clusters to identify network-specific biological functions. We choose a list of 24 diabetes associated pathways or diseases curated from Reactome, the Online Mendelian Inheritance in Man (OMIM), and the Kyoto Encyclopedia of Genes and Genomes (KEGG). We assess the enrichments of these pathways across the original and fused networks, and discuss the potential information loss that may occur due to the lack of consistent granularity levels.

To validate the relationship between aggregation granularity and knowledge extraction, hypothesis H3, we formulize granularity using three different approaches and add additional sources to expand on the number of discrete granularity levels that can be

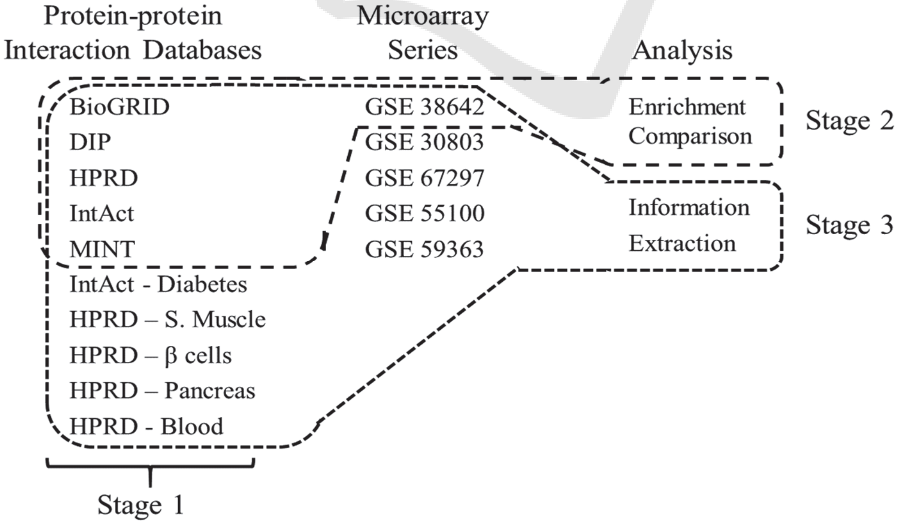


Figure 1: Data sources of this study. Stage one corresponds to hypothesis 1 and uses only the PPI databases. Stage 2 uses a selection from the PPI databases and conducts an enrichment comparison. Stage 3 uses all the data sources in an information extraction test to understand its interplay with aggregation.

formed. Extraction scores based on enrichment results are assigned to each network and correlation is measured.

2.1 Protein-protein Interaction Databases

The following protein-protein interaction databases were selected for this study since they reflect variability associated with experiments used to obtain them, they do not have a high-degree of integration among each other, and they were initially, seemingly sources of low granularity. The databases used were Database of Interacting Proteins (DIP) (Thorne and Stumpf, 2007), BioGRID (Zhang and Horvath, 2005), Human Protein Reference Database (HPRD) (Obayashi and Kinoshita, 2009), IntAct (Ingram et al., 2006), and Molecular INTeraction database (MINT) (Kashani et al., 2009).

DIP focuses on extracting experimental knowledge from publications and stores binary interactions between proteins, clarifying source and evidence. BioGRID is a database of protein and genetic interactions that are extracted from manually annotated publications, by a team of PhD curators. Text mining is used to rank relevant publications where interactions are manually extracted and added to BioGRID. HPRD uses laboratory submitted data through a tool called BioBuilder which helps researchers interact with the database and submit experimental information. In this way, HPRD has protein-protein interactions that are post-translational modification, disease, and tissue specific. It also has an overarching binary PPI source. IntAct takes an open-source approach, with all data and repository code available to the public. The stored interactions are publicly curated from literature but also have a design to allow for direct researcher annotation. Rules on curation are specified on the EBI website and interactions are reviewed by a second curator. MINT is highly similar to IntAct, using the same infrastructure and curation rules. The difference is the set of MINT curators.

For the third (aggregation) component of the study, we expand on those PPI databases with curation conducive to tissue or disease specificity. We add a diabetes sub-network for IntAct. HPRD has many tissue specific curations, but we use only the HPRD subnetworks with attribute overlap for the microarray series used in the third part. So, we include skeletal muscle, β-cell, pancreas, and blood HPRD PPI networks.

2.2 Network Creation

Although the protein-protein interaction databases contained evidence codes which may affect edge weights through confidence variance, the granting of specific edge weights was not implemented. This alleviated the necessity of consolidating the PPI edge weights with the microarray edge weights. Instead, edges exist where evidence supports an edge. Further, all types of experiments, including high-throughput evidences, were included if they were present in the original PPI data source. This may introduce a technology bias beyond what is incorporated into the research bias. However, correction of a technology bias may introduce unknown sensitivities. So, networks created were binary and non-directional. Protein-protein interaction networks were derived from the overarching sets of database information, such that tissue specific information was included without its specificity. Only complete proteins which correspond to at least one Ensembl gene Id were utilized. We attempt to highlight the issues of removing granularity from domain knowledge sources. Yet for validating the concept of the interaction between aggregation and information extraction, we use PPI networks with higher levels of granularity as mentioned above.

Microarray data was initially downloaded from the Gene Expression Omnibus series, GSE 38642 (Halevy et al., 2006). This series was chosen since it is human, has a large set of biological replicates, demonstrates a disease with a long list of well-characterized pathways, Type II Diabetes, and obtains expression through a relevant and specific tissue, pancreatic islets. Additionally for the third part of the study, we included series GSE 30803, a treatment based study on healthy β-cells, GSE 67297, a study on cold acclimation effects of diabetic adipose tissue, GSE 55100, a blood tissue study of diabetes, and GSE 59363, which uses skeletal muscle tissue in healthy and diabetic samples with exercise stages. These additional microarray series were chosen as they have at least a moderate number of biological replicates, and overlapping values across “tissue”, “disease state”, “treatment”, and “technology” attributes.

The raw expression files were downloaded, and robust multi-array (RMA) normalized. Pearson correlation was implemented to find expression relationships. The microarray networks then took two different paths, those filtered through false-discovery rate p-value correction and those with hard thresholds at 0.8 power and a 0.05 p-value. Base mapping of probes to Ensembl gene Ids was completed through the Biomart API. Ensembl gene Ids which correspond to multiple probes were assigned edge weights which matched the highest correlation scoring probe for each individual interaction. The strong influence of some protein domains (e.g. probes which correspond to multiple transcripts) reduce the accuracy of the correlations which use the probe's expression values. The conjugated expression values are representative of multiple transcripts. Depending on the abundance distribution of these transcripts either correlations may be assigned to the wrong protein, or more likely, the correlations will favor random correlation values, which are more likely to be insignificant and negligible. These multi-transcript probes are considered negligible in this study as they make up only a small percentage of the total probes.

With the lack of PPI exact interaction strength values, the integrated networks created were the union of the PPI matrices and the microarray matrices. Union is a surprisingly common kernel function when integrating and fusing biological data sources. We use it here as an example of an integration-based data fusion approach.

2.3 Identification of Unique Contributions from Protein-protein Interaction Data and Type II Diabetes Case Study

PPI networks were clustered with the Speed and Performance In Clustering (SPICi) algorithm, a fast and biologically driven clustering approach (Jiang and Singh, 2010). The standard parameters produced ideally sized clusters for enrichment. An in-house tool for enrichment which downloads source groups and group information for Reactome, OMIM, and KEGG datasets. It uses the multivariate hypergeometric function to find overly expressed source groups within network clusters. Then, it uses the Benjamini-Hochberg-Yekutieli false discovery rate p-value correction to address multiple hypothesis testing and dealing with the lack of independence for enrichment terms on a single cluster.

Unique contributions were determined by finding those enrichments for a PPI source that were not identified in any other PPI source. For visualization, unique Reactome enrichments were mapped to the Reactome pathway hierarchy and grouped by pathway similarity. Further, structural differences between PPI networks were uncovered at the node, edge, and cluster levels.

The microarray networks were fused with the PPI networks in a union fashion so that there were control microarray, diabetes microarray, PPI, control fused, and diabetes fused networks. These networks were filtered as to only include only those biological elements present in the microarray sets. Then they were clustered and enriched using SPICi and the in-house enrichment tool. Diabetes pathways were manually determined for Reactome, GO, OMIM, and KEGG. Enrichments of these pathways were examined across the networks to identify biological differences between control and diabetes networks.

2.4 Validation of Relationship between Aggregation and Information Extraction

A more formulized definition of granularity is required to characterize the relationship between granularity and information extraction. So far, we use the dimension of abstraction. This allows only for direct comparisons between objects or networks along the same scale. An extended discrete comparison scale is needed along the dimension of aggregation.

Shortly after the initial introduction of rough sets into uncertainty theory (Pawlak, 1982), Hobbs began to distinguish granularity as a significantly contributing factor towards uncertainty (Hobbs, 1985). This received formulization (Greer and McCalla, 1989) and then developed into concepts of discrete granularity scales (Hobbs, 1995). We use Hobbs scales of granularity with the concept of minimum rough sets to define levels of granularity from our *universe of objects* (i.e. our set of original data sources). Granularity over multiple universes in rough sets is currently used in decision support and management science (Słowiński et al., 2014; Sun and Ma, 2015). We use it here as a formulized approach to measuring granularity.

Given a universe, U, consisting of a set P of predicates over a number of objects in O. R is the relevant subset of predicates from P. So, we can define objects x and y as indistinguishable if they meet:

$$\forall(x, y)\ x \sim y \cong (\forall p \in R)(p(x) \cong p(y)) \qquad (1)$$

Two objects are indistinguishable if their values for every relevant predicate are equal. Expanding on this, given a set of predicates (or attributes), we can separate the complete list of objects into sets of indistinguishable elements or equivalence sets. In the first definition of aggregation, we define granularity by the number of attributes used to create the equivalence sets. In the second definition, each of these equivalence sets have membership at a discrete granularity level defined by the number of these indistinguishable sets. So, given a set of attributes we can determine the granularity level as well as group data sources for network fusion. In the third definition of aggregation, we can define granularity by the number of data sources in the equivalence set and separate these sets according to granularity.

We created three universes of objects as our complete set of data sources, using “source”, “tissue”, “disease state”, “treatment”, “technology”, “aggregation method”, and “species” as attributes. The first universe, the *overarching universe,* contained all data sources. The second two, *diabetes* and *control* universes, representatively used diabetic or non-diabetic data sources. In doing so we can see the effect of experimental condition on information extraction. We used each combination of every length of these attributes, defining a set of fused networks and a defined granularity level. We can use the enrichment and granularity level to characterize the relationship between the two, given our defined universe.

To score information extraction, we use a similar method as above, measuring the enrichment of diabetes related terms from Reactome, KEGG, and OMIM. We define the information extraction score in two ways. First, we use the proportion of relevant enrichment terms found over the total number of relevant enrichment terms. To standardize enrichment term impact on the score, we also use an information extraction score which weights the contribution of an enriched term by the probability of finding the term, as defined by the calculated probability of finding the term across all used networks produced by the universe. In this equation, N is the set of enrichment terms in a given network, T is the complete set of diabetic enrichment terms, and *P(t)* is the probability of finding term *t* in any network.

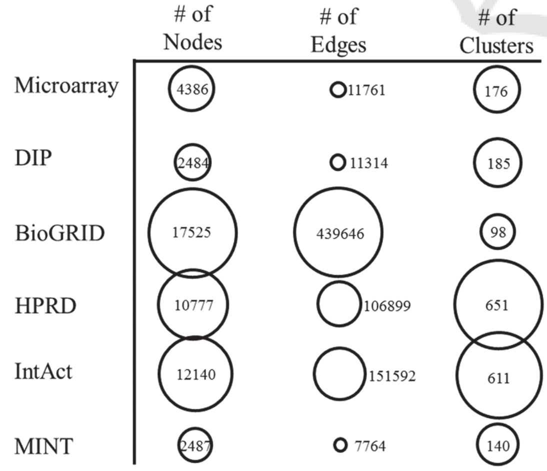


Figure 2: Data Source Sizes – The relative sizes for the data sources as the number of nodes, number of edges, and number of clusters are displayed as numbers and represented as the area of their corresponding circles in order to show relative size.

$$weighted\ score = \frac{\sum_{t \in N} 1 - P(t)}{\sum_{t \in T} 1 - P(t)} \qquad (2)$$

Then we find the correlation between discrete levels of granularity and information extraction scores, utilizing equivalent set derived fused networks as each point. In total, we obtain six correlation and p-value pairs for each aggregation definition from the three universes and the two scoring techniques. These correlations are applied to each of the definitions for aggregation granularity: number of attributes, number of equivalence sets, and number of contributing data sources.

3 RESULTS

3.1 Protein-protein Interaction Databases Show Low Structural Similarity

Structural differences between networks were examined at the node, edge, and cluster levels. Figure 2 shows the number of biological elements found in each database, i.e. proteins for the PPI databases, and transcripts for the microarray series. The overlap percent of these node sets were calculated by dividing the intersection of the two sets by their union. As would be expected the larger databases have low overlap percent with the smaller databases since their potential overlap is small. Table 1 shows this overlap between the PPI networks and the 0.8 power threshold control microarray network. The larger, more inclusive networks tend to have higher similarity, but DIP and MINT, even with a close number of nodes, had a low overlap.

More so than the overlap between biological elements, the interactions derived from each data source showed almost no overlap. The number of edges in each network seemingly enhanced the distance in size between data sources. Figure 2 shows the number of interactions in each network; Table 2 shows the overlap, calculated by taking the intersection over the union of two interaction sets.

The overlap of clusters from each network was determined. Only clusters of size five or higher were used and two clusters needed a 70% member overlap as determined by the smallest cluster to be determined the same. Figure 4 shows the number of clusters in each network; Table 3 shows the overlap between these clusters. The BioGRID network had a high density and clustered into small, yet huge clusters. Once again, the structural overlap of these networks is negligible.

Table 1: Node Overlap.

	MicroArray	DIP	Biogrid	HPRD	IntAct
MINT	0.08	0.22	0.14	0.20	0.20
IntAct	0.18	0.21	0.65	0.50	
HPRD	0.16	0.23	0.56		
Biogrid	0.19	0.16			
DIP	0.09				

Table 2: Edge Overlap.

	MicroArray	**DIP**	**Biogrid**	**HPRD**	**IntAct**
MINT	0.00	0.02	0.00	0.02	0.04
IntAct	0.00	0.03	0.02	0.06	
HPRD	0.00	0.04	0.03		
Biogrid	0.00	0.02			
DIP	0.00				

Table 3: Cluster Overlap.

	MicroArray	**DIP**	**Biogrid**	**HPRD**	**IntAct**
MINT	**0.00**	**0.01**	**0.01**	**0.01**	**0.02**
IntAct	**0.00**	**0.01**	**0.08**	**0.06**	
HPRD	**0.00**	**0.02**	**0.06**		
Biogrid	**0.00**	**0.01**			
DIP	**0.00**				

Table 4: Potential Enrichment Overlap.

	MicroArray	**DIP**	**Biogrid**	**HPRD**	**IntAct**
MINT	0.30	0.52	0.60	0.56	0.57
IntAct	0.74	0.43	0.40	0.40	
HPRD	0.71	0.49	0.46		
Biogrid	0.72	0.49			
DIP	0.54				

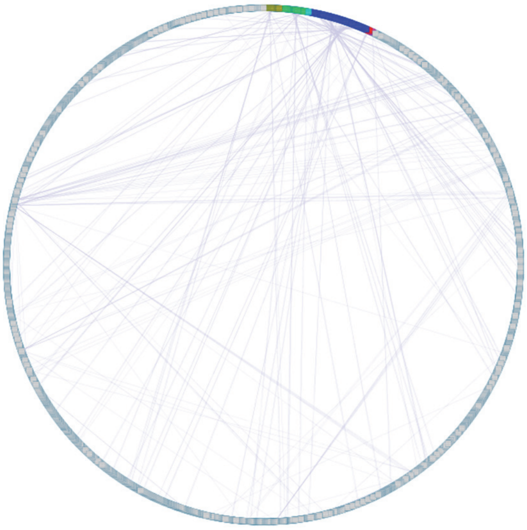


Figure 3: Full hierarchy of Reactome human pathways. The entire list of human Reactome pathways and their hierarchy was graphed so that nodes represent pathways and edges represent the child-parent relationships in the Reactome hierarchy. The unique Reactome enrichments for each PPI network are highlighted in color: HPRD (green), IntAct (gold), BioGRID (blue), DIP (pink), and MINT (red). These unique enrichments represent a small proportion of the total human pathway hierarchy.

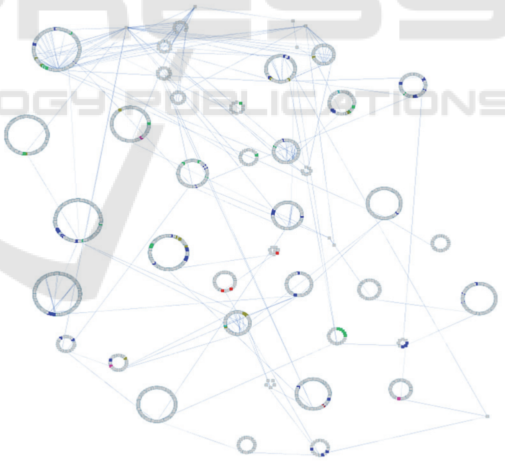
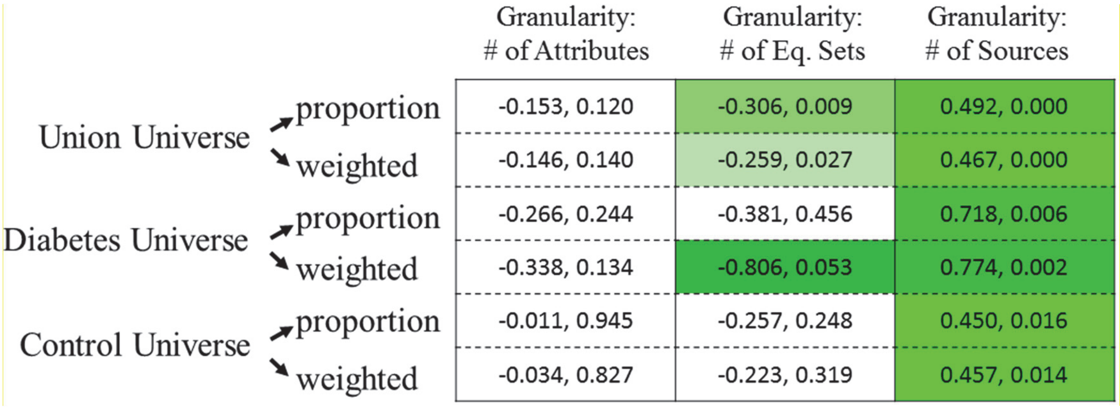


Figure 4: Organized hierarchy of Reactome human pathways - Fig. 3 is restructured to group pathways from the same branches of the Reactome hierarchy together. The unique pathway enrichments show low grouping tendency, and the PPI sources do not demonstrate biological specificity. Enrichments for each PPI network are highlighted in color: HPRD (green), IntAct (gold), BioGRID (blue), DIP (pink), and MINT (red).



		Granularity: # of Attributes	Granularity: # of Eq. Sets	Granularity: # of Sources
Union Universe	proportion	-0.153, 0.120	-0.306, 0.009	0.492, 0.000
	weighted	-0.146, 0.140	-0.259, 0.027	0.467, 0.000
Diabetes Universe	proportion	-0.266, 0.244	-0.381, 0.456	0.718, 0.006
	weighted	-0.338, 0.134	-0.806, 0.053	0.774, 0.002
Control Universe	proportion	-0.011, 0.945	-0.257, 0.248	0.450, 0.016
	weighted	-0.034, 0.827	-0.223, 0.319	0.457, 0.014

Figure 5: Relationship between Granularity (Aggregation) Definitions and Information Extraction Scores – For each universe and each information extraction score type, the correlation and p-value between score type and granularity is shown (correlation, pvalue). Only significant scores are highlighted and the darker the coloring, the higher the correlation value.

3.2 Reactome Enrichment: Overlap and Unique Contributions

Although the structural aspects of the networks had low similarity, the biological properties as determined through Reactome enrichments had comparatively high overlap. Table 4 shows the potential enrichment overlap between data sources. Here, the intersection is divided by the size of the smaller enrichment size to highlight the low availability for unique contributions by the smaller datasets.

For visualization, we examine only the Reactome enrichments of each PPI network. The unique enrichments for individual networks would delineate any source as specific towards an individual biological domain. Figure 3 shows the unique Reactome pathway enrichments for each individual PPI source in the setting of the entire set of human Reactome pathways. Although the structural differences between networks are small, unique pathway enrichments only make up a small proportion of the total potential pathway space. Initially, this indicates that any bias that does exist towards a specific biological condition or theme, is weak. However, the impact of these biases can only be examined by segmenting the Reactome hierarchy into biologically relevant clusters.

The manual grouping of these pathways into groups of similar function, as shown in Figure 4, does not distinguish confident unique themes of biological extraction. Yet a few sets of unique contributions show significant grouping within the pathway hierarchy. HPRD highlights gamma carboxylation; IntAct highlights GAG protein metabolism; and BioGRID highlights ER to Golgi transport and single-nucleotide replacement. However, these tendencies are insufficient to specify particular granularity for individual PPI data sources. Rather, they each demonstrate generic pathway enrichment across the human pathway hierarchy.

3.3 Data Fusion with PPI Sources Drowns Microarray Conditional Differences

We compare the differences between control and diabetic conditions for the microarray networks, the PPI networks, and the fusion networks. For the microarray networks, the false-discovery rate adjustment diminished the interactions and enrichment so that there are only three differences between the control and diabetic conditions. The power and p-value threshold networks showed ten pathway differences between the control and diabetic conditions out of 24 total diabetes related pathways. After fusion, the network structure for the FDR adjusted and the thresholded networks were enriched for nearly every single available pathway. Table 5 shows these enrichments, only showing 0.05 p-value adjustment. The ten differences from the microarray networks are not seen in the fusion networks.

3.4 A Significant Interaction between Granularity and Information Extraction Exists

The currently defined universes of predicates and objects has seven relevant attributes; however, we remove the "source" attribute as it does not produce equivalence sets greater than one, leaving 60 total sets of attributes. A total of 57 equivalence sets were determined across 7 discrete granularity levels for the first definition of aggregation granularity, 24 discrete granularity levels for the second, and 24 for the third. We found the correlations between the information extraction scores based on enrichment. Of these, we found no significant correlations between granularity and information extraction when using the number of attributes determining equivalence sets. When using the number of equivalence sets, half of the correlations were significant. Finally, when considering the number of sources as the scale of granularity, each of the correlations was significant.

Table 5: Pathway Enrichment Network Spectrum.

	Micro Array Control 0.05 p	Micro Array T2D 0.05 p	DIP	Bio GRID	HPRD	IntAct	MINT	Fusion Control 0.05p	Fusion T2D 0.05p
Metabolism of lipids and lipoproteins		▨	▨	▨	▨	▨	▨	▨	▨
PERK regulates gene expression				▨	▨	▨		▨	▨
Protein processing in endoplasmic reticulum		▨	▨	▨	▨	▨		▨	▨
Adrenaline, noradrenaline inhibits insulin secretion				▨	▨			▨	▨
Calcitonin-like ligand receptors					▨			▨	▨
Glucagon-like Peptide-1 (GLP1) regulates insulin secretion				▨	▨	▨		▨	▨
Signaling by Leptin			▨	▨	▨	▨		▨	▨
Notch signaling pathway		▨	▨	▨	▨	▨		▨	▨
Wnt signaling pathway		▨	▨	▨	▨	▨		▨	▨
TGF-beta signaling pathway			▨	▨	▨	▨	▨	▨	▨
Hormone-sensitive lipase (HSL)-mediated triacylglycerol hydrolysis				▨				▨	▨
PPAR signaling pathway				▨	▨	▨		▨	▨
Cell cycle		▨	▨	▨	▨	▨		▨	▨
p53 signaling pathway			▨	▨	▨	▨	▨	▨	▨
Advanced glycosylation end-product receptor signaling				▨	▨			▨	▨
Regulation of insulin secretion		▨		▨	▨	▨		▨	▨
Unfolded Protein Response (UPR)				▨	▨	▨		▨	▨
Type II diabetes mellitus		▨		▨	▨	▨		▨	▨
Diabetes Mellitus, noninsulin-dependent; NIDDM	▨			▨	▨			▨	▨
Pancreatic secretion		▨		▨	▨		▨	▨	▨
Maturity onset diabetes of the young	▨							▨	▨
mTOR signaling			▨	▨	▨	▨		▨	▨
Insulin secretion	▨	▨	▨	▨	▨	▨		▨	▨

4 DISCUSSION

The cascading importance of high confidence necessary in medical and biological data puts an emphasis on reproducibility, stability, and sensitivity of analytical workflows. Due to the complexity of biological data analysis, results have a high sensitivity to small changes in parameters, producing results that are unstable and difficult to reproduce. This concept is accentuated and expanded in data fusion, granularity being just a single potential for sensitivity. The data fusion approach presented here demonstrates the sensitivity of these biological data towards the various levels of granularity along two different dimensions.

4.1 Protein-protein Interaction Database Differences and Sensitivity

The structural differences between the protein-protein interaction networks are byproduct of slight differences in curation methods. Although each PPI database retrieves their information from the same population of publications, the knowledge presented in the databases is different. These curation differences which lead to vast node and edge network differences, also lead to different structural or clustering differences.

Conversely, although the structure of the networks is sensitive to the curation methods, the biological enrichment of the networks is not. The biological enrichment had a relatively large overlap between databases. Had the creation of the PPI databases led to significant biological differences, as a total, they would have represented a higher granularity. However, as it stands, the small unique pathway enrichments are not representative of highly granular data. To address our hypothesis, *H1*, the unique biological extractions of the PPI networks do not represent any apparent biological themes or conditions.

4.2 Flooding of High Granular Data through Data Fusion

The promise of data fusion is a more accurate depiction of biological reality through the combination of data sources to compensate for individual source inadequacies. Yet a key component to data fusion is within its own definition: the combination of two or more data elements to create a novel and meaningful data element. “Meaningful” is vitally important. A good data fusion result captures a biologically relevant meaning and treats the data accordingly.

Hypothesis 2 states that the fusion of low and high granular data sources will remove experimentally derived information. The union function utilized here, innately, favors a low granularity. The PPI databases, created through the union function, result in “potential” networks. These networks illustrate the potential of protein interaction partners and structure, but may not be specific enough to differentiate specific biological conditions or pathways, and ultimately as seen in Table 5 the larger PPI databases capture the majority of this selection of Type 2 Diabetes enrichments. So, the union between high granularity data, and low granular data initially created through the union function, results in a low granularity data set. As with the PPI networks covering the potential of interaction partners, this fusion creates a potential of pathways list, making it impossible to differentiate between experimental conditions. I.e. the fusion networks do not show enrichment dissimilarity. In this case, the experimental specific differences are those which differentiate the control tissue from the diabetic tissue. These differences are flooded and unable to be extracted after fusion.

4.3 Information Extraction Sensitivity towards Granularity

The third hypothesis, *a granularity scale exists in which aggregation is associated with information extraction*, was not supported by each of the defined scales of aggregation. The first scale of aggregation, number of attributes, did not demonstrate any relationship with information extraction. When aggregation was defined as the number of equivalence sets, half of the correlations were significant. Explicitly, we find that the diabetes universe and weighted score using this definition of granularity had the highest correlation out of all the tested conditions. The lack of significant correlation in the control universe indicates that these diabetes data sources are the reason that significant correlation was found in the overarching universe. We note that, biologically, diabetic data sources are likely to have increased diabetic information extraction; however, the relationship between granularity and information extraction is not innately evident. Defining aggregation by the number of equivalence sets is only satisfactory under certain data source combinations and a weighted information extraction score.

The final definition of granularity, as the number of data sources used in the fused network, had a complete suite of significant correlations. Yet the diabetic set of data sources carried a higher bias in generating a strong relationship between granularity and information extraction. This result defends the proposition that more available information innately present in a data fusion indicates a higher potential for information extraction after the fusion has taken place.

By supporting the third hypothesis, we suggest that sensitivity to granularity contributes to the confidence in the limits of a data fusion function. Yet the field of data fusion is diverse and we are not certain that granularity is important for all data fusion functions, specifically those which may correct for abstraction or aggregation among sensor technologies. Further, granularity is a high-level uncertainty term and can be defined in various ways beyond the two dimensions suggested in this study. An intelligent data fusion must consider the biology, the technology, and the sensitivity of the function to initial parameters, including granularity, in order to obtain confidence in its results.

4.4 Generalizability across Biomedical Data Sources

When conducting multivariate data analysis, univariate normality does not guarantee multivariate normality. In the same way, the sensitivities of individual biomedical data sources, including the sensitivity to granularity, must be examined in a multi-modal perspective. We can only speculate to the sensitivity of biomedical data sources not included in this study, but we suggest that while granularity may not be an issue in an individual data source, data fusion approaches should check for sensitivity to granularity.

5 CONCLUSIONS

As the technology associated with biomedical research continues to advance, larger and more diverse data sources are becoming available to researchers. Each data source has its own attributes that influence the way its data can be used or integrated with other data. As a result, there is a growing need for sophisticated ways to effectively integrate different types of biological data and improve the outcome of using data mining algorithms. In this study, we proposed several tests for characterizing granularity within the integration of protein-protein interaction and gene expression data using the network model. The results indicate that using high aggregation of information provides a context bias that alters the composition of various substructures in the network and enhances the significance of the signals obtained from the integrated networks, under certain conditions. In addition, abstraction with union data fusion favors high abstraction information extraction, flooding condition-specific results.

This study serves as a case study to highlight the need to study data integration methods further in the domain of biomedical informatics and explore different ways to characterize the impact of uncertainty variables throughout alternate data integration methodologies. These characterizations must also include topological information regarding substructure changes in order to further classify the relationships among elements in biological networks. The underlying principle here is that each network represents a form of an expert system, the more relevant data incorporated in the network, the more knowledgeable the network becomes. Yet the dependency of the extraction of this knowledge is dependent on data source variables (including granularity) which impact the topology. In turn, proper handling of these variables would allow the researchers to extract more biologically relevant signals while limiting the impact of noise that will always be associated with raw biological data. Ultimately, the attainment of the more useful biological networks, dependent on the type and environment of a network or biological replicate, is contingent on the ability to successfully integrate data types through characterization of their sensitivities.

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