Full Text Literature Mining for Gene Disease Relationships

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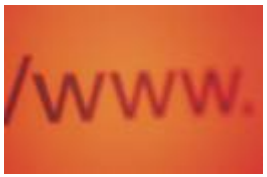
Outline

- Introduction to text mining
- Introduction to gene disease relationships
- Objective
- Data and Process
- Results
- Conclusion
- Acknowledgements

What is text mining?

- Finding useful data in “noisy” formats
  - Human readable
  - Not intended for machines

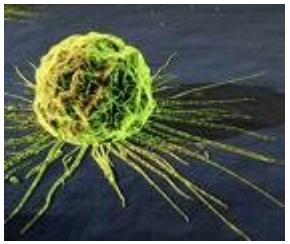


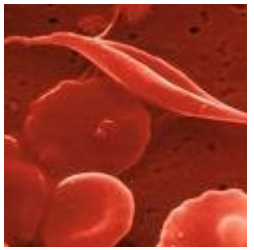
- Example formats
  - Websites
  - Biomedical research journals

- Typically seen in search engines

What are gene disease relationships?

- A correlation between a gene and a disease
  - Cancer and TP53
- Weak vs. strong relationships
  - Over-expressed genes
  - Causative mutation
    - Cystic Fibrosis and CFTR
    - Sicle cell anemia and HBB
  - Consequence of disease
    - Hypertension, cardiac arrest, diabetes





Why use text mining?

- Curated databases are slow to take on new relationships
  - OMIM – genotype/phenotype
  - SwissProt – protein information
  - PharmGKB – drug response
  - HGMD – gene mutation

Why use text mining?

- Technology allows for more experiments, resulting in more gene-disease relationships
- Community is increasing in size
- Published biomedical literature contains these gene-disease relationships
- Text mining is a way to effectively parse this data from the ever increasing amounts of published literature
  - Database curating assistance

Why use full text mining? Advantages and Disadvantages

Abstracts

- Density of useful information is at its highest
- Less text, allowing for less computational power

Full Text

- Higher coverage of information
- More text, requires clusters of computers
- Noise from more text (conjectures, future work, citations)
- Variety of formats: PDF, HTML, XML, etc

Jimmy Lin. **Is Searching Full Text More Effective Than Searching Abstracts?** *BMC Bioinformatics*, 10:46 (3 February 2009)

Literature Mining Objectives

- Extracting facts from literature
  - Verification, data creation
- Automated annotation
  - Curating, scoring
- Relationship discovery
  - Hypothesis generation

Journal Crawler

- Journals do not allow users to easily download their articles for text mining
- A custom journal crawler script was written
  - Hand tailored for each journal website
- Parses link anchors and urls and uses regular expressions to match for articles

Article Data

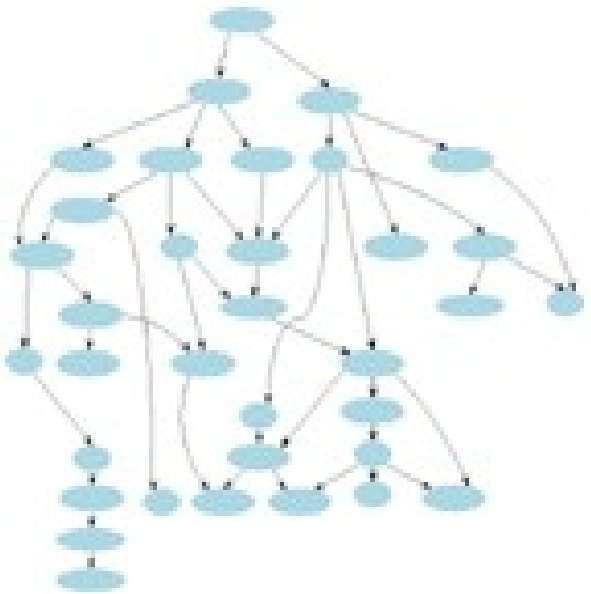
- 48 journals
  - Expected to have gene-disease relationships
  - 259,051 total articles from 1996 – 2008
- Examples:

Journal	Years	Articles	% of all articles
Science	1996 - 2008	44,392	8.71%
Bioinformatics	2005 - 2008	5,032	0.99%
Annals of Oncology	2002 - 2008	4,336	0.85%
BMC Biology	2003 - 2008	416	0.08%

- Each article was given an index for identification

Disease Data

- 14,464 disease terms from the “Disease Ontology”
  - Collaboration between the NuGene project and the Center for Genetic Medicine
  - http://diseaseontology.sourceforge.net
  - Version 2.1
  - Structure of ontology ignored
- Each disease was indexed according to its identifier DOID

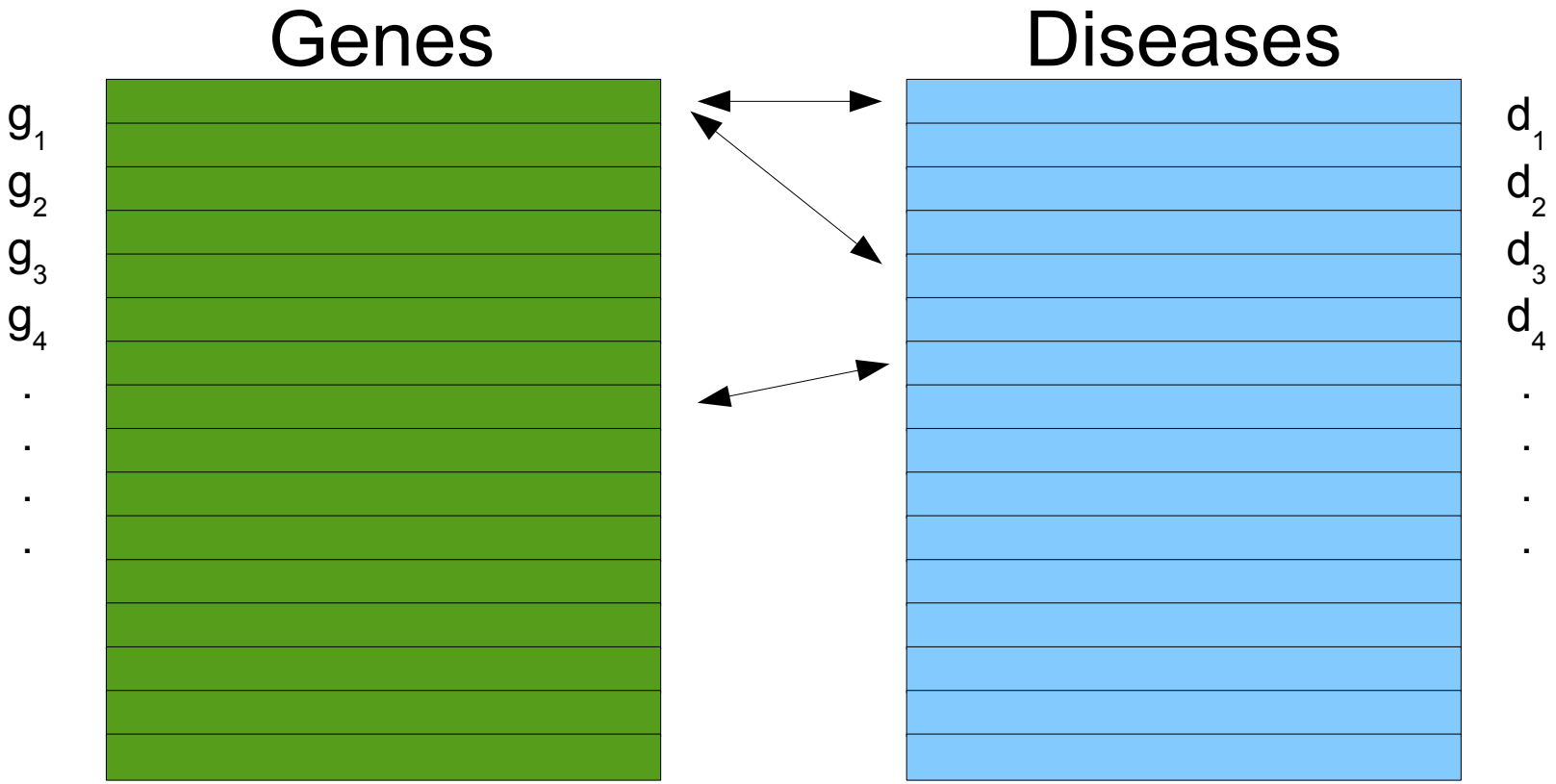


Gene Data

- 26,414 genes from the HUGO Gene Nomenclature Committee
  - Official gene symbols
  - http://www.genenames.org
- Symbols and synonyms extracted
  - Three characters or more
- Each gene was indexed to its HGNC identifier

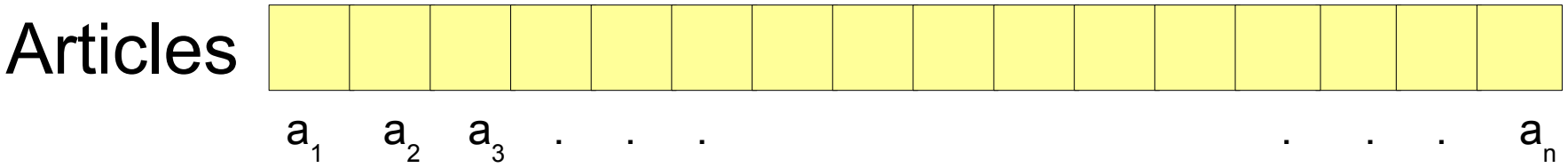
Text Retrieval

- We need to map the gene and disease indexes to one another to get relationships
- So how do we discover the relationships?

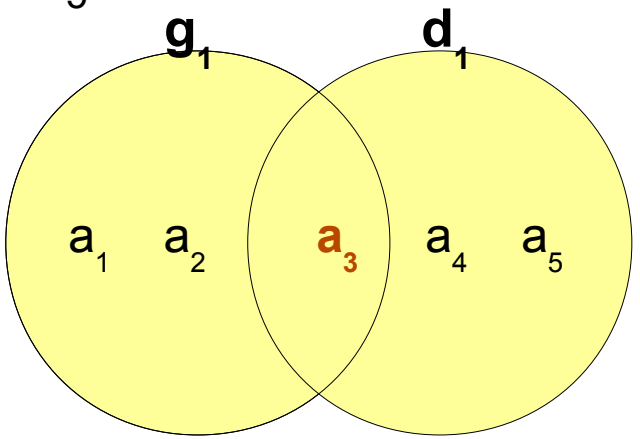


Text Retrieval

- We search the articles for the diseases and genes



- Gene g_1 was found in articles { a_1, a_2, a_3 }
- Disease d_1 was found in articles { a_3, a_4, a_5 }
- A potential relationship would be the intersect of g_1 and d_1: a_3



Text Retrieval

- All articles were indexed and searched using SWISH-E, an open source search engine
- Hits were whether or not a term was found in an article

- 5,206 disease terms found (36% of all terms within the disease ontology)
- 19,395 genes found (73% of all genes)
- 5,734,417 gene-diseases joint terms found (6% of all pairs found in at least one article)

Similarity Measures

- How do we identify a probable relationship?

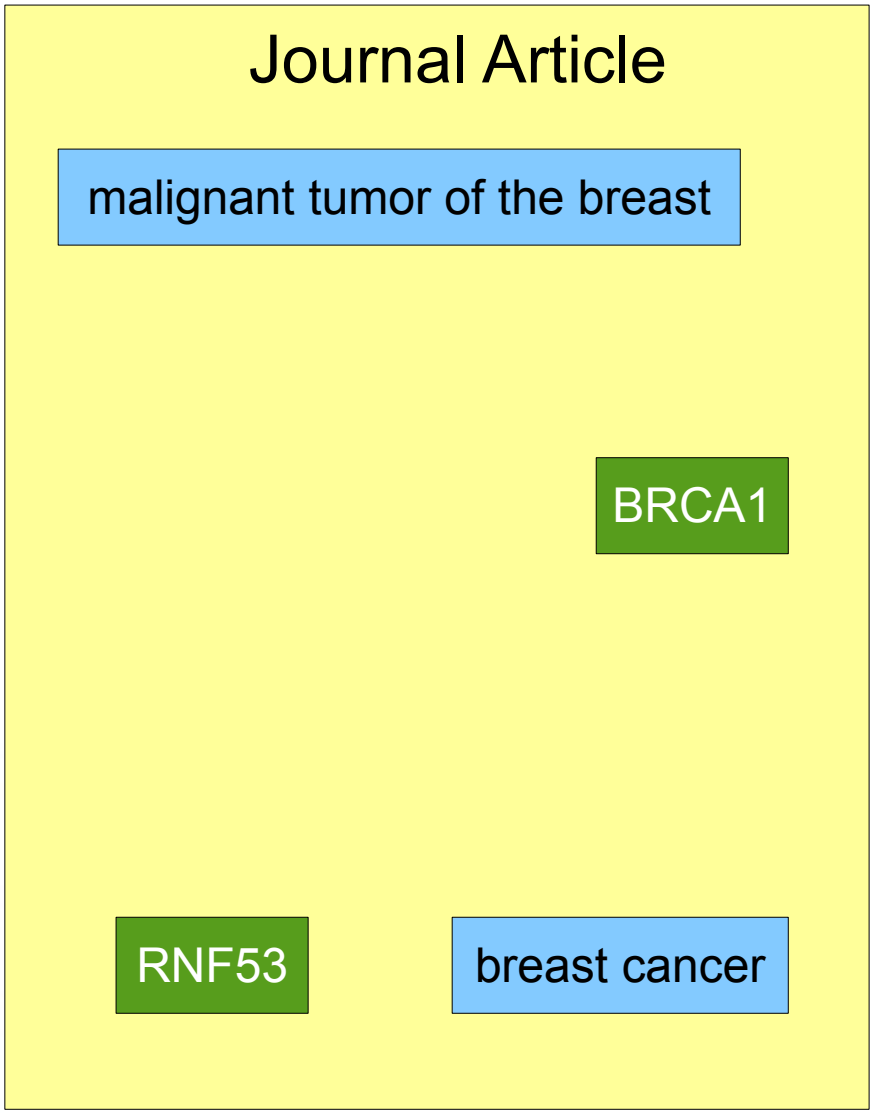
$$I(g;d) = \log \frac{p(g,d)}{p(d)\,p(g)}$$

- Mutual information
  - *p(g)* – probability that gene *g* occurs
  - *p(d)* – probability that disease *d* occurs
  - *p(g, d)* – probably that gene *g* and disease *d* occurs
- We rank articles based on this score

Word Proximity Method

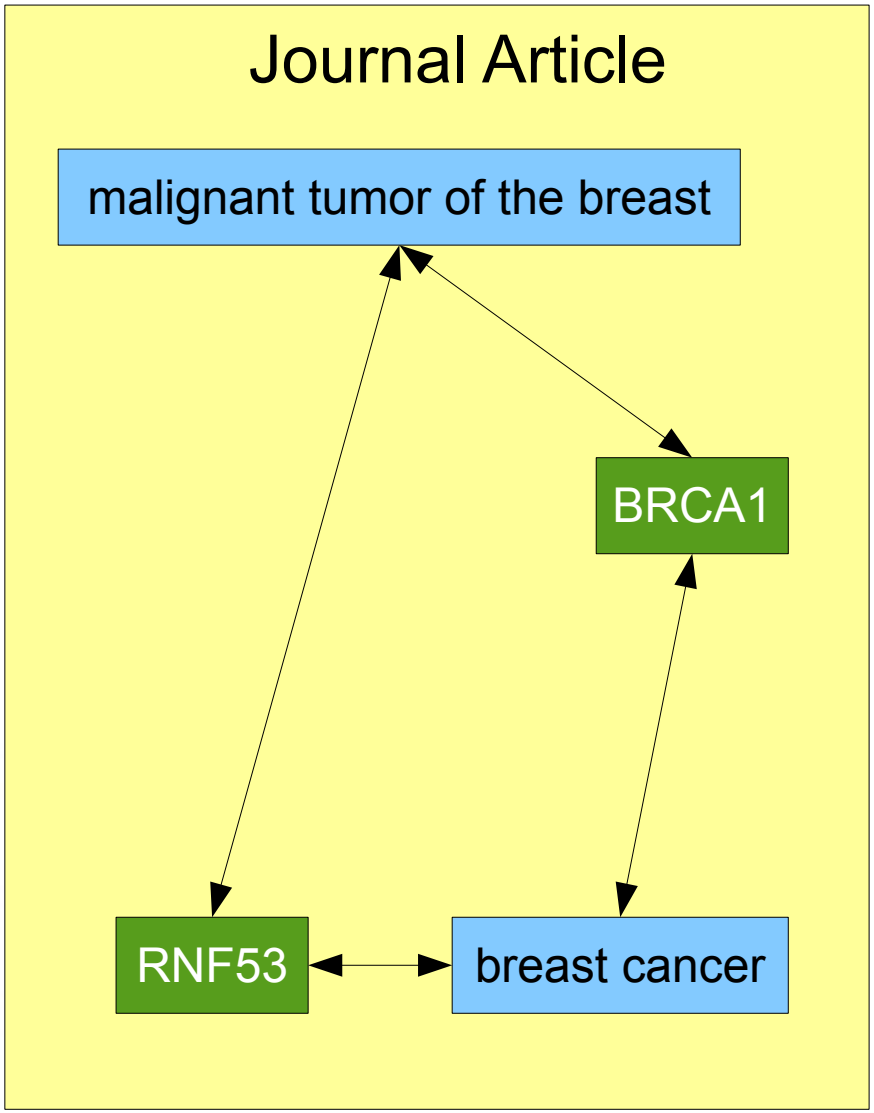
- How to improve the simple “term hits” in the baseline method
- Joint terms could mean a gene in the abstract and a disease in the citations
- This noise can be filtered out

Word Proximity Method



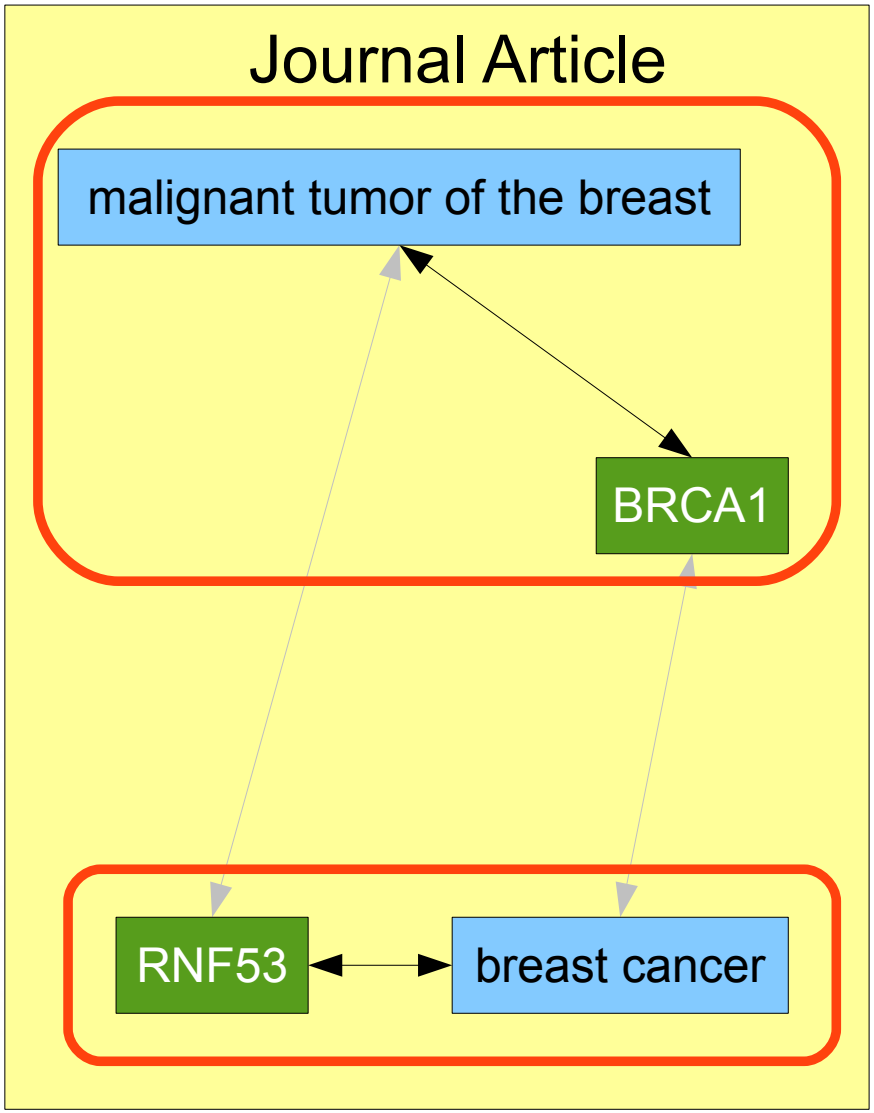
- Take the disease “breast cancer” and the gene “BRCA1” along with their synonyms

Word Proximity Method



- Take the disease “breast cancer” and the gene “BRCA1” along with their synonyms
- We now count the distance in characters between each disease and gene, creating a pair

Word Proximity Method



- Take the disease “breast cancer” and the gene “BRCA1” along with their synonyms
- We now count the distance in characters between each disease and gene, creating a pair
- Given a disease name, we select the gene symbol that is closest
- These terms are most likely to be related and be a possible gene-disease relationship

Word Proximity Method

- We score each article given a gene-disease pair, consider one article
  - we have a set of gene positions $G=\{g_1, g_2, \ldots, g_m\}$
  - and a set of all diseases positions $D=\{d_1, d_2, \ldots, d_n\}$
- The summed score is for the given article $S=\sum_{i=1}^{n} pair\_score(d_i, G)$
- Where $pair\_score(d_i, G)=f(|d_i-g_k|)$
- and $k=\text{argmin}_{j=1\ldots m}|(d_i-g_j|$
- The function $f(x)=e^{-d\,x}$ is used, where *d* is a positive constant, *e* is Euler's constant, and *x* is the distance

Similarity Measures

- How do we turn word proximity into a similarity measure, such as mutual information?

$$I'(g;d) = \log \frac{p(S(g,d) \geq t)}{p(d)\,p(g)}$$

- where $p(S(g,d) \geq t)$ is the number of word proximity scores above threshold t over all possible articles

Word Proximity Method

- Various values used for the threshold t and constant d

$$p(S(g,d) \geq t) \qquad f(x) = e^{-dx}$$

- The parameter of t was tested from
  - 0 through 5×10^{-230}
- The constant d was tested from
  - 0.0005 to 3
- This was done to find the best results

Measuring Accuracy

- True gene-disease relationships were taken from:
  - “Disease Ontology”
  - PharmGKB
- The gene associations were propagated up the diseases ontology
  - Breast Cancer/BRCA1 would imply Cancer/BRCA1

Measuring Accuracy

- True positive rate: fraction of correctly identified true positives (known, correct gene disease relationships)
- False positive rate: fraction of incorrectly identified negatives
- AUC is the area under the receiver operating characteristic: Plot of the two operating characteristics TPR vs FPR
- Mutual information is used to rank the relationships

Similarity Measure AUCs

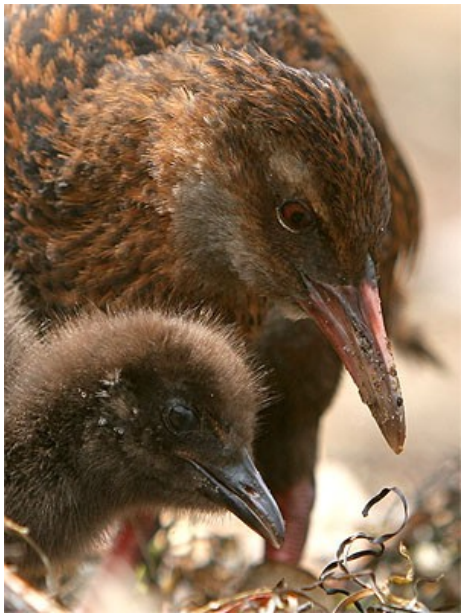
- Calculated on all gene-disease pairs with some pruning
- The disease had to be within the known set of true gene disease relationships
- The relationships needed at least 10 articles of evidence

Similarity Measure AUCs

- Mutual information (base line)
  - 67.6%
- Word Proximity (t=0.05, d=0.04)
  - 68%
- Word Proximity (t=5×10^{-145}, d=2.98)
  - 68.7%

Machine Learning

- WEKA 3, a data mining suite
  - http://www.cs.waikato.ac.nz/ml/weka/
- Algorithms used in a 10 fold cross-validation:
  - Random Forests
  - Neural Network



Machine Learning

- 86 attributes and 1 class
  - 2 attributes for gene HGNC and disease DOID
  - 84 attributes were based the best and some random *t* and *d* pairs, with scores being their word proximity mutual information
  - 1 class whether it was a true relationship
- Gene and disease attributes included to allow for supervised learning on the interacting genes and diseases
- A total of 184,041 instances

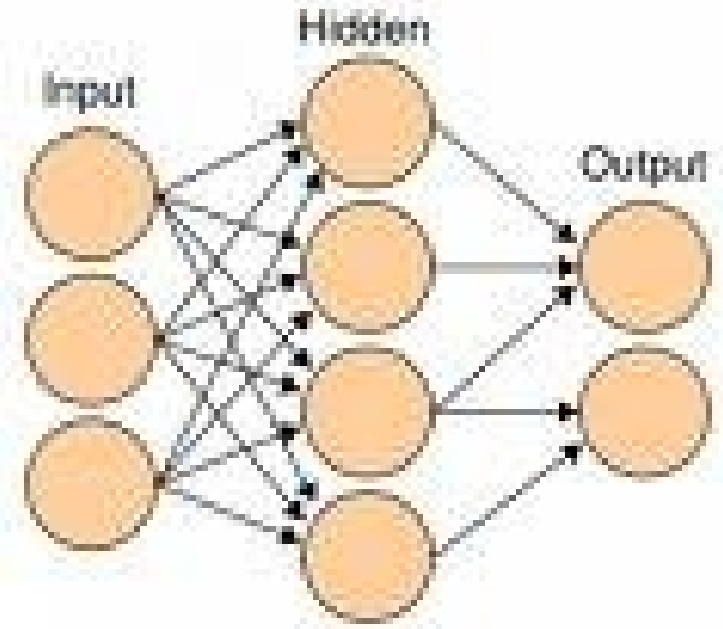
Random Forests

- Consists of decision/regression trees
- Uses information gain/variance
- Prunes itself using reduced-error pruning (with backfitting)

- AUC of 86.5%
- Precision of 65.4%
- Recall of 12.6%

Artificial Neural Network

- Feed-forward artificial neural network
- Simulates the structure of a biological neural network
- 3 hidden layers

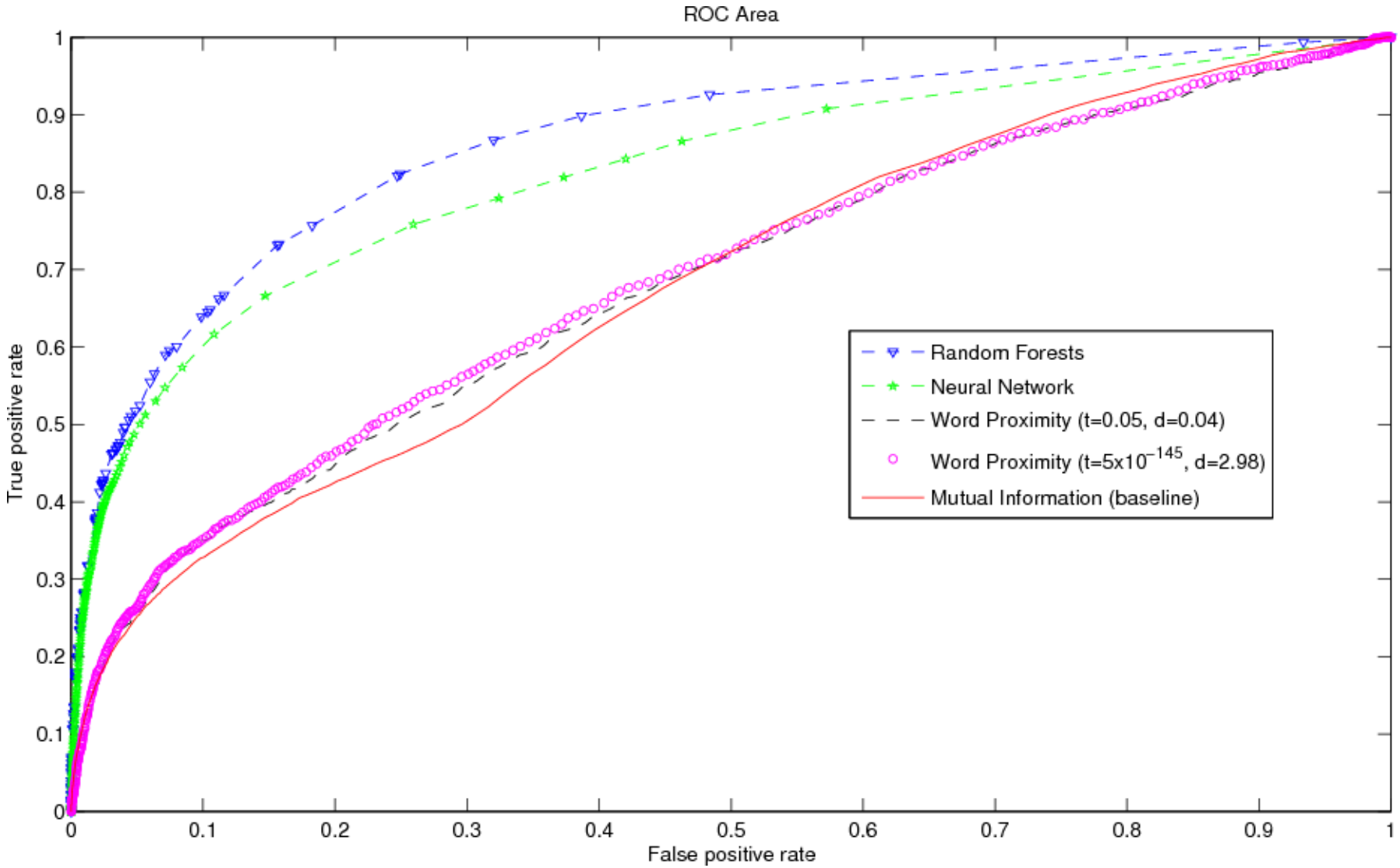


- AUC of 82.7%
- Precision of 60%
- Recall of 6.6%

AUC Results

- Mutual information (base line)
  - 67.6%
- Word Proximity (t=0.05, d=0.04)
  - 68%
- Word Proximity ($t=5x10^{-145}$, d=2.98)
  - 68.7%
- Random Forests
  - 86.5%
- Neural Network
  - 82.7%

AUC Results


ROC Area
True positive rate
False positive rate
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Random Forests
Neural Network
Word Proximity (t=0.05, d=0.04)
Word Proximity (t=5x10^-145, d=2.98)
Mutual Information (baseline)

Other Attempted Features

- Gene and disease features work better with word proximity mutual information scores

		AUC	Precision	Recall
Implemented	**Random Forests**	86%	65%	13%
	Neural Network	83%	60%	7%
with out gene and disease features	**Random Forests**	70%	74%	2%
	Neural Network	65%	63%	5%
only gene and disease features	**Random Forests**	80%	70%	6%
	Neural Network	66%	0%	0%

Result Analysis

- False positives
  - Might be true as they can be gene disease relationships that are not in already in the curated databases
  - Can be noise, conjectures, etc
- Machine learning provides a huge increase in the highly ranked true positive results!

Top 10 Inferred Predictions

- Random Forests

Rank	Gene	Disease	Evidence
1)	RECQL5	Congenital poikiloderma	European Journal of Human Genetics
2)	PGLYRP1	Muscular Dystrophy, Emery-Dreifuss	PlosBiology article glob
3)	SLC11A2	microcytic anemia	PubMed
4)	IGFALS	Amyotrophic Lateral Sclerosis	PubMed
5)	FRAXA	Fragile X syndrome disorder	FRAXA is a organization
6)	IGHVOR15@	Leukemia	PubMed
7)	SIX5	Steinert myotonic dystrophy syndrome disorder	Articles cite correlation, not definitive proof
8)	FAH	Tyrosinemias	Wiley Interscience
9)	DGCR6	Deletion 22q11.2 syndrome	Wiley Interscience
10)	DGCR	Deletion 22q11.2 syndrome	Wiley Interscience

Top 10 Inferred Predictions

- Neural Network

Rank	Gene	Disease	Evidence
1)	NPEPPS	cancer	Molecular Endocrinology
2)	KLK3	cancer	Carcinogenesis
3)	PSAT1	cancer	Molecular Cancer
4)	EGF	cancer	Annals of Oncology
5)	CD19	lymphoma	Wiley Interscience
6)	SERPINB3	cancer	PubMed
7)	ZBED1	cancer	Nucleic Acids Research
8)	COX8A	cancer	BMC Cancer
9)	DLD	cancer	PubMed
10)	TNFSF10	cancer	Nature

Conclusion

- Word proximity is a simple method that can filter a large amount of noise is present within full text journal articles
- Some manual curating is still necessary because some gene-disease relationships are incorrect
  - Conjectures
  - Common examples (cancer)
  - Article inconsistencies (citations, etc)
- The system works very well at filtering large amounts of data

Acknowledgements

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- School of Informatics

Questions?