Inferring disease-associated lncRNAs using expression data and disease-associated protein coding genes

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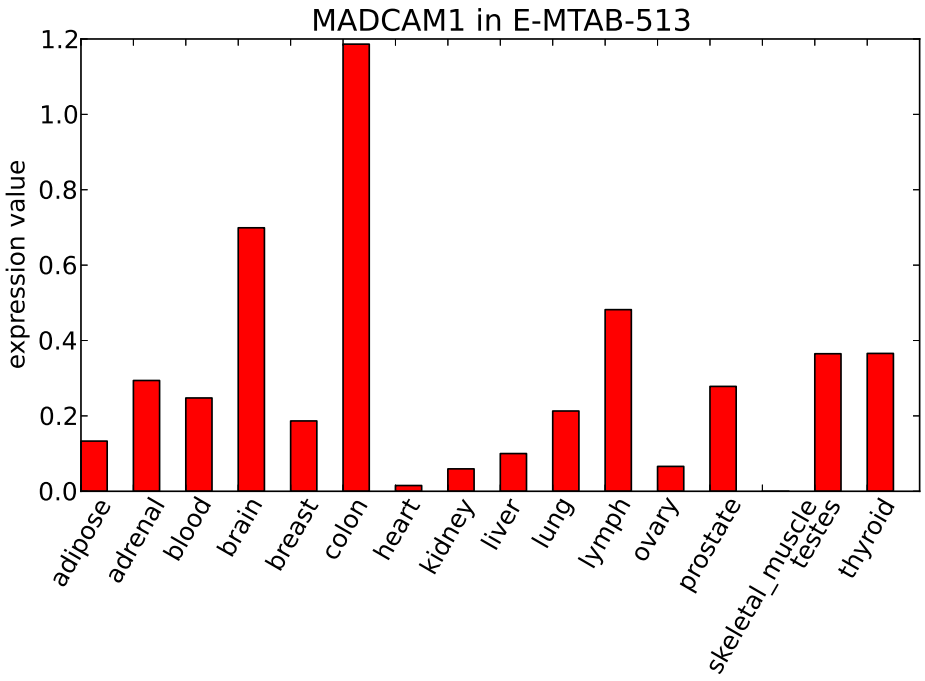
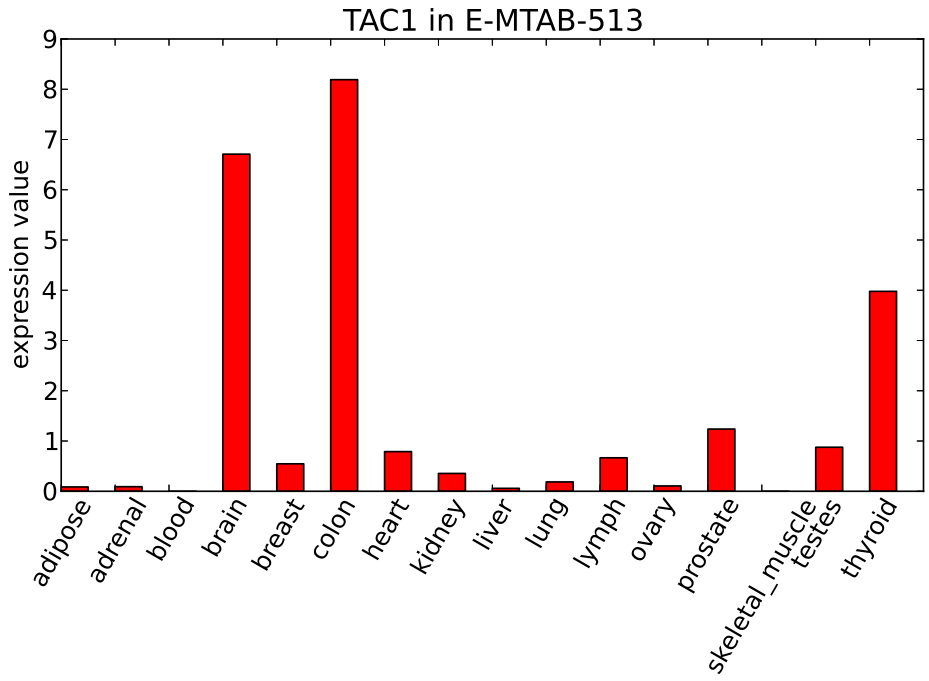
Introduction

1. lncRNAs are emerging as important regulator in different diseases.
2. Gene is more tissue-specific than individual-specific [Melé 2015, Science]
3. Different diseases relevant to specific tissues[Lage 2008, PNAS]
4. Disease-associated genes have similar expression pattern.

Two genes associated with inflammatory bowel disease





Tissue

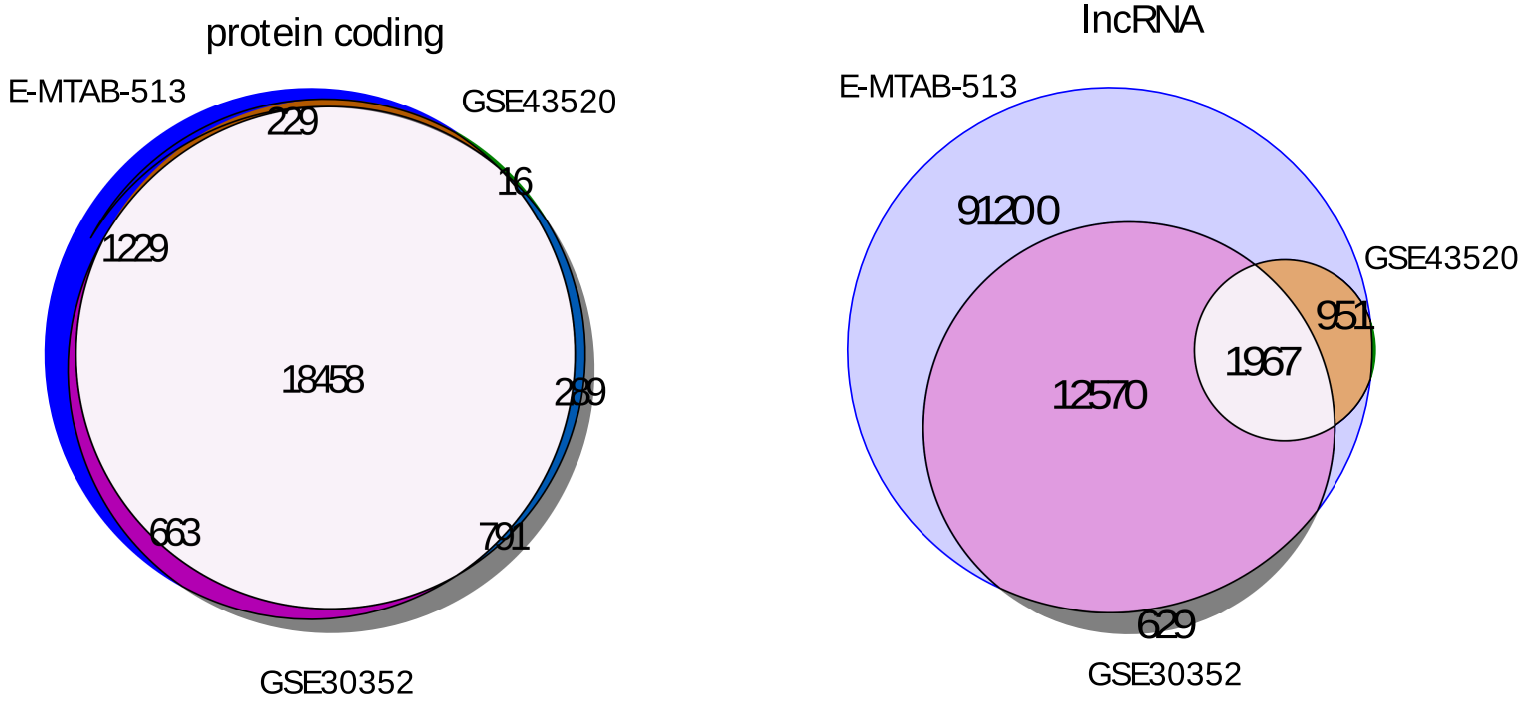
Project goal

1. Infer disease-associated lncRNAs from protein coding and lncRNA co-expression dataset.

2. **Method**: Train random forest model on disease-associated protein coding gene expression profiles, then predict for lncRNA.

Dataset

1. 3 RNAseq datasets:
   - E-MTAB-513, human body map, 16 tissues, GENCODE v7.
   - GSE43520, evolution of lncRNA in tetrapods, 15 tissues, highly conserved lncRNAs.
   - GSE30352, evolution of genes in mammalians, 6 tissues, Ensembl based annotation.



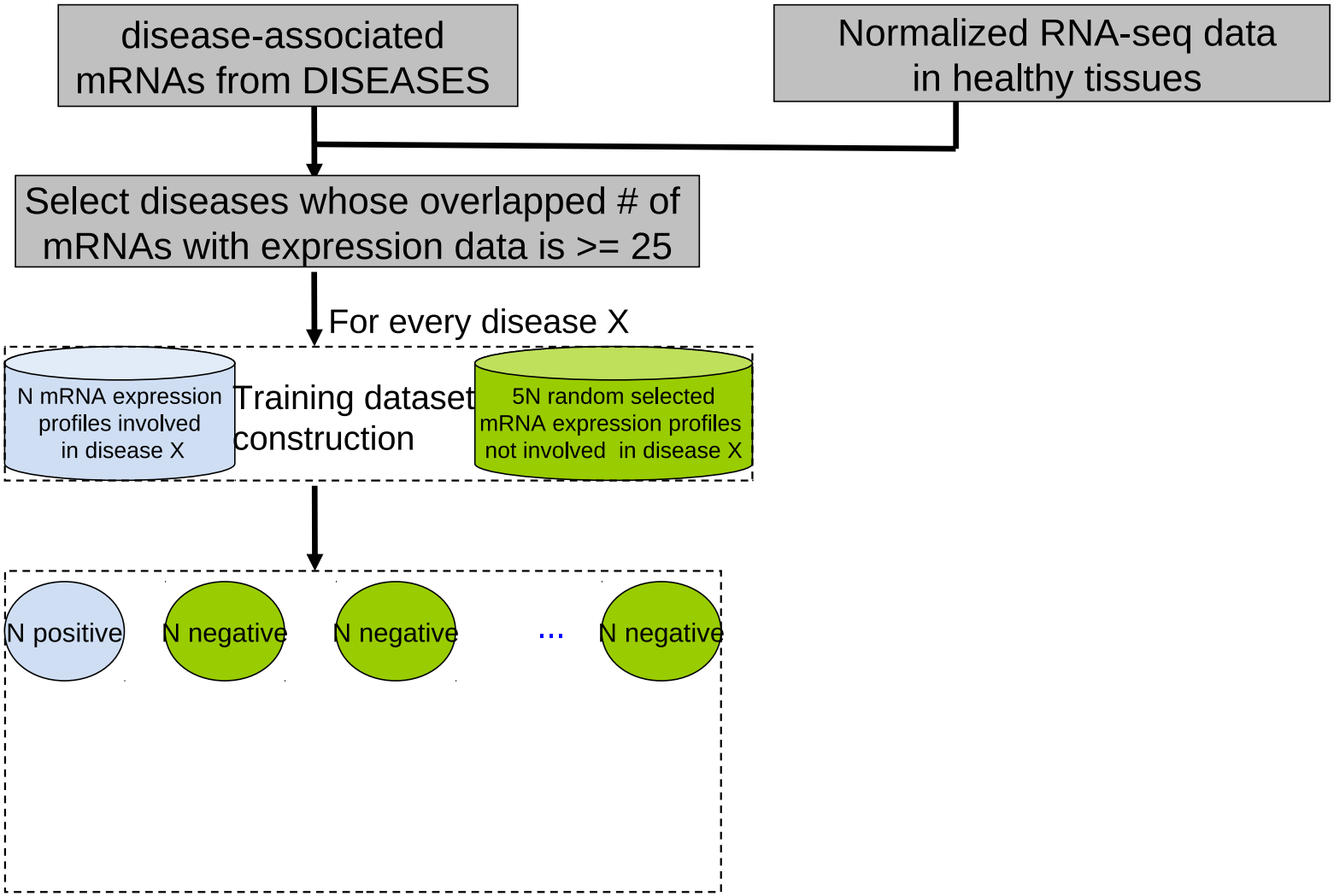
[Derrien 2012, Genome Res], [Necsulea 2014, Nature], [Brawand 2011, Nature]

Dataset

1. DISEASES [Pletscher-Frankild 2015, Methods] database for disease-associated protein coding genes.
   - 543,405 associations between 17,606 genes and 4,610 diseases.

2. LncRNADisease [Chen 2013, Nucleic Acids Res] for verified disease-associated lncRNAs.
   - More than 1,000 association between 321 lncRNAs and 221 diseases.

Infer disease-associated lncRNA from co-expression profile



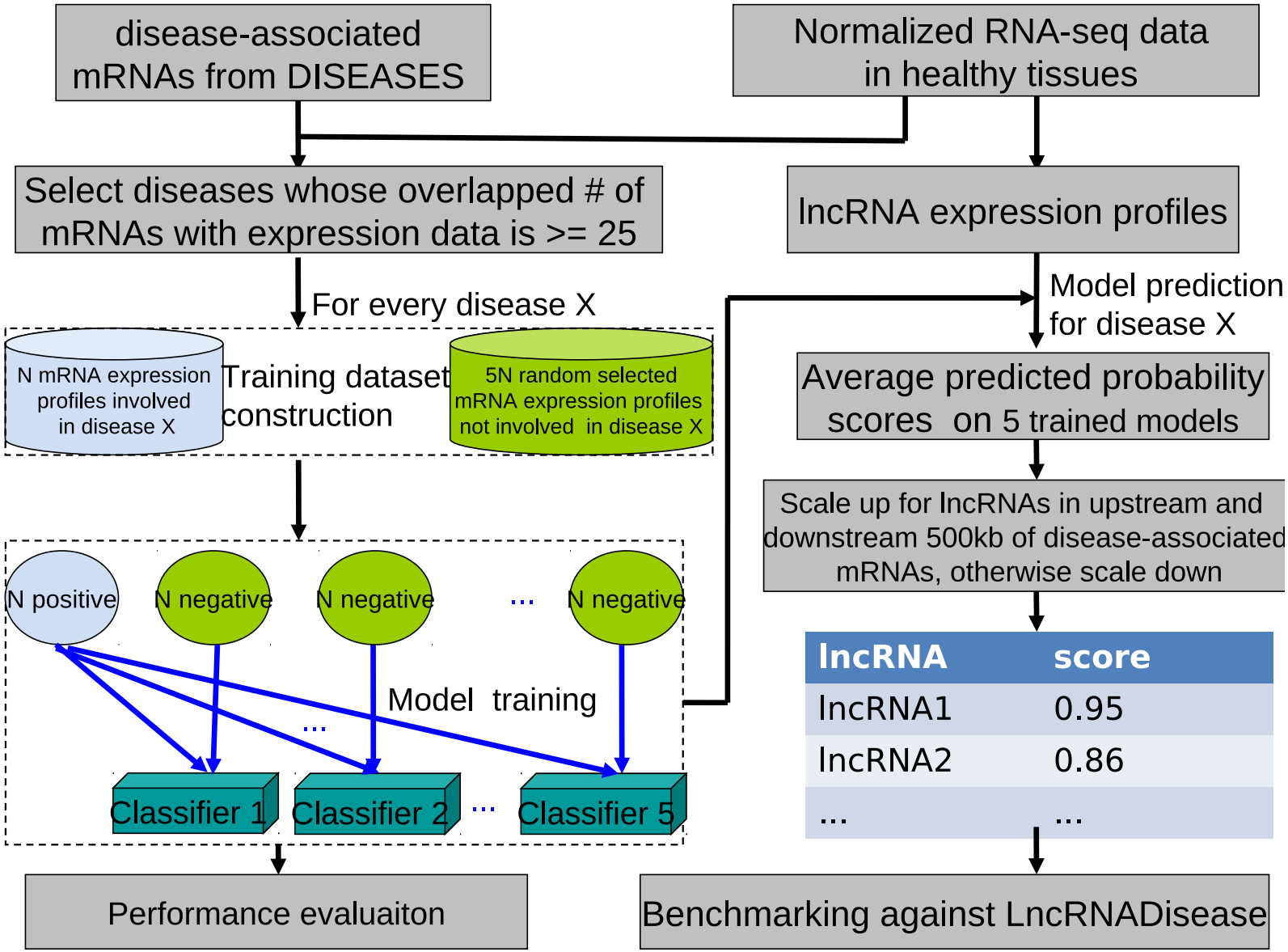
Constructing training data

1. For each disease X:
   - Randomly sampling 5N mRNAs subsets not involved in disease X with 5 times the number of mRNAs associated with disease X.
   - assign label 1 to disease-associated mRNAs, otherwise 0.

Label		adipose	adrenal	blood	brain	breast	colon	heart	kidney	liver
1	PFKP	0.95426	0.64932	0.04886	0.65482	0.36988	0.340933	0.08663	0.131352	0.06026
1	GALT	0	0.04175	0.01892	0.1727	0.01518	5.43E-09	0	0.031027	0
1	ACAA1	49.50935	188.05339	23.36094	44.89562	101.19716	33.72076	31.20994	57.01054	19.12016
1	7SK	105.66857	128.62117	4.06798	113.55834	124.79909	48.27836	13.8542	42.67313	4.27873
...	...	...	...	...	...	...	...	...	...	...
0	A-575C2.4	1.38353	4.154284	0.84911	2.68101	2.292396	0.92442	0.80375	1.66876	0.86089
0	A1BG	3.74192	6.41188	5.59976	2.97937	1.36397	4.04595	0.55942	1.77137	392.052
0	A1BG-AS1	0.87483	2.75723	2.50365	1.19136	0.52167	1.03712	0.62707	1.83091	15.2022
0	A1CF	0	0.03268	0	0.02983	0	0.536022	0	1.672	17.6027

2. NOTICE: when randomly select negative mRNAs, this mRNAs should be associated with other diseases (well studied genes instead of rare genes), have no any evidence for disease X in DISEASES database.

Infer disease-associated lncRNA from co-expression profile



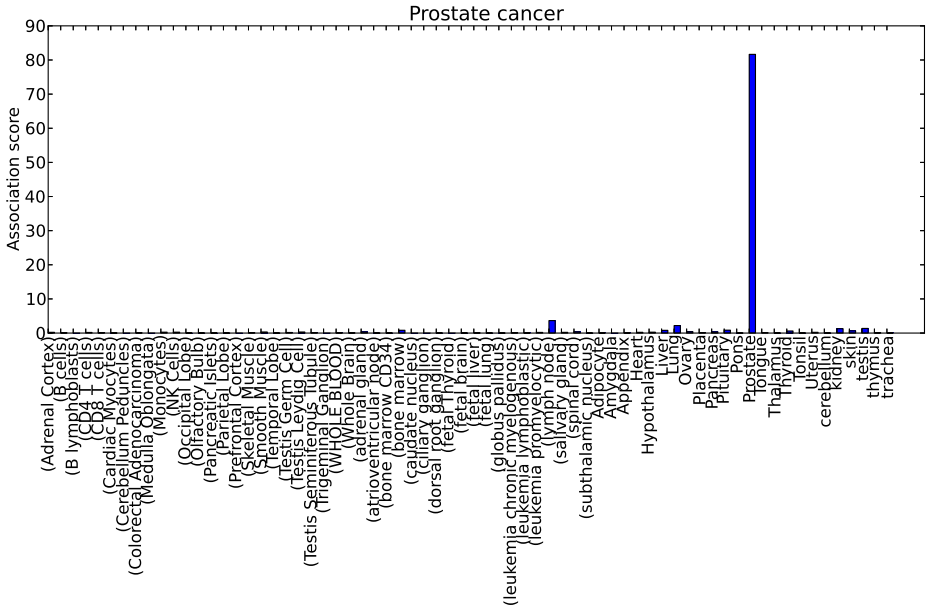
Performance using mRNA expression profile

Table: Average performance for diseases, whose # of associated mRNAs overlapping with mRNAs in expression data is greater than 25 in DISEASES database, using mRNA expression profiles.

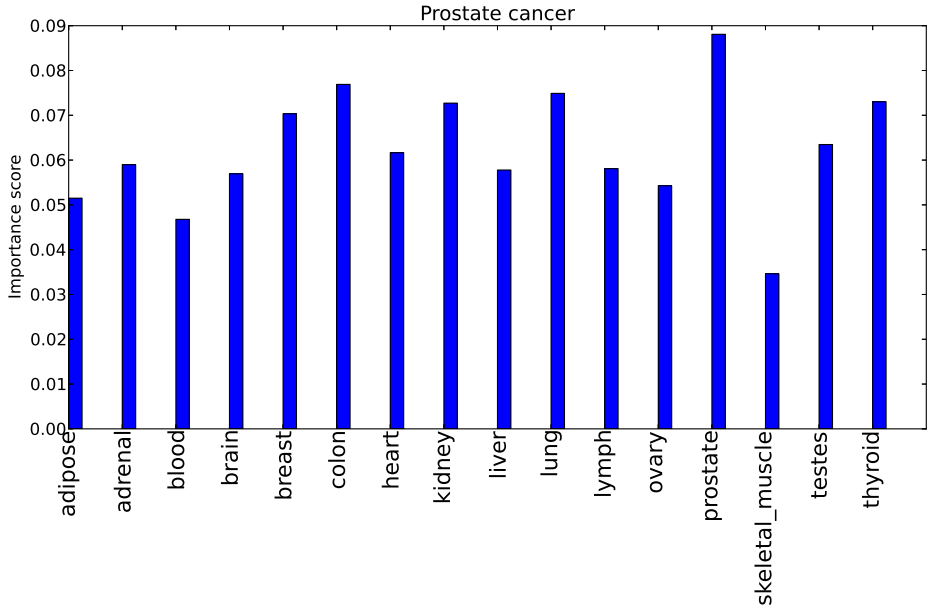
Dataset	# diseases	Accuracy	Sensitivity	Specificity	Precision	MCC
E-MTAB-513	114	0.851	0.568	0.895	0.842	0.631
GSE43520	114	0.864	0.589	0.917	0.854	0.661
GSE30352	120	0.831	0.536	0.905	0.817	0.607

Tissue importance for disease-associated gene classification

- disease-tissue association score[Lage 2008, PNAS].
- Random forest feature importance analysis.
- Expression value in tissues are features, tissue important score is ranked by random forest.



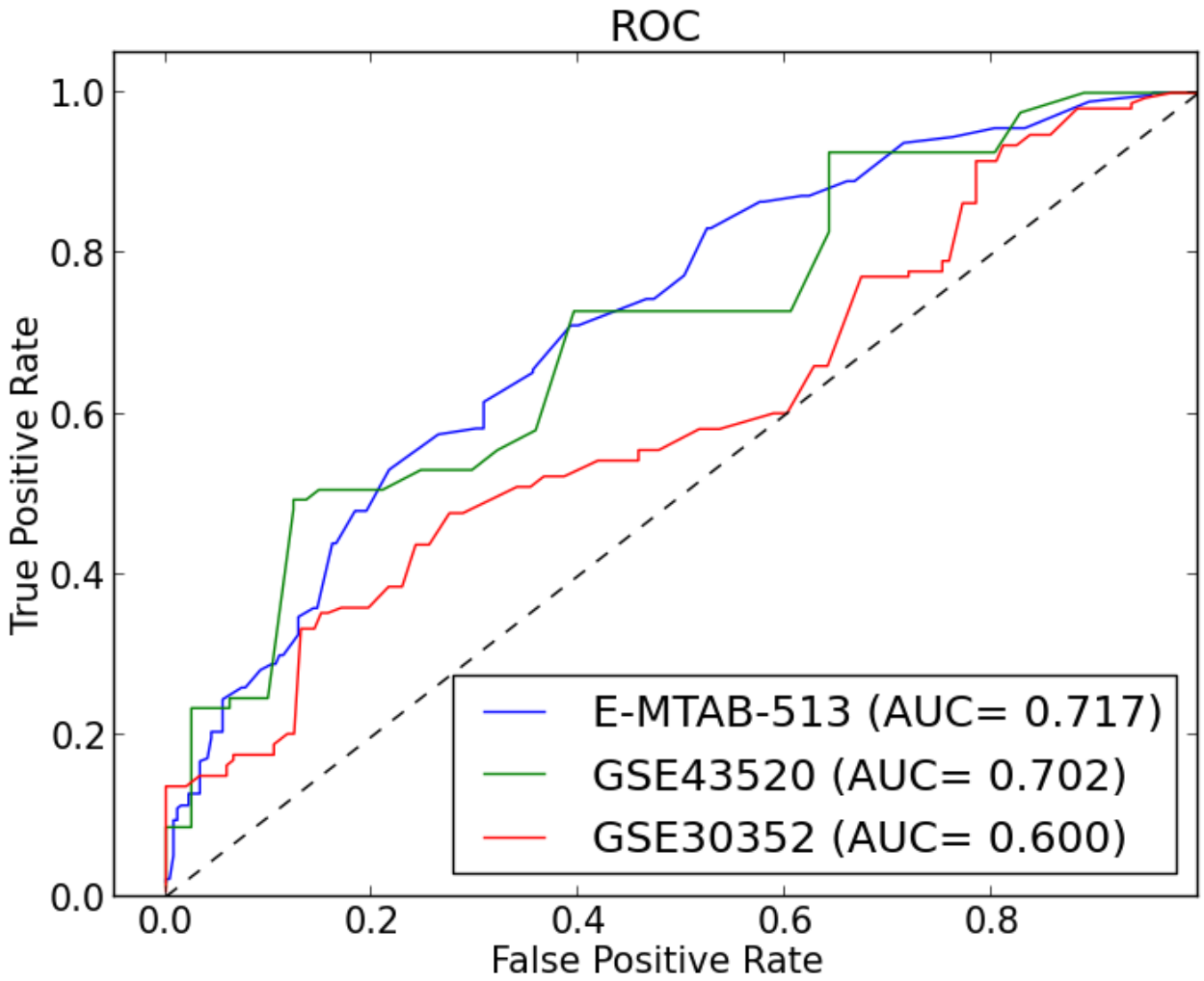
Lage 2008, PNAS



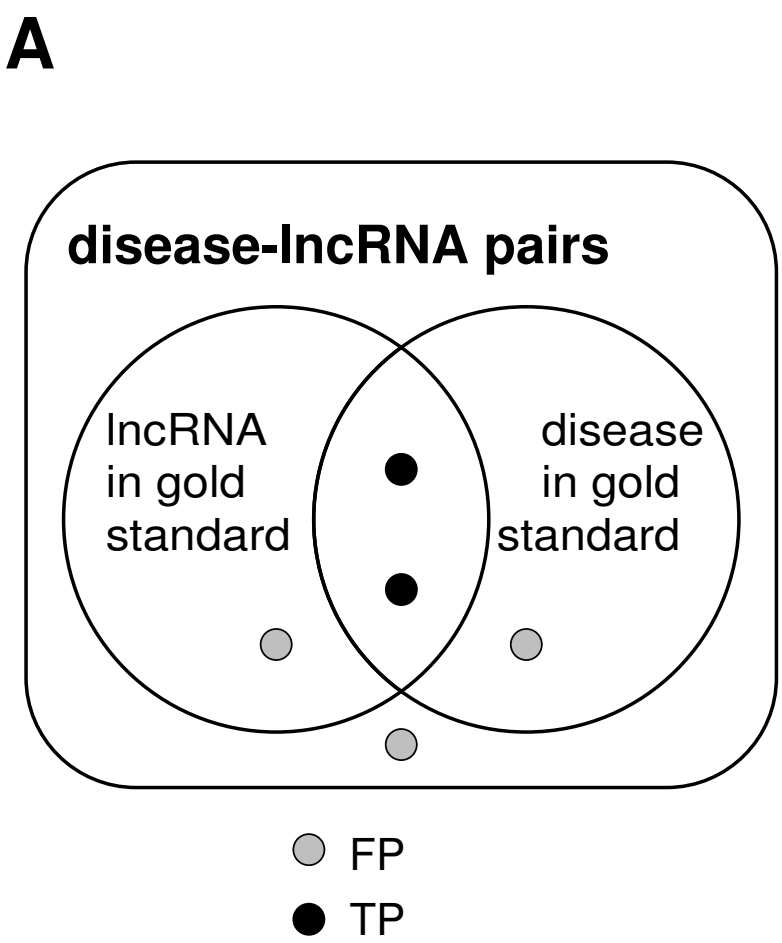
Tissue

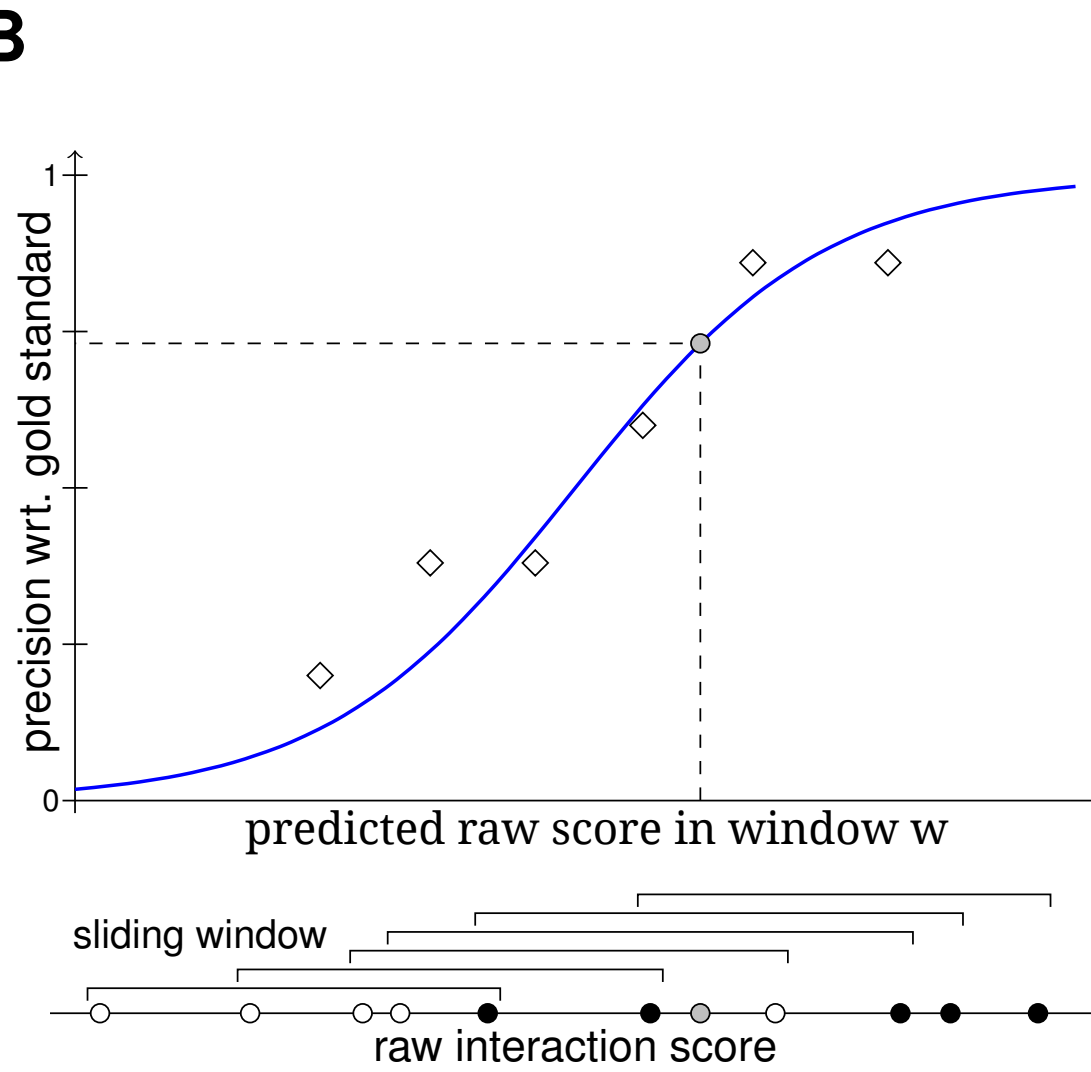
Infer disease-associated lncRNA

1. For each association in LncRNADisease, randomly select another lncRNA for this disease as negative pair.

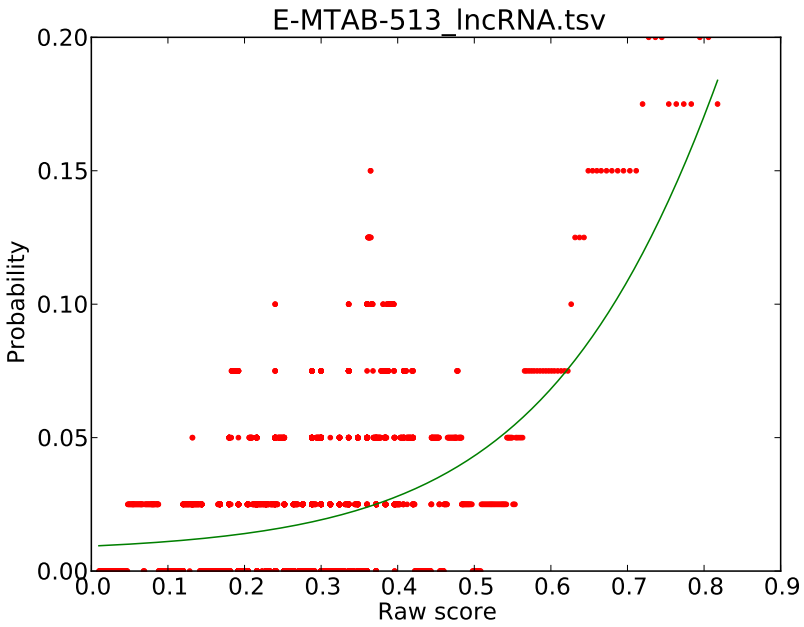


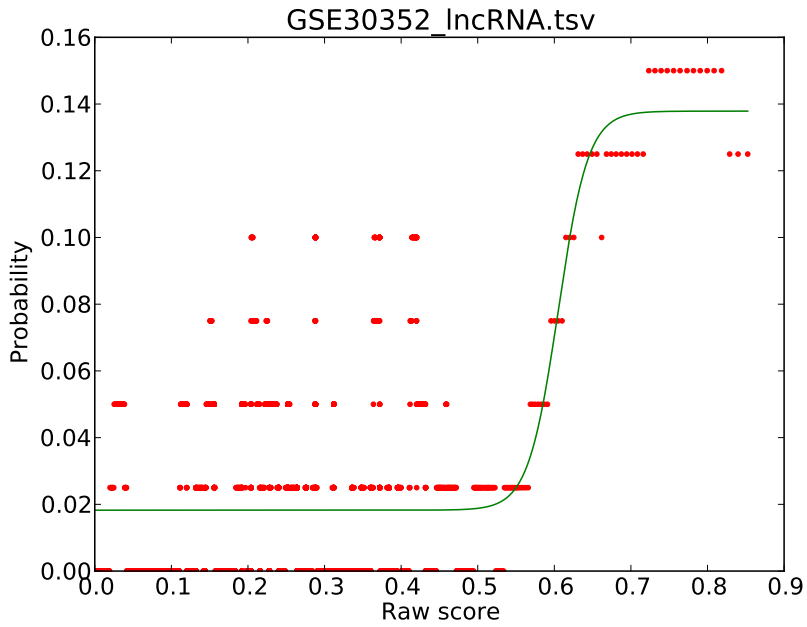
Benchmarking predicted disease-association lncRNAs

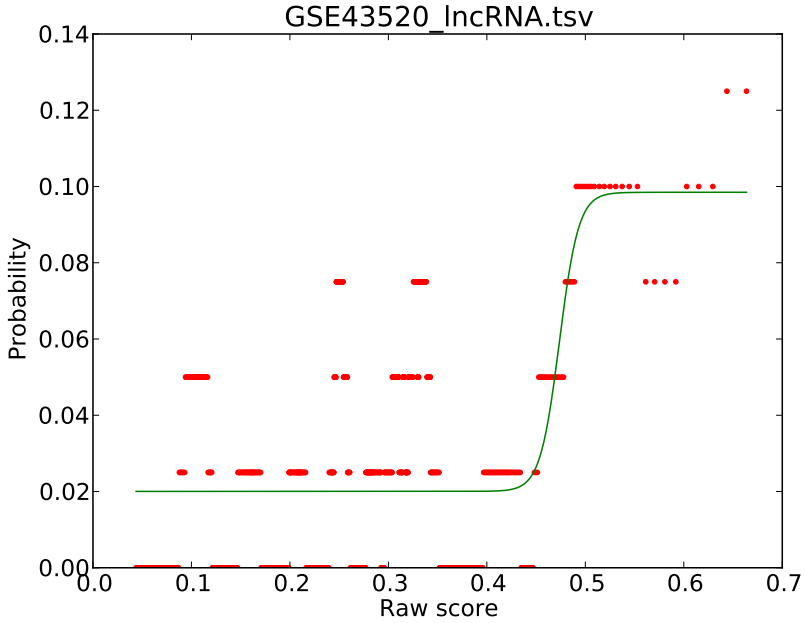




Benchmark against disease-lncRNA from LncRNADisease







Conclusion and outlook

1. In this study, we infer disease-associated lncRNA from expression data and disease-associated protein coding genes.
2. Integrate GWAS SNP data with predicted score to prioritize disease-associated lncRNAs.
3. Text mining disease-lncRNA associations and compared our prediction to it.
4. How to better select negative genes for model training.

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