Novel bioinformatics methods for the identification of coexpressed, differentially expressed, and differentially coexpressed genes with application to cancer

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GENOME Sciences Centre

BC Cancer Agency
CARE & RESEARCH

How can we use gene expression data to investigate cancer?

I. Multi-platform Coexpression

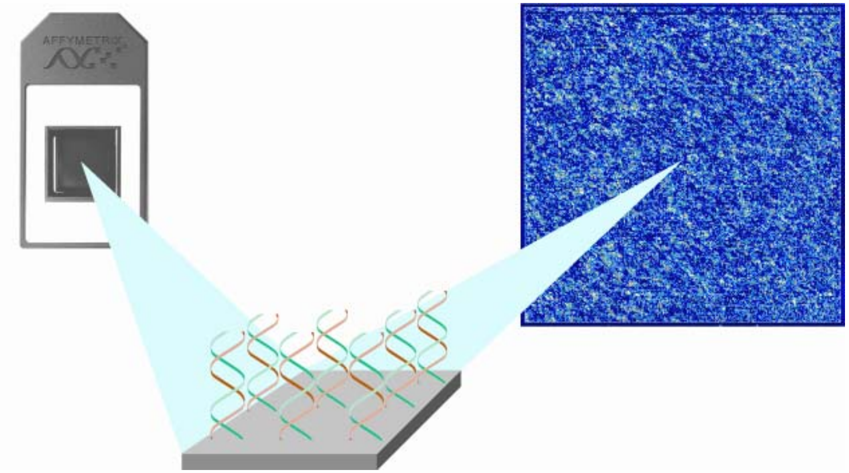
II. Multi-platform differential expression – Thyroid cancer

III. Differential Coexpression – Prostate cancer

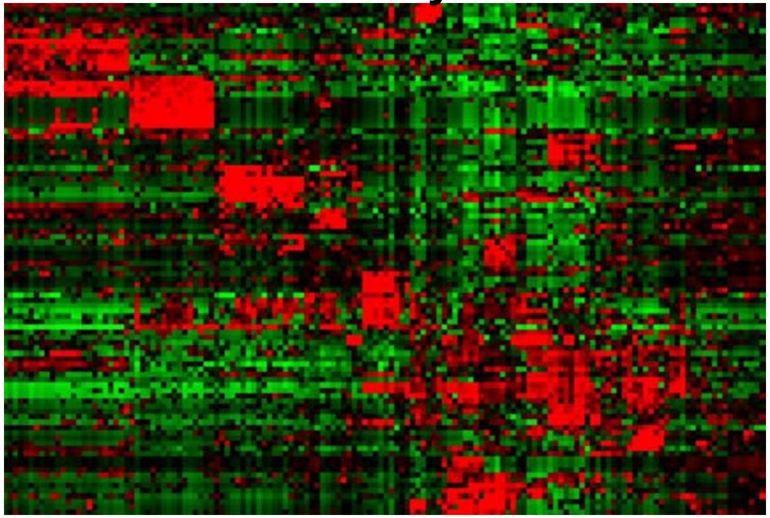
IV. Subspace Coexpression

Three major expression platforms

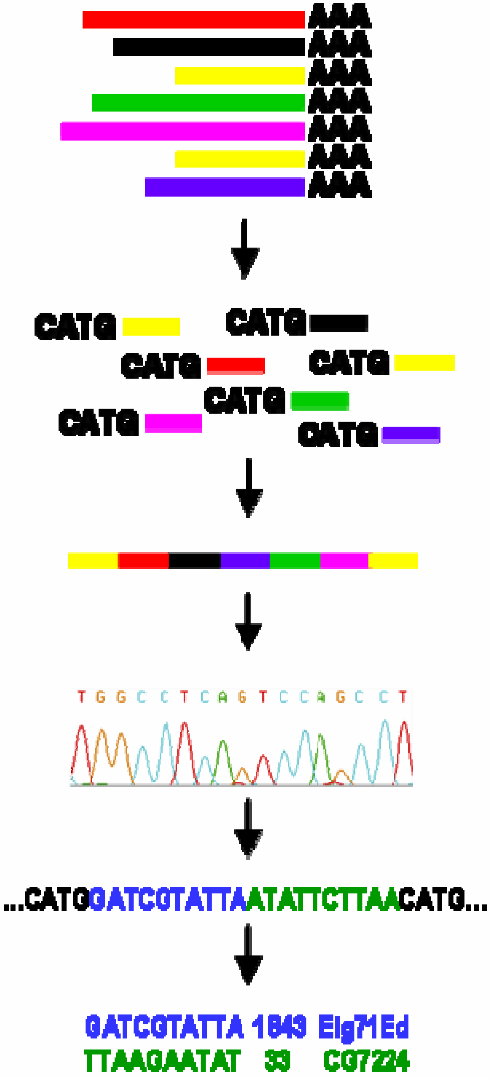
1. Oligonucleotide arrays



2. cDNA microarrays



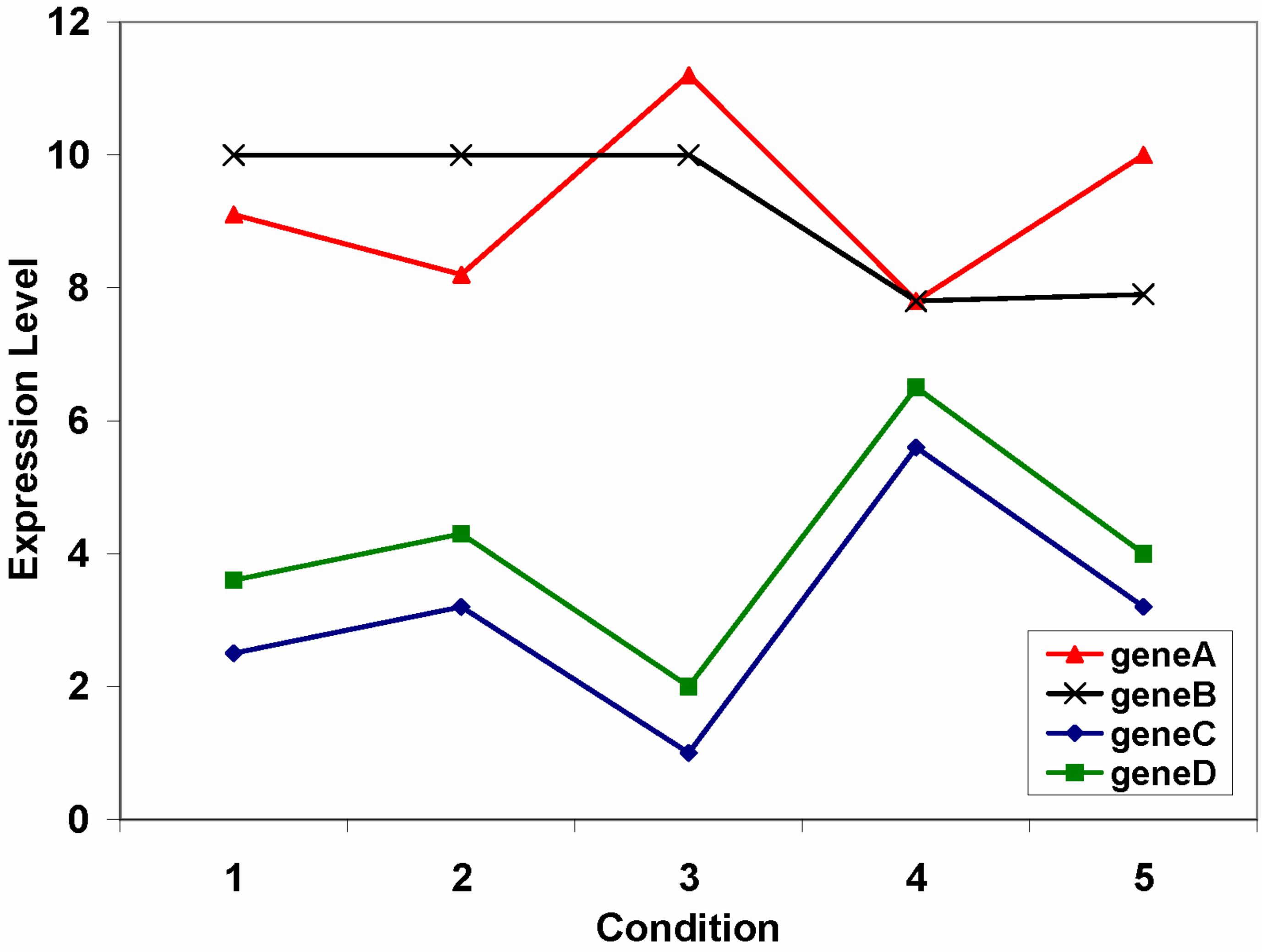
3. SAGE



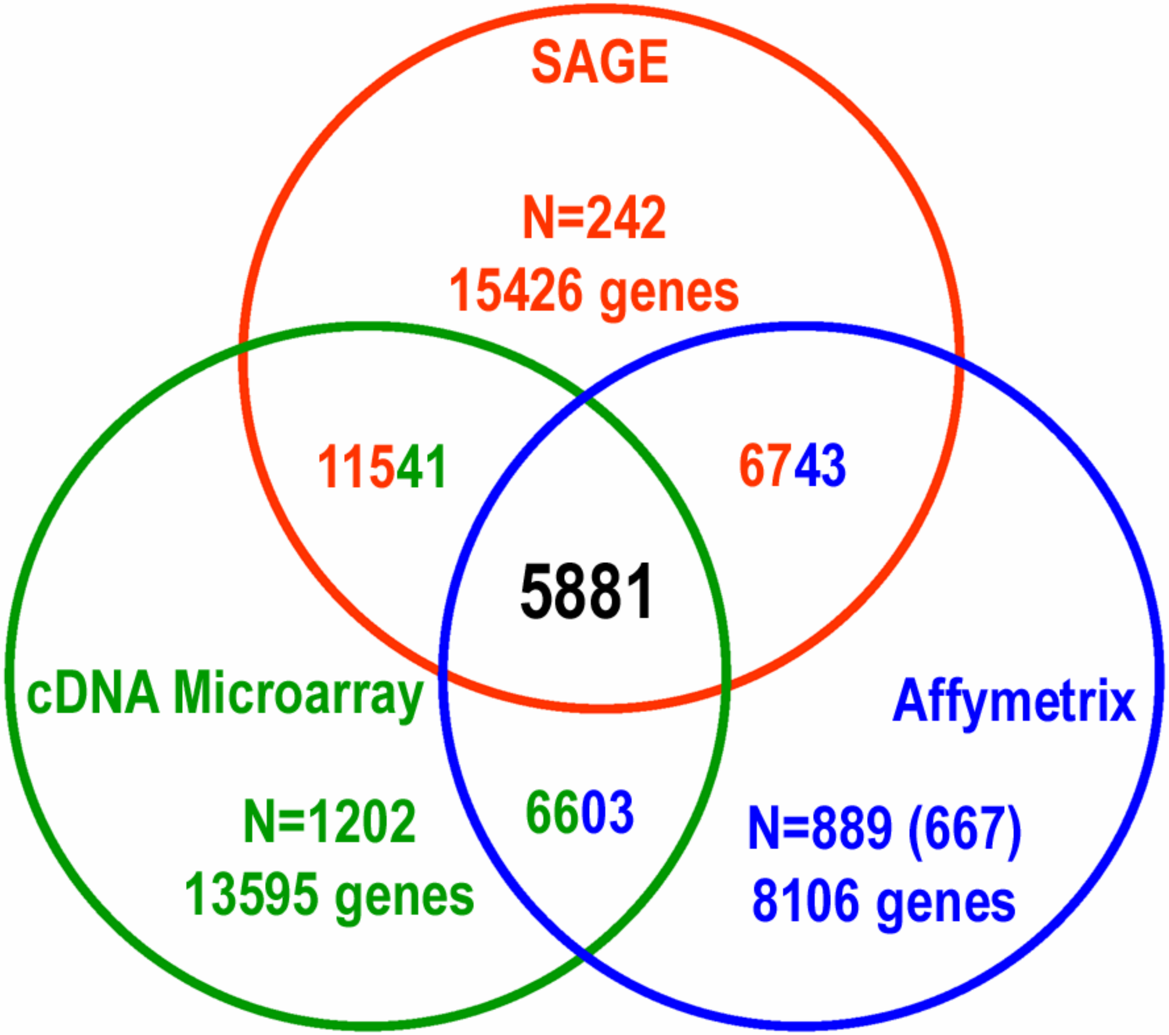
I) Multi-platform coexpression

- Coexpression can be used to
  - define clusters of genes with common biological processes
  - infer functional associations between genes
  - for integration with other large-scale datasets
  - for the generation of high-quality biological interaction networks
  - to identify co-regulation
  - identify groups of related genes that are important in specific cancers or represent common tumour progression mechanisms

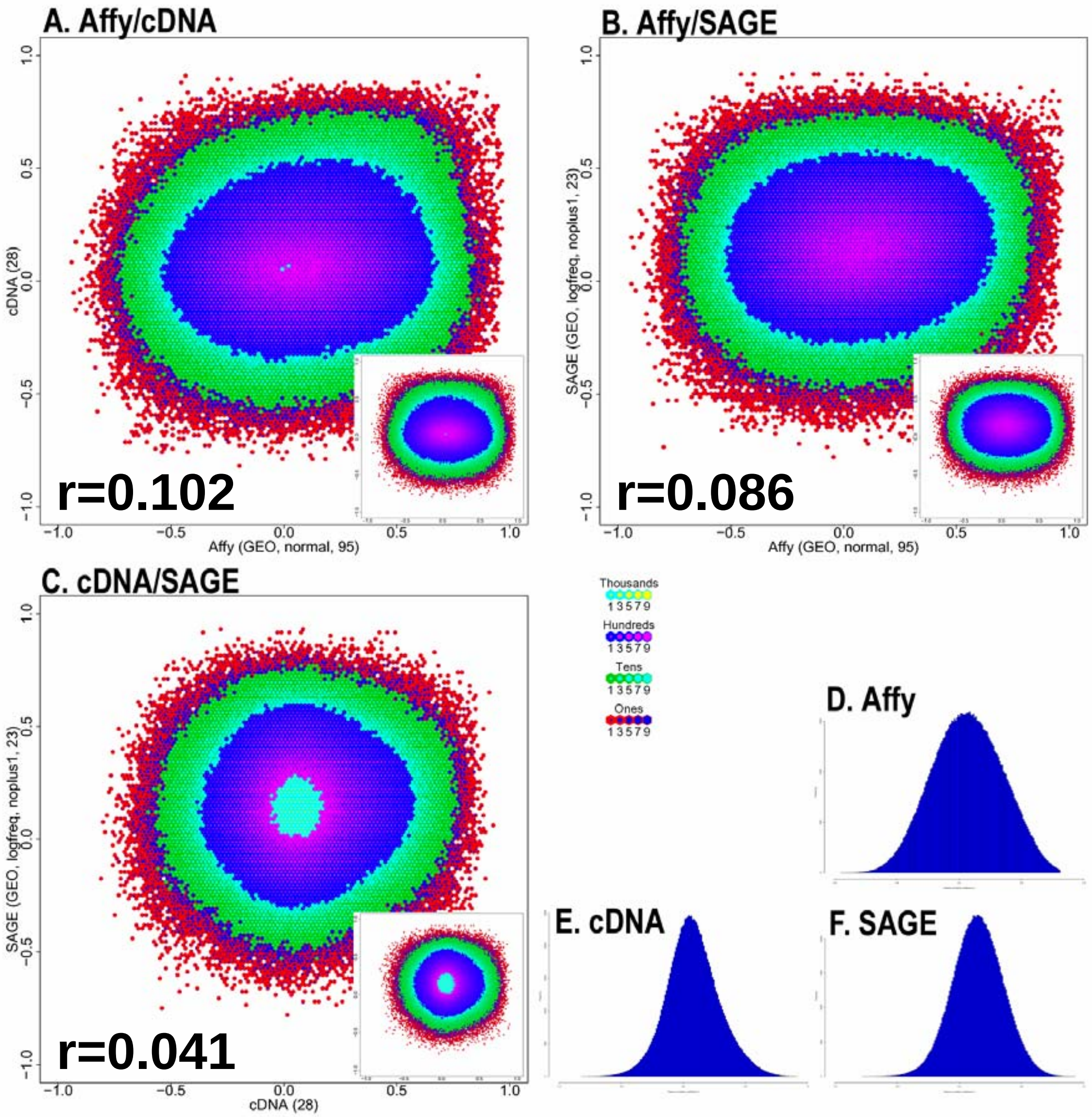
What is Coexpression?



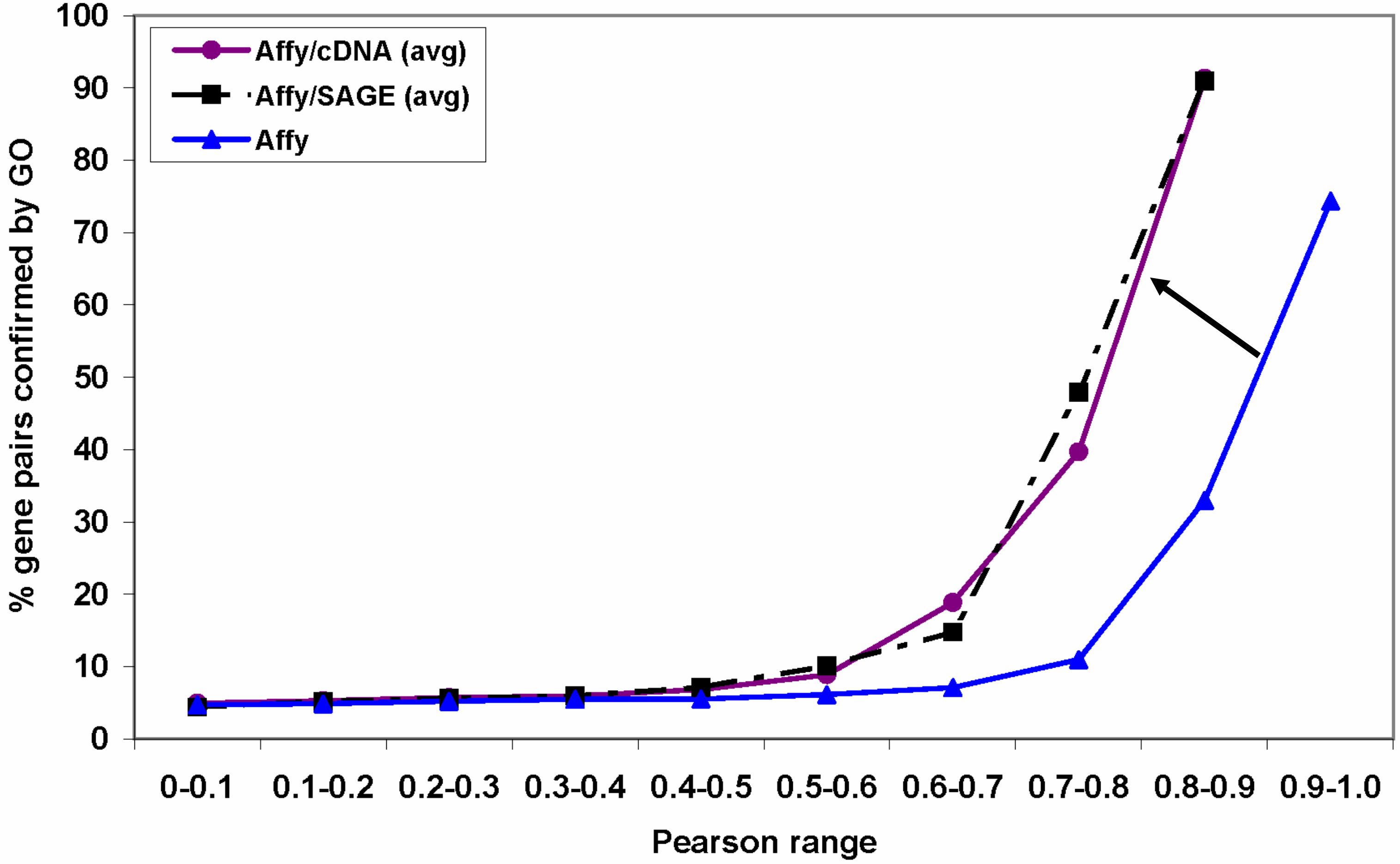
Available data



Platform Comparisons



Coexpression methods that combine different platforms or datasets improve quality of predictions (according to GO)



OL Griffith, ED Pleasance, DL Fulton, M Oveisi, M Ester, AS Siddiqui, SJM Jones. 2005. Assessment and Integration of Publicly Available SAGE, cDNA Microarray, and Oligonucleotide Microarray Expression Data for Global Coexpression Analyses. Genomics. 86:476-488

Conclusions

- Platforms compare significantly better than random but in general correlations are poor
- GO analysis indicates that all 3 platforms identify some biologically relevant gene pairs
- Higher Pearson indicates increased biological relevance
- Combining different platforms improves quality of predictions

II) Multi-platform differential expression in thyroid cancer

- Thyroid nodules are extremely common
  - 4-7% of North American adult population
- Fine needle aspiration biopsy (FNAB) is most important initial test
  - **10-20% indeterminate or suspicious → Surgery**
- After thyroid surgery as little as 20% are confirmed as malignant

Rationale

- Improved diagnostic markers are needed
- Gene expression profiling attempts to identify such markers
- A large number of thyroid cancer expression profiling studies exist
- Hundreds/thousands of potential markers (genes) have been identified
- What markers are most consistently reported?

Literature review reveals 21 studies

Study	Platform	Genes/ features	Comparison		Up-/down
			Condition 1 (No. samples)	Condition 2 (No. samples)	
Chen *et al*. 2001	Atlas cDNA (Clontech)	588	M (1)	FTC (1)	18/40
Arnaldi *et al*. 2005	Custom cDNA	1807	FCL(1)	Norm (1)	9/20
			PCL(1)	Norm (1)	1/8
			UCL(1)	Norm (1)	1/7
			FCL(1), PCL(1), UCL(1)	Norm (1)	3/6
Huang *et al*. 2001	Affymetrix HG-U95A	12558	PTC (8)	Norm (8)	24/27
Aldred *et al*. 2004	Affymetrix HG-U95A	12558	FTC (9)	PTC(6), Norm(13)	142/0
			PTC (6)	FTC(9), Norm(13)	0/68
Cerutti *et al*. 2004	SAGE	N/A	FA(1)	FTC(1), Norm(1)	5/0
			FTC(1)	FA(1), Norm(1)	12/0
Eszlinger *et al*. 2001	Atlas cDNA (Clontech)	588	AFTN(3), CTN(3)	Norm(6)	0/16
Finley *et al*. 2004	Affymetrix HG-U95A	12558	PTC(7), FVPTC(7)	FA(14), HN(7)	48/85
Zou *et al*. 2004	Atlas cancer array	1176	MACL(1)	ACL(1)	43/21
Weber *et al*. 2005	Affymetrix HG-U133A	22283	FA(12)	FTC(12)	12/84
Hawthorne *et al*. 2004	Affymetrix HG-U95A	12558	GT(6)	Norm(6)	1/7
			PTC(8)	GT(6)	10/28
			PTC(8)	Norm(8)	4/4
Onda *et al*. 2004	Amersham custom cDNA	27648	ACL(11), ATC(10)	Norm(10)	31/56
Wasenius *et al*. 2003	Atlas cancer cDNA	1176	PTC(18)	Norm(3)	12/9
Barden *et al*. 2003	Affymetrix HG-U95A	12558	FTC(9)	FA(10)	59/45
Yano *et al*. 2004	Amersham custom cDNA	3968	PTC(7)	Norm(7)	54/0
Chevillard *et al*. 2004	custom cDNA	5760	FTC(3)	FA(4)	12/31
			FVPTC(3)	PTC(2)	123/16
Mazzanti *et al*. 2004	Hs-UniGem2 cDNA	10000	PTC(17), FVPTC(15)	FA(16), HN(15)	5/41
Takano *et al*. 2000	SAGE	N/A	FTC(1)	ATC(1)	3/10
			FTC(1)	FA(1)	4/1
			Norm(1)	FA(1)	6/0
			PTC(1)	ATC(1)	2/11
			PTC(1)	FA(1)	7/0
			PTC(1)	FTC(1)	2/1
Finley *et al*. 2004	Affymetrix HG-U95A	12558	FTC(9), PTC(11), FVPTC(13)	FA(16), HN(10)	50/55
Pauws *et al*. 2004	SAGE	N/A	FVPTC(1)	Norm(1)	33/9
Jarzab *et al*. 2005	Affymetrix HG-U133A	22283	PTC(16)	Norm(16)	75/27
Giordano *et al*. 2005	Affymetrix HG-U133A	22283	PTC(51)	Norm(4)	90/151
21 studies	**10 platforms**		**34 comparisons (473 samples)**		**1785**

Griffith OL, Melck A, Jones SJM, Wiseman SM. 2006. JCO. 24(31):5043-5051.

21 cancer vs. non-cancer comparisons

Study	Platform	Genes/ features	Comparison		Up-/down
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Chen *et al.* 2001	Atlas cDNA (Clontech)	588	M (1)	FTC (1)	18/40
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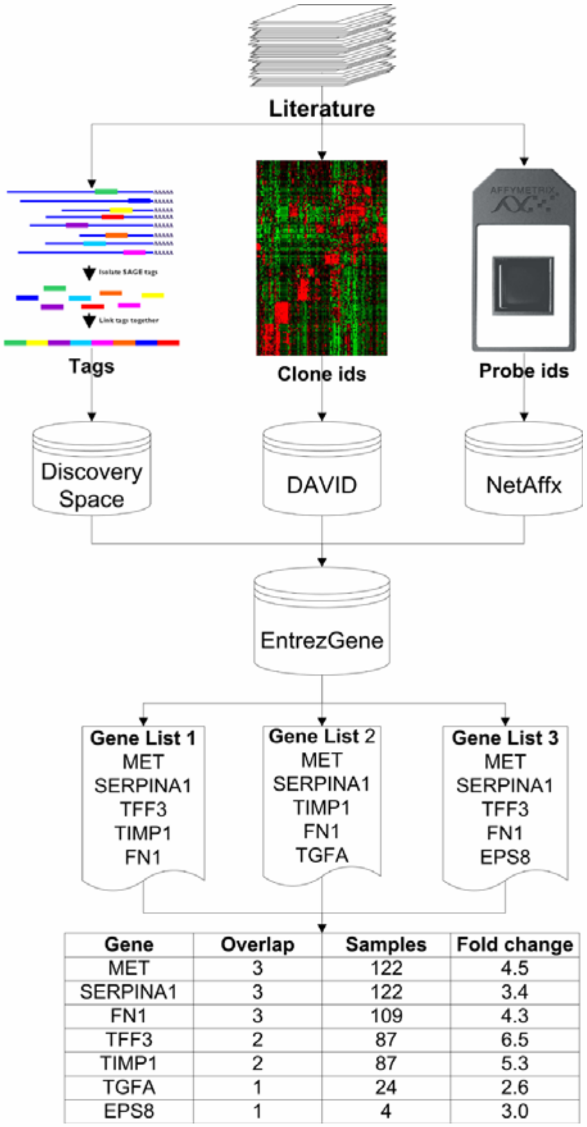
Multi-platform approach



Gene List 1
MET
SERPINA1
TFF3
TIMP1
FN1

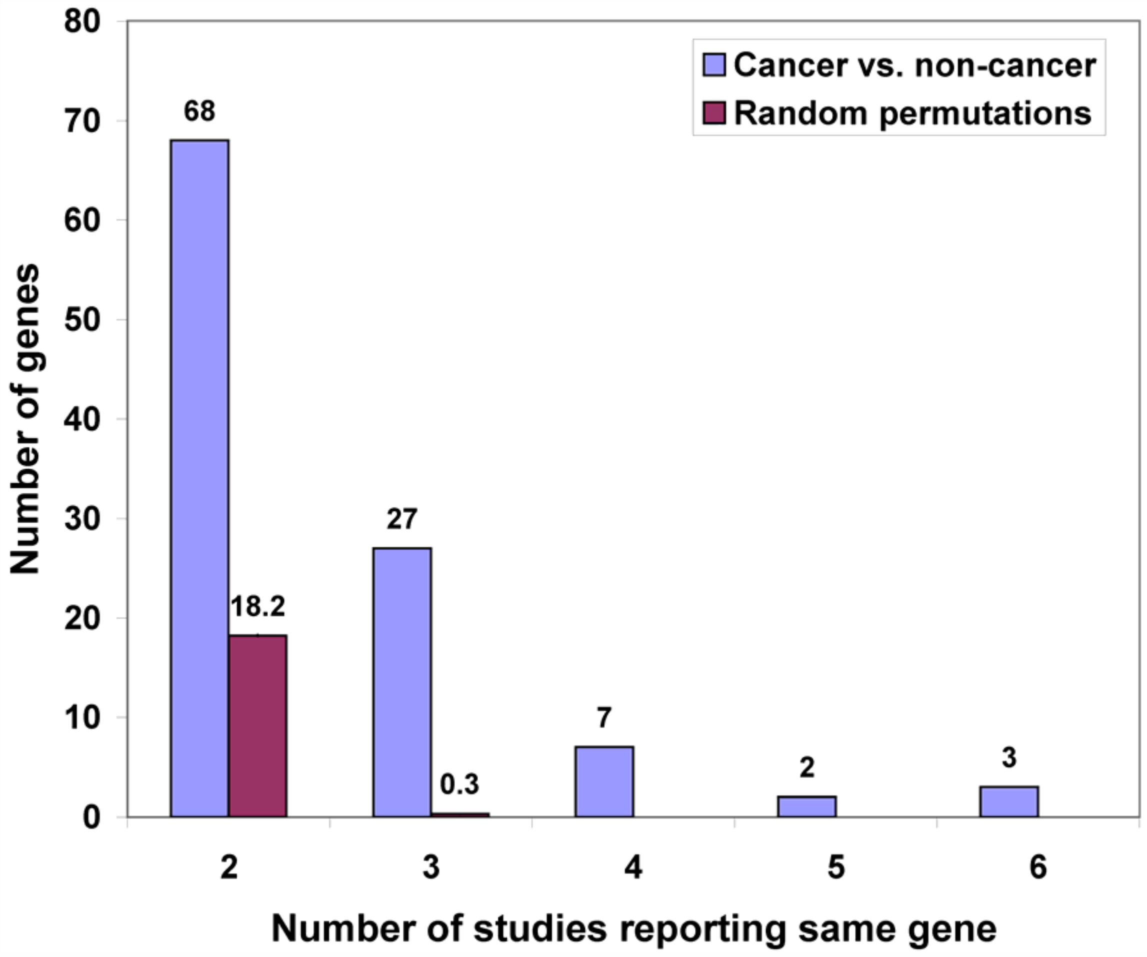
Gene List 2
MET
SERPINA1
TIMP1
FN1
TGFA

Gene List 3
MET
SERPINA1
TFF3
FN1
EPS8

Gene	Overlap	Samples	Fold change
MET	3	122	4.5
SERPINA1	3	122	3.4
FN1	3	109	4.3
TFF3	2	87	6.5
TIMP1	2	87	5.3
TGFA	1	24	2.6
EPS8	1	4	3.0

- Collect and curate data from over 20 studies
- Map various IDs to Entrez Gene ID
- Analyze datasets for overlap
- Rank genes according to:
  - amount of overlap
  - size of studies
  - fold change
- Assess significance of result

A significant number of genes are consistently reported as differentially expressed from multiple independent studies



Griffith OL, Melck A, Jones SJM, Wiseman SM. 2006. JCO. 24(31):5043-5051.

Top 12 most consistently differentially expressed genes (cancer vs. non-cancer)

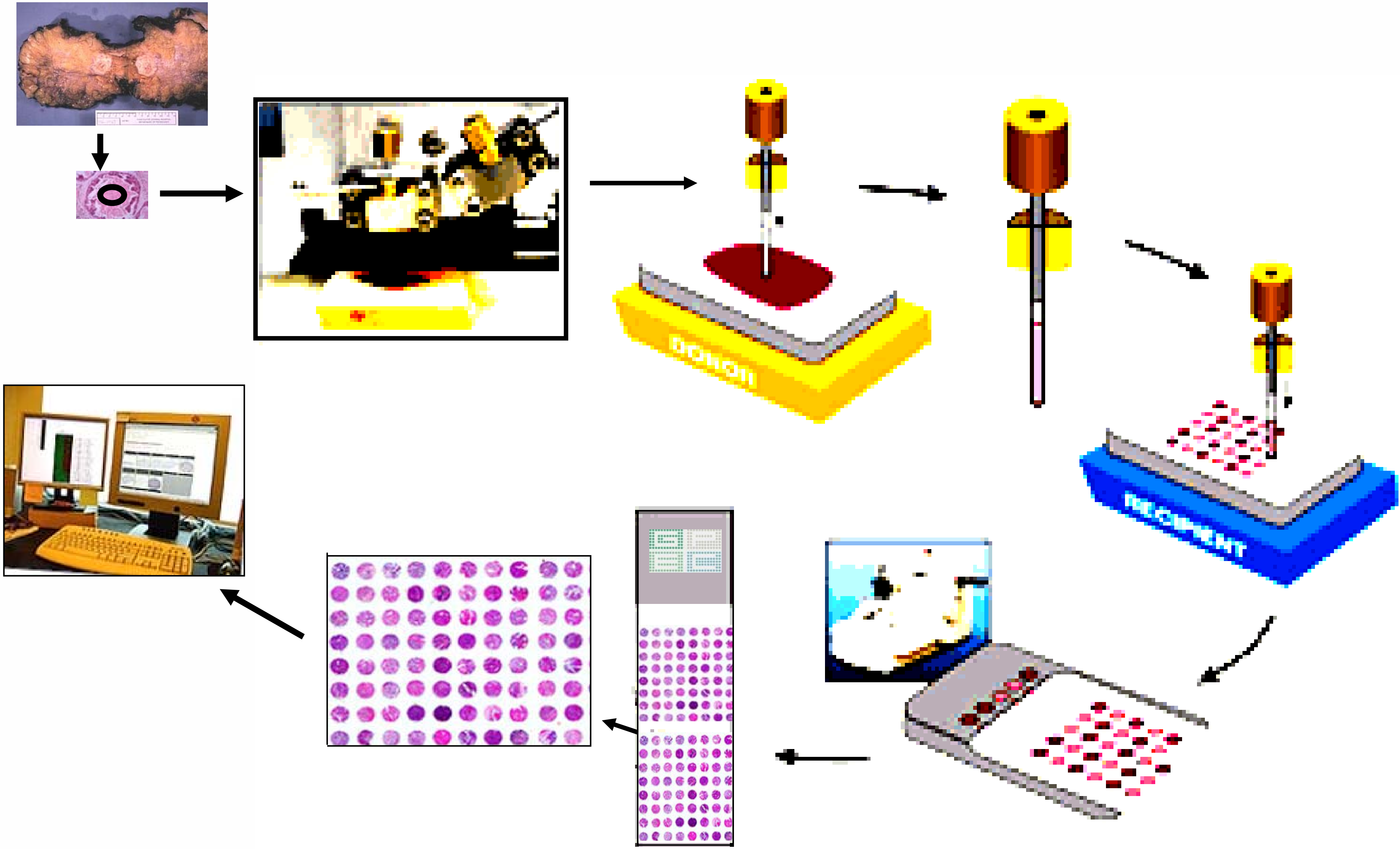
Gene	Description	Comps Up/Down	N	Mean FC (Range)
MET	met proto-oncogene (hepatocyte growth factor receptor)	6/0	202	4.54 (2.60 to 6.60)
TFF3	trefoil factor 3 (intestinal)	0/6	196	-22.04 (-63.55 to -3.80)
SERPINA1	serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	6/0	192	15.84 (5.00 to 27.64)
EPS8	epidermal growth factor receptor pathway substrate 8	5/0	186	3.14 (2.10 to 3.80)
TIMP1	tissue inhibitor of metalloproteinase 1 (erythroid potentiating activity, collagenase inhibitor)	5/0	142	5.37 (3.20 to 10.31)
TGFA	transforming growth factor, alpha	4/0	165	6.18 (3.20 to 7.91)
QPCT	glutaminyl-peptide cyclotransferase (glutaminyl cyclase)	4/0	153	7.31 (3.40 to 11.67)
PROS1	protein S (alpha)	4/0	149	5.76 (3.40 to 7.39)
CRABP1	cellular retinoic acid binding protein 1	0/4	146	-11.54 (-24.45 to -2.20)
FN1	fibronectin 1	4/0	128	7.67 (5.20 to 10.30)
FCGBP	Fc fragment of IgG binding protein	0/4	108	-3.20 (-3.30 to -3.10)
TPO	thyroid peroxidase	0/4	91	-6.25 (-8.60 to -2.70)

Griffith OL, Melck A, Jones SJM, Wiseman SM. 2006. JCO. 24(31):5043-5051.

What’s next? Tissue microarrays

- Two arrays (Dr. Sam Wiseman):
  - 100 Benign versus 105 Cancer patient samples
    - 57 markers stained
  - 12 differentiated vs. 12 undifferentiated samples
    - Matched samples from patients with extremely rare and aggressive Anaplastic cancer
    - A model for cancer progression
    - 62 markers stained

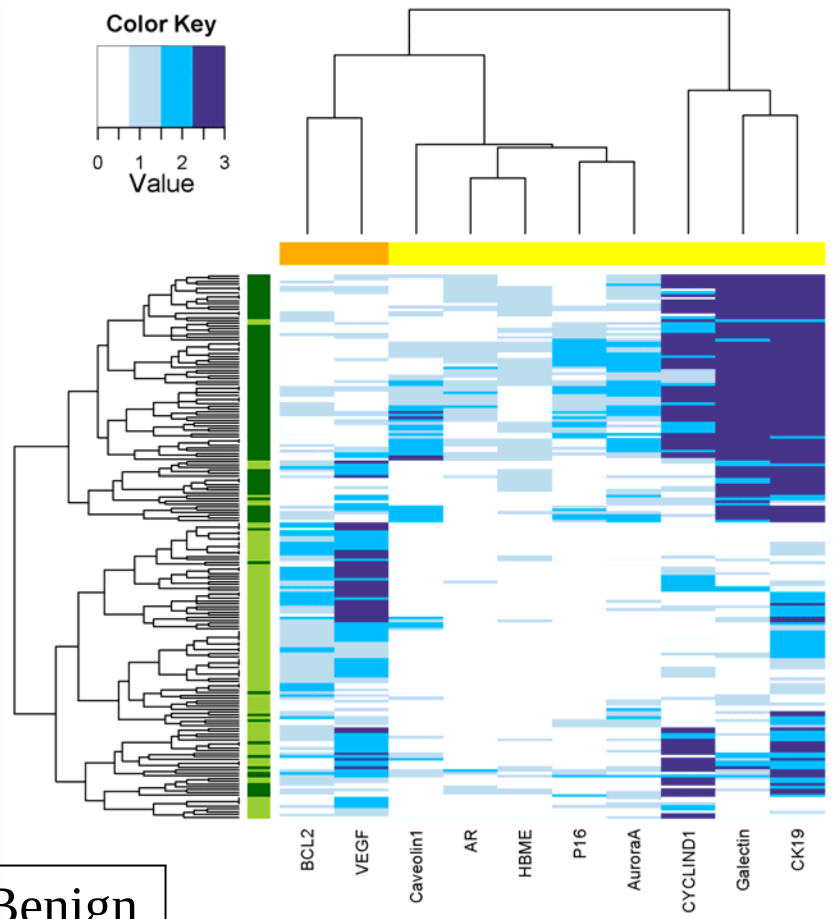
Methods: Tissue Array Construction



Benign versus cancer array: Results for top 25 markers

Marker	Benign Mean Rank	Malignant Mean Rank	Change	P-value	Corr. P-value	Variable Imp.
VEGF	130.3	65.3	Down	0.0000	0.0000	6.909
Galectin	59.1	139.6	Up	0.0000	0.0000	15.895
CK19	60.1	138.5	Up	0.0000	0.0000	13.942
AR	74.7	123.3	Up	0.0000	0.0000	5.048
AuroraA	68.1	123.2	Up	0.0000	0.0000	4.437
HBME	74.4	123.6	Up	0.0000	0.0000	5.309
P16	73.8	123.5	Up	0.0000	0.0000	4.174
BCL2	121.1	71.1	Down	0.0000	0.0000	2.383
CYCLIND1	67.0	115.5	Up	0.0000	0.0000	2.852
Caveolin1	77.5	119.1	Up	0.0000	0.0000	2.308
ECAD	120.2	75.9	Down	0.0000	0.0000	3.186
CYCLINE	77.1	118.0	Up	0.0000	0.0000	1.633
CR3	77.5	113.9	Up	0.0000	0.0000	1.045
Clusterin	79.6	117.0	Up	0.0000	0.0000	2.478
IGFBP5	79.0	112.2	Up	0.0000	0.0000	1.144
P21	81.0	113.4	Up	0.0000	0.0000	0.549
BetaCatenin	89.5	107.9	Up	0.0000	0.0000	0.295
IGFBP2	82.1	109.7	Up	0.0000	0.0001	1.051
Caveolin	78.8	109.0	Up	0.0001	0.0002	2.359
HER4	82.7	112.6	Up	0.0001	0.0003	1.273
TG	104.0	87.7	Down	0.0001	0.0003	1.268
CKIT	104.8	88.6	Down	0.0002	0.0004	0.810
S100	89.0	101.6	Up	0.0002	0.0004	0.230
KI67	86.9	101.6	Up	0.0003	0.0007	0.793
AuroraC	79.7	104.7	Up	0.0007	0.0015	1.059

TMA marker data can be used to attempt to classify benign vs. cancer patient samples



🟩 Benign
🟩 Cancer

Random Forests classifier performance:

- overall accuracy=91.3%
- sensitivity=88.5%
- specificity=94.0%
- Misclassification:
  - 6 benign; 11 cancer

Thyroid cancer: Conclusions and future work

Conclusions:

- A significant number of genes are consistently identified by multiple expression profiling studies
- Both known and novel markers
- Preliminary IHC analysis on TMAs show promising results

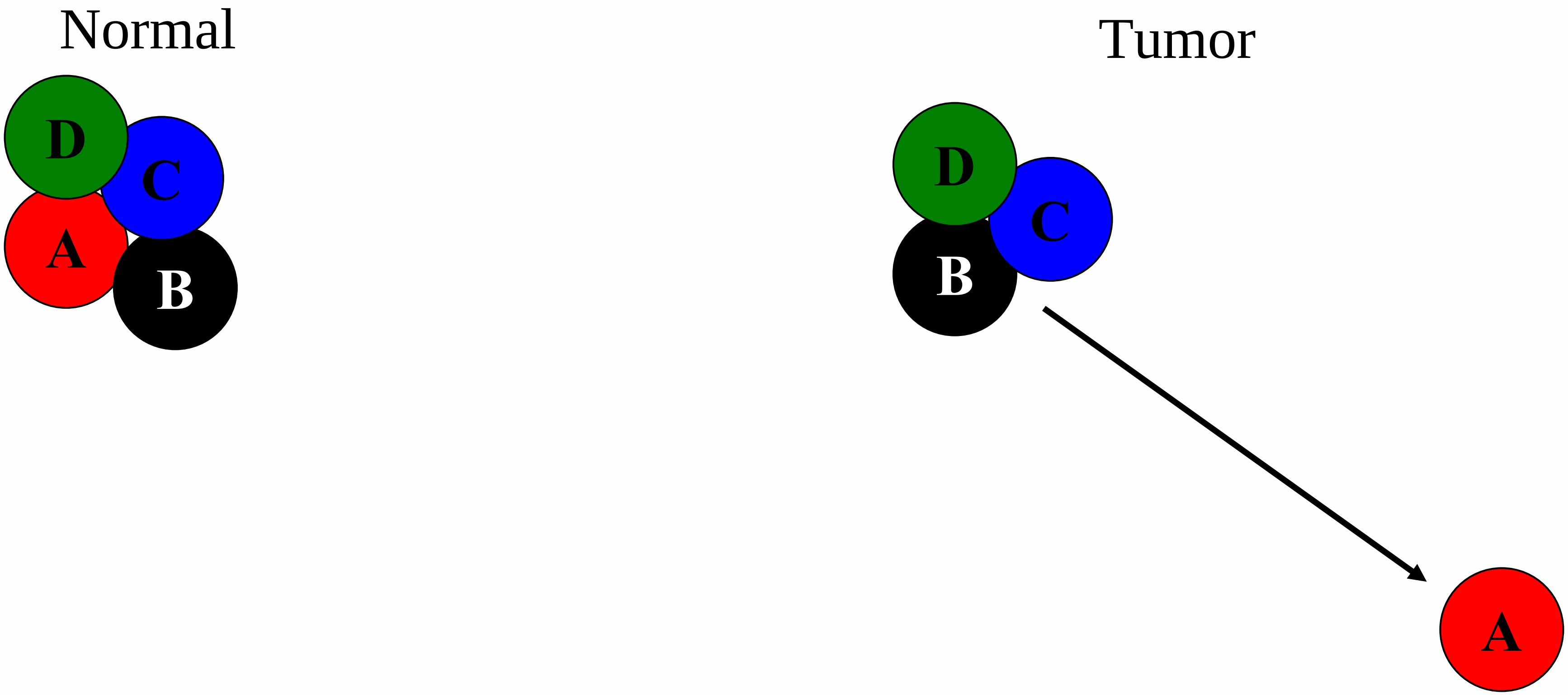
Future work:

- Addition of candidate genes from the meta-analysis to TMA analysis
- Development of a clinically useful classifier for thyroid tissue based on results of TMA

III) Differential coexpression in cancer

- Hypothesis: In some cases progression of cancer is mediated through changes in genetic regulatory regions that can be detected through gene expression studies and bioinformatics analyses.
- Specific hypothesis: Genes with significant changes in coexpression patterns will represent good candidates for regulatory changes
- Objective: Develop methods to assess differential coexpression.

Genes in coexpression space – differential coexpression



Difference in Mean correlation

Norm	Exp1	Exp2	Exp3	Exp4	Exp5	…
geneA	1.2	1.3	-1.4	0.1	2.2	…
geneB	1.3	1.3	-0.9	0.1	2.3	…
geneC	-1.2	1.0	0.1	0.5	1.4	…
…	…	…	…	…	…	…

Tumor	Exp1	Exp2	Exp3	Exp4	Exp5	…
geneA	11	35	2	4	50	…
geneB	12	35	0	3	47	…
geneC	0	10	4	15	20	…
…	…	…	…	…	…	…

Calculate all PCCs for each gene

Norm	geneA	geneB	geneC	geneD	…
geneA	NA	0.91	0.01	0.99	…
geneB	0.91	NA	-0.03	0.87	…

Tumor	geneA	geneB	geneC	geneD	…
geneA	NA	0.31	0.01	0.23	…
geneB	0.31	NA	-0.03	0.90	…

Find n nearest genes in normal and compare to tumor

Norm	geneD	geneB	geneX	geneY	…
geneA	0.99	0.91	0.90	0.89	…

Tumor	geneD	geneB	geneX	geneY	…
geneA	0.23	0.31	0.18	0.01	…

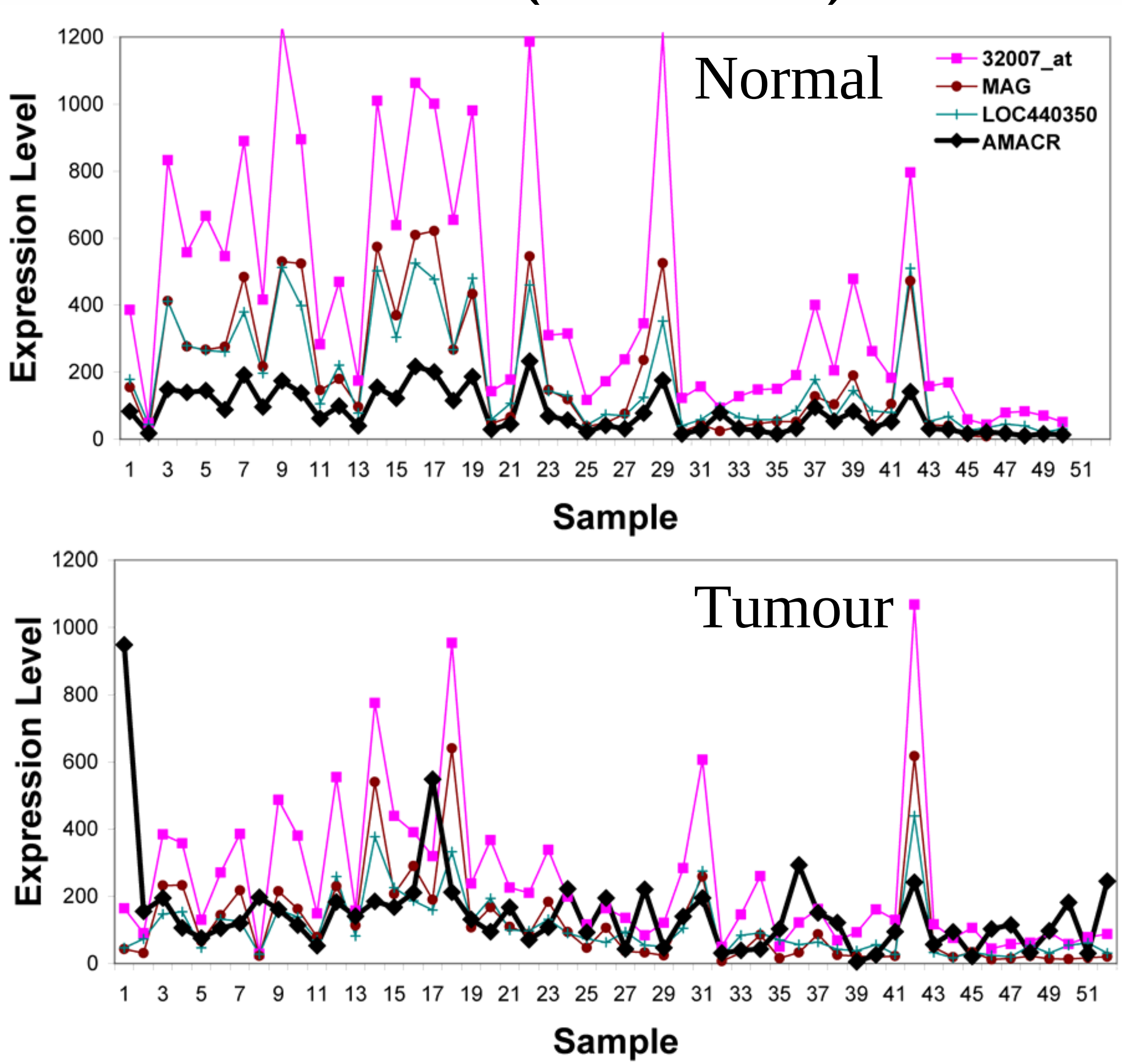
Calculate difference in mean PCC

Differential coexpression analysis

Expression Data

- Singh et al (2002)
- 52 prostate tumor
- 50 normal prostate
- Affymetrix U95Av2
- ~12,500 genes

An example of differential coexpression in prostate cancer (AMACR)



Candidate prostate cancer genes

Symbol	Comments
SLC26A3	Protein downregulated in colon adenoma and adenocarcinoma
CELSR1	Developmentally regulated, neural-specific gene which plays an unspecified role in early embryogenesis
AMACR	Proven biomarker that can help distinguish cancer from benign cells, with high sensitivity and specificity for prostate carcinoma.
PEX5	peroxisomal biogenesis factor
G1P2	Induced by camptothecin and Retinoic Acid in human tumor cells
SOX9	Overexpression results in suppression of growth and tumorigenicity in the prostate tumor cell line M12
ATP6V1E1	ATPase
LOC153561	function unknown
SEMG1	Interacts with PSA
MGC5576	function unknown
RAD51C	mRNA and protein levels elevated ~2- to 5-fold in malignant prostate cell lines
RAD23B	Highly expressed in the human testis and in ejaculated spermatozoa. Down-regulated during early apoptosis in human hepatoma cells exposed to Paeoniae Radix extract in vitro
SEMG2	Interacts with PSA
SNX4	not well characterized (only 4 pubmed)
DLGAP2	putative tumor suppressor gene. Chromosomal region (8p23.2) frequently deleted in prostate cancer.
TFDP2	Differential expression shown in some cancer cell lines
HGF	c-Met/HGF receptor have roles in prostate neoplasm progression
PEX10	peroxisomal biogenesis factor
ABL1	Important in leukemia - Bcr-Abl translocation
GSPT1	Overexpressed in gastric cancer
DNAJA2	function unknown
C7orf24	function unknown
GRM5	glutamate receptor, metabotropic

Cancer

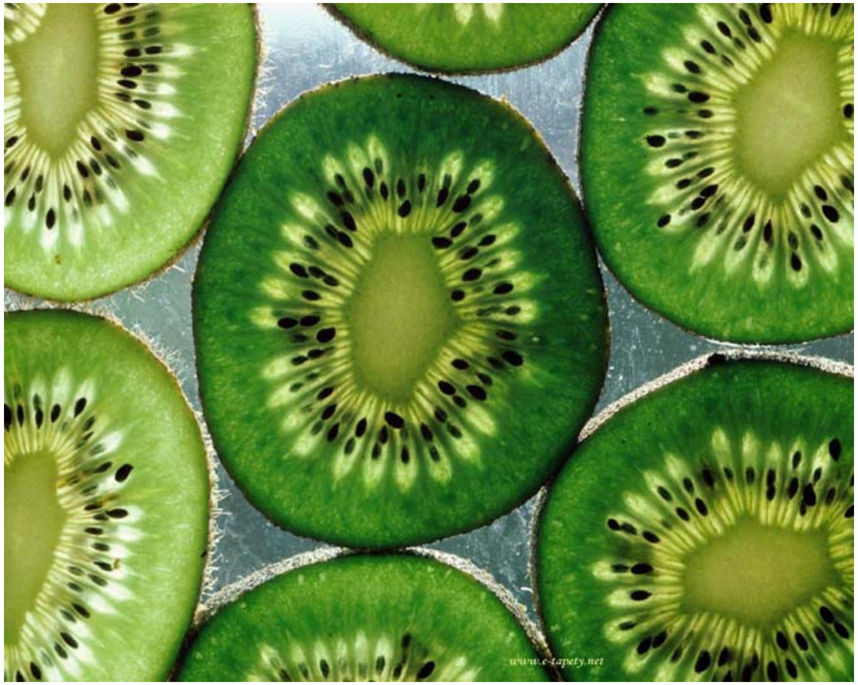
Prostate Cancer

Summary

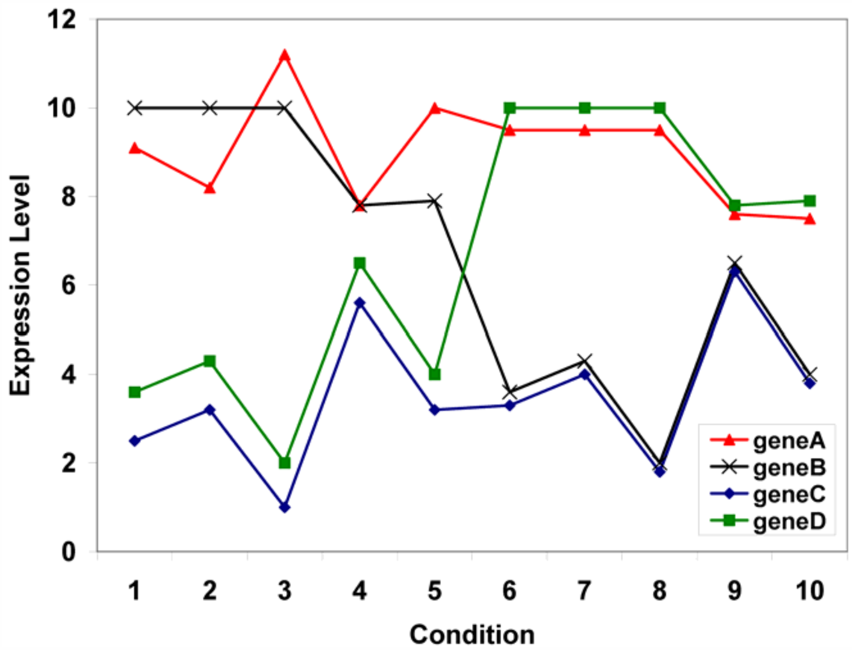
- Differential coexpression analysis represents a useful and complementary method to traditional differential expression methods for identifying potentially relevant cancer genes.
- Such genes may represent novel prostate cancer genes and would make good candidates for regulatory mutation analysis.

IV. Subspace coexpression

- Background
- KiWi method
- KiWi Interface
- Datasets
- Biological evaluation
- Results
- Conclusions

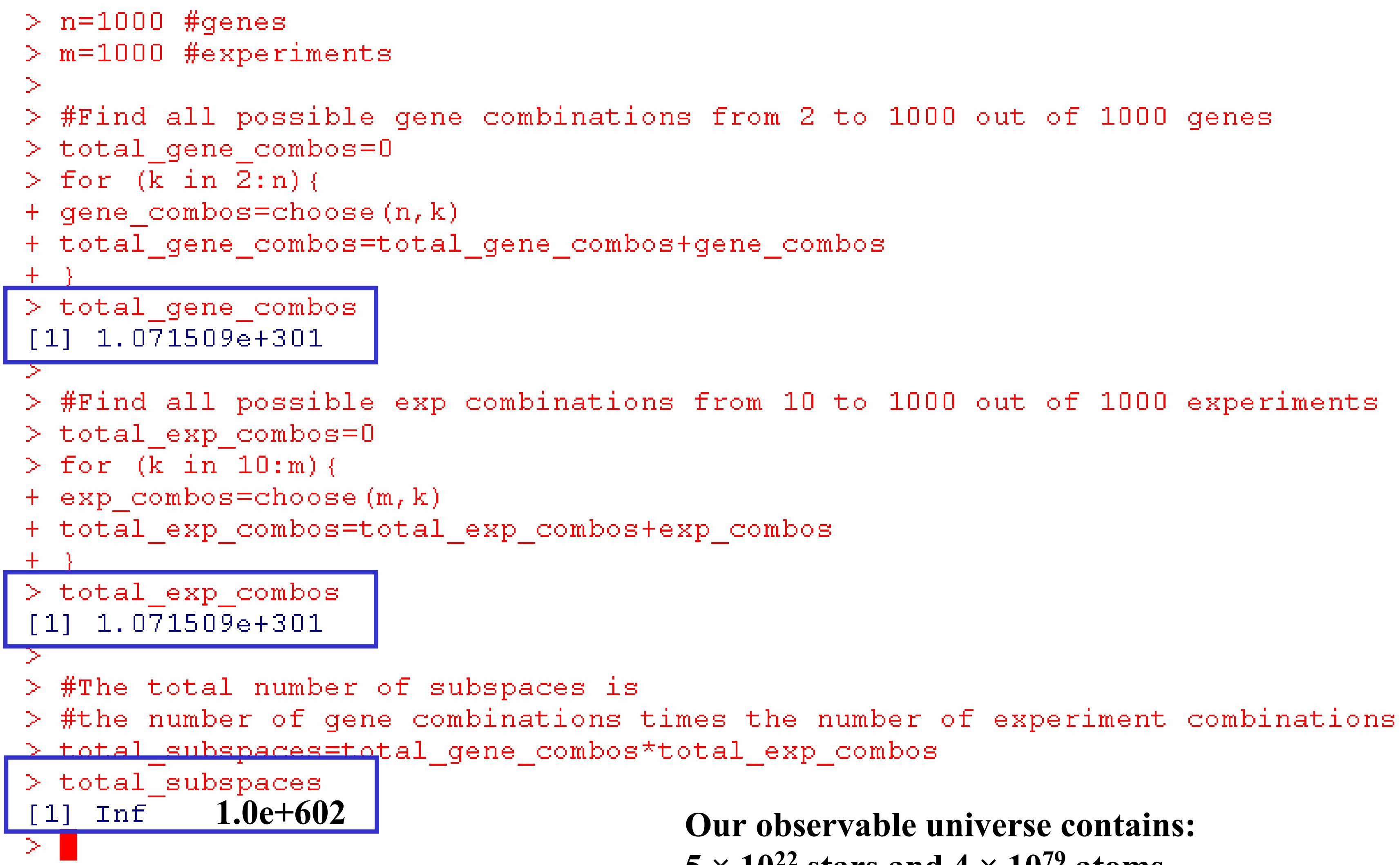

www.e-tapety.net

What is subspace clustering?



- Also called biclustering
- Identifies genes coexpressed in a subset of conditions (not global)
  - conditions or tissues
- Less sensitive to outliers or noisy data
- Genes can belong to multiple clusters
- Computationally intense

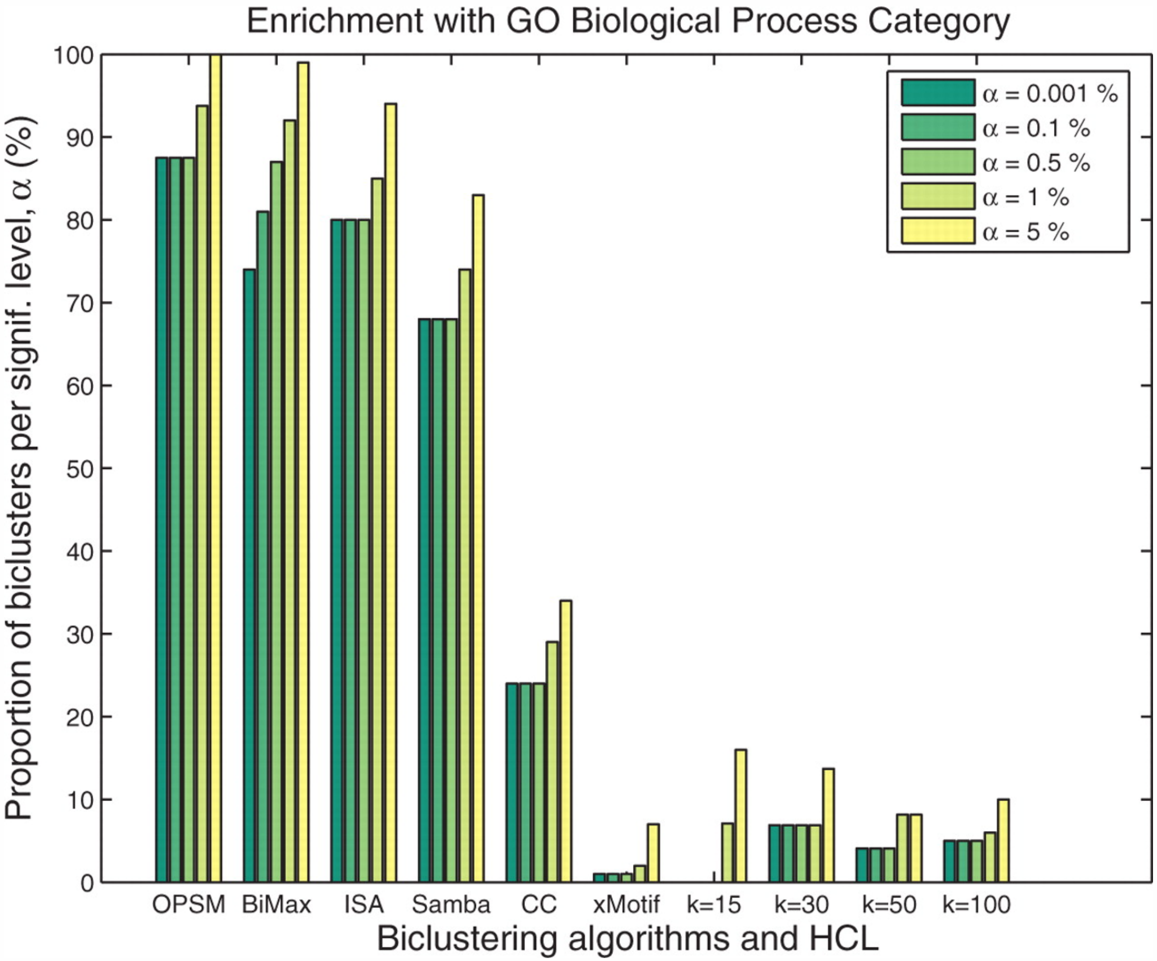
A virtually infinite number of possible subspaces exist



```
> n=1000 #genes
> m=1000 #experiments
>
> #Find all possible gene combinations from 2 to 1000 out of 1000 genes
> total_gene_combos=0
> for (k in 2:n){
+ gene_combos=choose(n,k)
+ total_gene_combos=total_gene_combos+gene_combos
+ }
> total_gene_combos
[1] 1.071509e+301
>
> #Find all possible exp combinations from 10 to 1000 out of 1000 experiments
> total_exp_combos=0
> for (k in 10:m){
+ exp_combos=choose(m,k)
+ total_exp_combos=total_exp_combos+exp_combos
+ }
> total_exp_combos
[1] 1.071509e+301
>
> #The total number of subspaces is
> #the number of gene combinations times the number of experiment combinations
> total_subspaces=total_gene_combos*total_exp_combos
> total_subspaces
[1] Inf      1.0e+602
>
```

Our observable universe contains:
5×10^{22} stars and 4×10^{79} atoms

Subspace clustering methods outperform traditional clustering methods



Prelic et al. 2006. Bioinformatics. 22(9):1122-9.

Subspace clustering: rationale

- Subspace clustering may represent a better or complementary method for identifying coregulated genes than global methods.
- Existing subspace clustering algorithms do not work for large datasets.

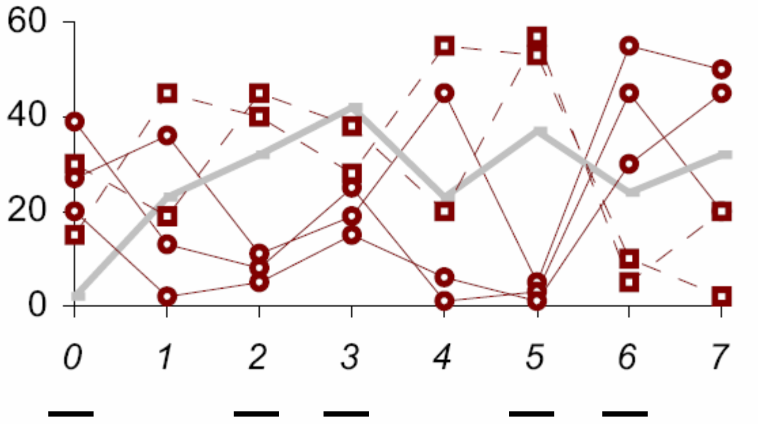
Design criteria for KiWi

- All members of clusters should be highly coexpressed
- Genes can belong to more than one cluster
- Clusters can be as small 2 members (twig clusters)
- Should be able to identify anti-correlated patterns.
- Must be able to handle very large datasets

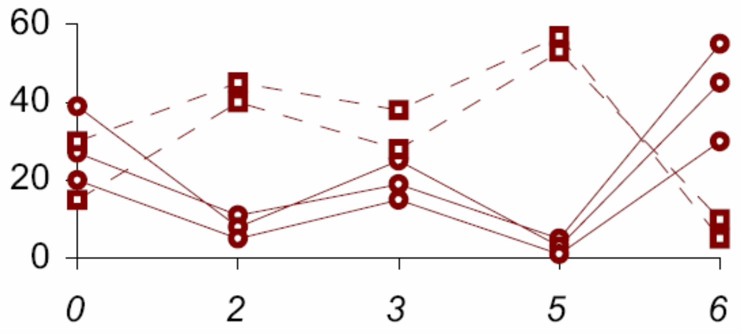
KiWi: an extension of OPSM (Order-Preserving Submatrix)

	0	1	2	3	4	5	6	7
I	27	36	11	19	45	5	55	50
II	39	13	8	25	1	3	45	20
III	2	23	32	42	23	37	24	32
IV	30	19	45	38	20	57	5	20
V	15	45	40	28	55	53	10	2
VI	20	2	5	15	6	1	30	45

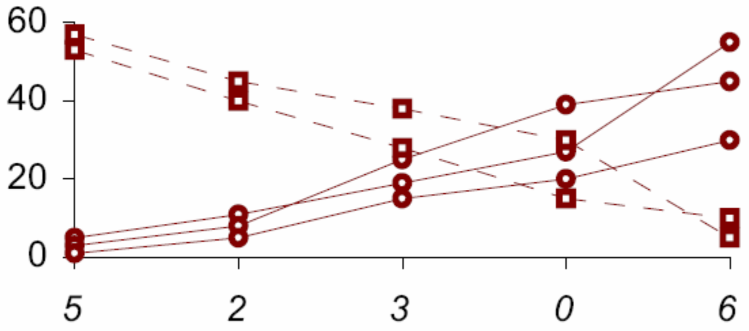
(a) Data matrix



(b) Data matrix plotted



(c) GOPSM consisting of two OPSMs



(d) GOPSM rearranged

Gao BJ, Griffith OL, Ester M, Jones SJ. 2006. KDD 2006. ACM Press. USA. 922-928.

How does KiWi work?

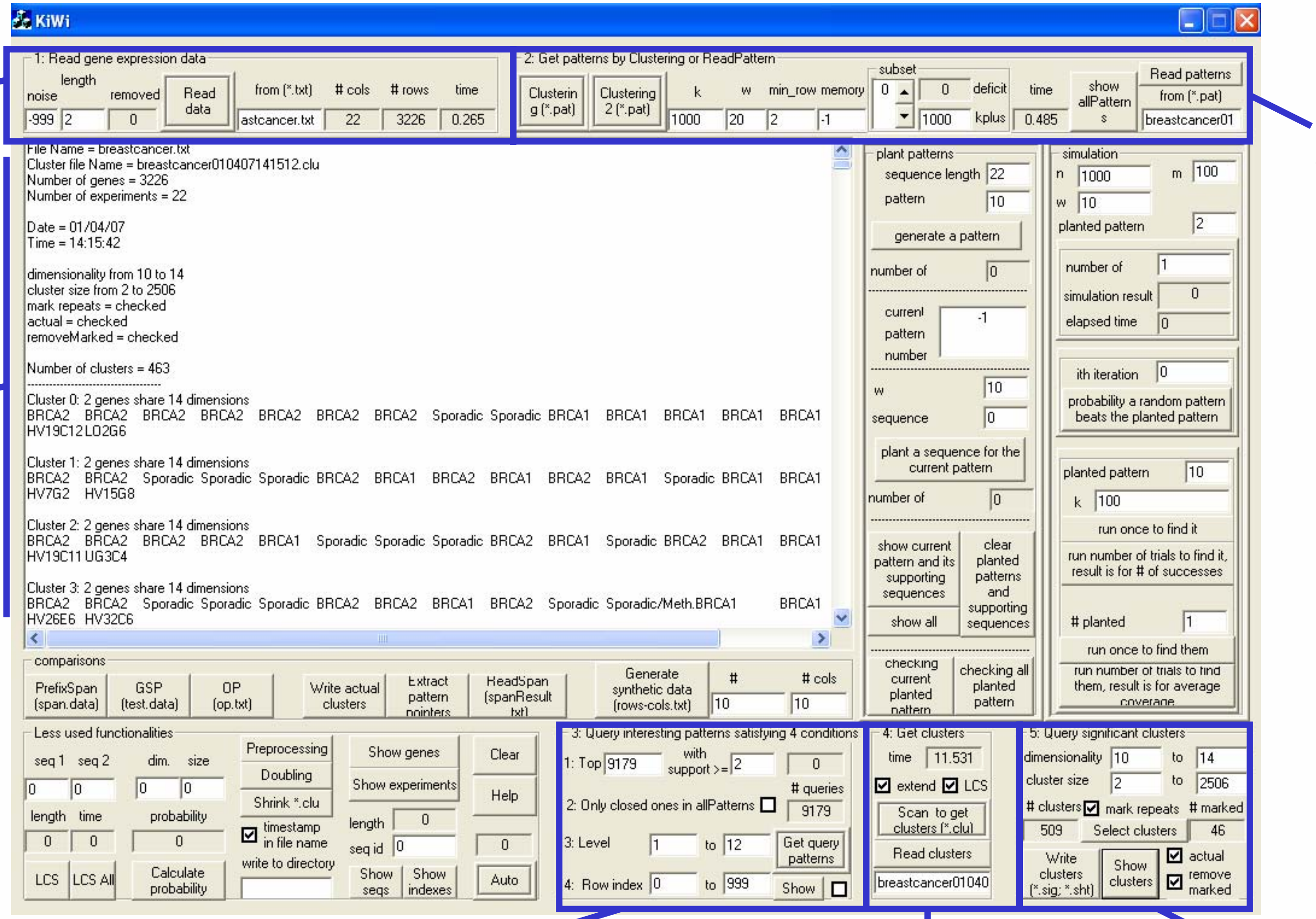
- Depends on two parameters: k and w
- A biased testing on a bounded number of candidates
- k = the number of candidates to be searched for a qualifying pattern
- w = width of a vertical slice to search for a qualifying pattern
- Both k and w dramatically reduce the search space and problem scale
- Targets highly promising seeds that are likely to lead to long patterns

KiWi graphical user interface

Load Data

Perform clustering

Visualize results


KiWi
1: Read gene expression data
2: Get patterns by Clustering or ReadPattern
Read data
Clusterin g (*.pat)
Clustering 2 (*.pat)
subset
show allPatterns
Read patterns from (*.pat)
plant patterns
generate a pattern
plant a sequence for the current pattern
show current pattern and its supporting sequences
clear planted patterns and supporting sequences
show all
checking current planted pattern
checking all planted pattern
simulation
probability a random pattern beats the planted pattern
run once to find it
run number of trials to find it, result is for # of successes
run once to find them
run number of trials to find them, result is for average coverage
comparisons
PrefixSpan (span.data)
GSP (test.data)
OP (op.txt)
Write actual clusters
Extract pattern pointers
ReadSpan (spanResult txt)
Generate synthetic data (rows-cols.txt)
Less used functionalities
LCS
LCS All
Calculate probability
Preprocessing
Doubling
Shrink *.clu
Show genes
Show experiments
Show seqs
Show indexes
Clear
Help
Auto
3: Query interesting patterns satisfying 4 conditions
Get query patterns
Show
4: Get clusters
Scan to get clusters (*.clu)
Read clusters
5: Query significant clusters
Select clusters
Write clusters (*.sig; *.sht)
Show clusters

1: Read gene expression data

noise	length	removed	from (*.txt)	# cols	# rows	time
-999	2	0	astcancer.txt	22	3226	0.265

2: Get patterns by Clustering or ReadPattern

k	w	min_row	memory	subset	deficit	kplus	time	from (*.pat)
1000	20	2	-1	0	0	1000	0.485	breastcancer01

```
File Name = breastcancer.txt
Cluster file Name = breastcancer010407141512.clu
Number of genes = 3226
Number of experiments = 22

Date = 01/04/07
Time = 14:15:42

dimensionality from 10 to 14
cluster size from 2 to 2506
mark repeats = checked
actual = checked
removeMarked = checked

Number of clusters = 463
------------------------------
Cluster 0: 2 genes share 14 dimensions
BRCA2   BRCA2   BRCA2   BRCA2   BRCA2   BRCA2   BRCA2   Sporadic  Sporadic  BRCA1   BRCA1   BRCA1   BRCA1   BRCA1
HV19C12 LO2G6

Cluster 1: 2 genes share 14 dimensions
BRCA2   BRCA2   Sporadic  Sporadic  Sporadic  BRCA2   BRCA1   BRCA2   BRCA1   BRCA2   BRCA1   Sporadic  BRCA1   BRCA1
HV7G2   HV15G8

Cluster 2: 2 genes share 14 dimensions
BRCA2   BRCA2   BRCA2   BRCA2   BRCA1   Sporadic  Sporadic  Sporadic  BRCA2   BRCA1   Sporadic  BRCA2   BRCA1   BRCA1
HV19C11 UG3C4

Cluster 3: 2 genes share 14 dimensions
BRCA2   BRCA2   Sporadic  Sporadic  Sporadic  BRCA2   BRCA2   BRCA1   BRCA2   Sporadic  Sporadic/Meth.BRCA1     BRCA1
HV26E6  HV32C6
```

plant patterns: sequence length 22; pattern 10; number of 0; current pattern number -1; w 10; sequence 0; number of 0

simulation: n 1000; m 100; w 10; planted pattern 2; number of 1; simulation result 0; elapsed time 0; ith iteration 0; planted pattern 10; k 100; # planted 1

comparisons: # 10; # cols 10

Less used functionalities: seq 1 0; seq 2 0; dim. 0; size 0; length 0; time 0; probability 0; ☑ timestamp in file name; write to directory; length 0; seq id 0; 0

3: Query interesting patterns satisfying 4 conditions
1: Top 9179 with support >= 2 0
# queries 9179
2: Only closed ones in allPatterns □
3: Level 1 to 12
4: Row index 0 to 999 Show □

4: Get clusters: time 11.531; ☑ extend ☑ LCS; breastcancer01040

5: Query significant clusters: dimensionality 10 to 14; cluster size 2 to 2506; # clusters 509; ☑ mark repeats; # marked 46; ☑ actual; ☑ remove marked

Scan for interesting results

Extract clusters

Output selected results

GENOME Sciences Centre

BC Cancer Agency CARE & RESEARCH

Kiwi clusters – a simple list of genes and experiments

```
Number of clusters = 44
------------------------------------
Cluster 0: 7 genes share 9 dimensions
BRCA2 BRCA2 BRCA2 Sporadic Sporadic BRCA2 BRCA2 BRCA1 BRCA1
HV2E3 HV13B12 HV21G2 HV25A10 HV28E8 HV52H12 TNF1H10

Cluster 1: 7 genes share 9 dimensions
BRCA2 BRCA2 Sporadic Sporadic BRCA2 BRCA2 Sporadic BRCA1 BRCA2
HV4D12 HV17B8 HV19H3 HV25A10 HV27E10 HV28G8 HV52H12

…
```

Datasets analyzed

Misc. GEO data

- Affymetrix (HG-U133A) experiments from the Gene Expression Omnibus (GPL96)
- 1640 experiments from wide range of tissues and conditions
- Not well annotated
- 12332 mapped genes
- Simple (within experiment) normalization

expO data

- Expression Project for Oncology (expO; GSE2109)
- 1026 tissue samples from dozens of different cancer types
- Well annotated
- GCRMA normalized
- 20113 mapped genes (Uniprot and ENSG)

Also, a Luciferase promoter dataset (Stanford)

Not all clusters are created equal

For expO data:

- 23,705 clusters found by KiWi
  - k = 100,000; w = 18; runtime = 2 to 3 days
  - 10 to 249 experiments
  - 2 to 37 genes

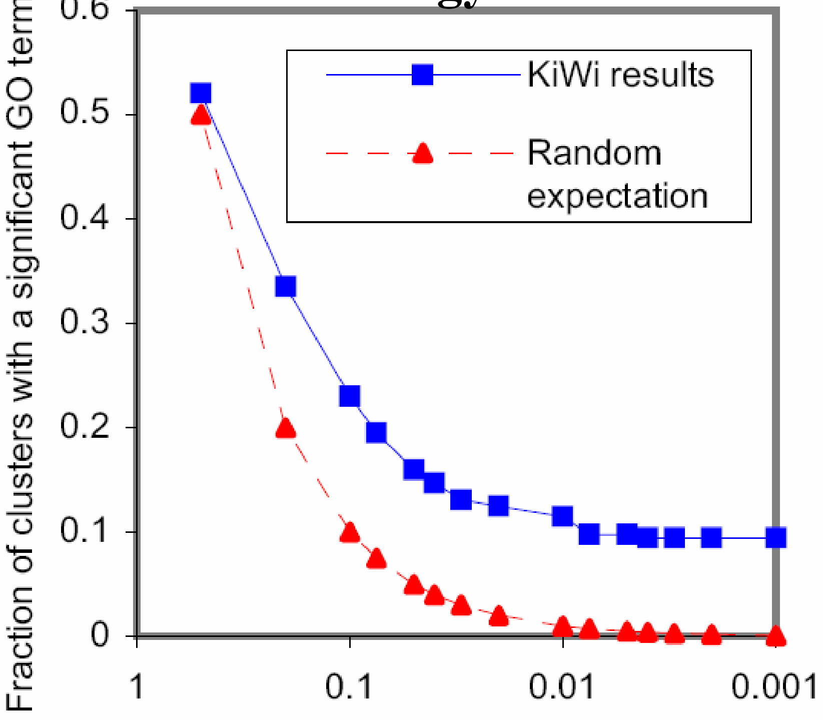
- 1,063 clusters after further filtering for analysis:
  - Minimum 5 genes
  - Minimum 15 experiments
  - Note: many clusters lost because probes correspond to identical genes

Biological validation methods

- Gene Ontology (GO) analysis
  - High-throughput GoMiner
  - Identify over-represented GO terms
  - Fisher exact statistics (FDR corrected)
- TFBS analysis
  - oPossum (Wasserman lab)
  - Identify over-represented TFBSs in promoter region
  - Z-score
- Cancer term analysis
  - Identify over-represented experiment annotation terms (e.g. tissue type)
  - Fisher Exact Statistics in R
- Stanford Promoter dataset evaluation
- cisRED analysis

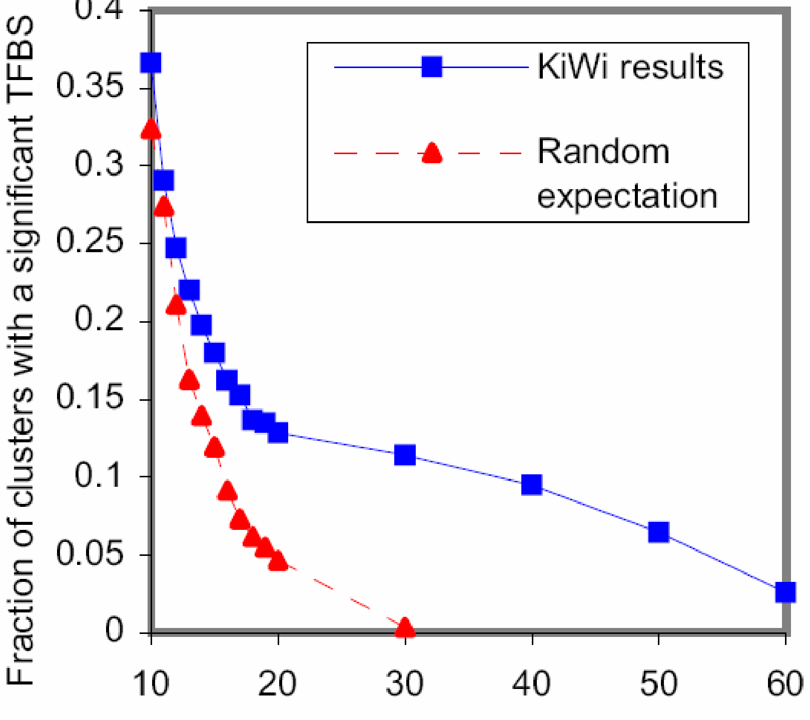
KiWi clusters share common biological processes and TFBSs (Misc. GEO data)

Gene Ontology



(a) *P*-value (FDR corrected, 100 permutations)

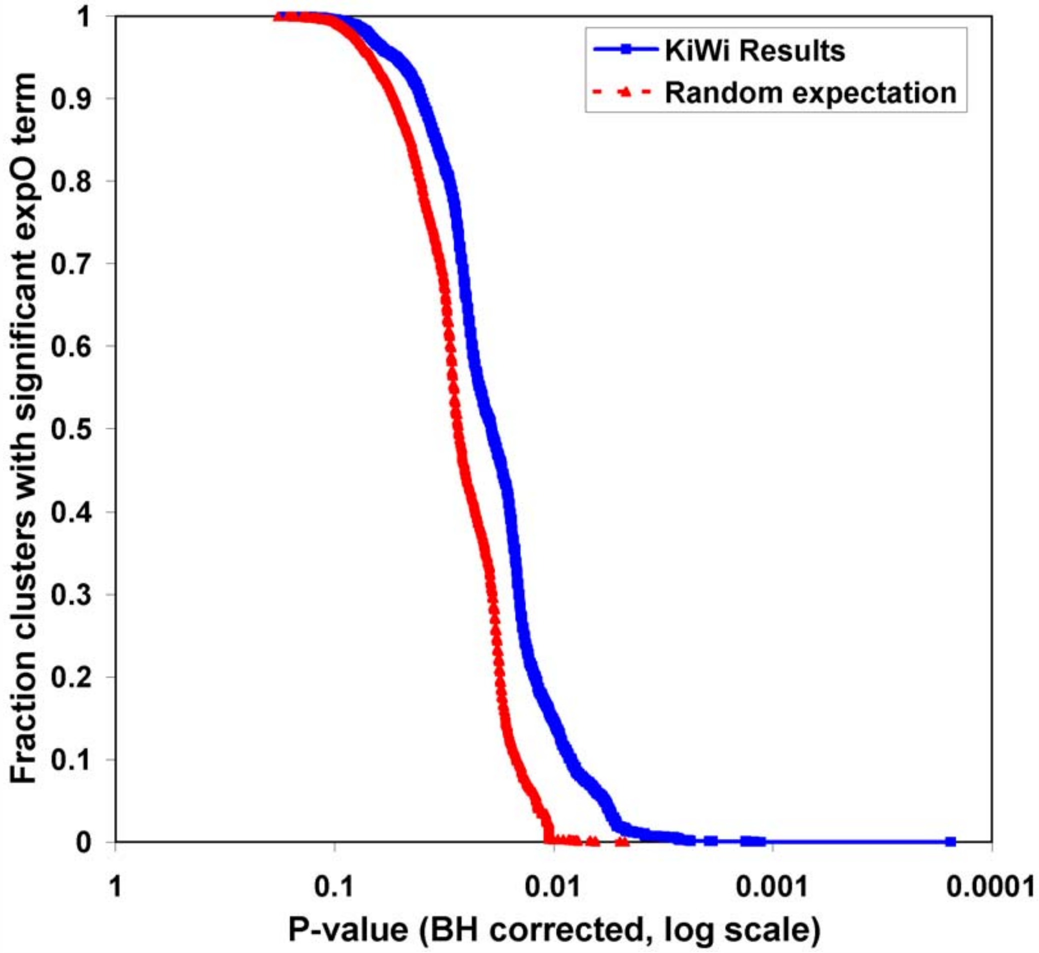
oPOSSUM



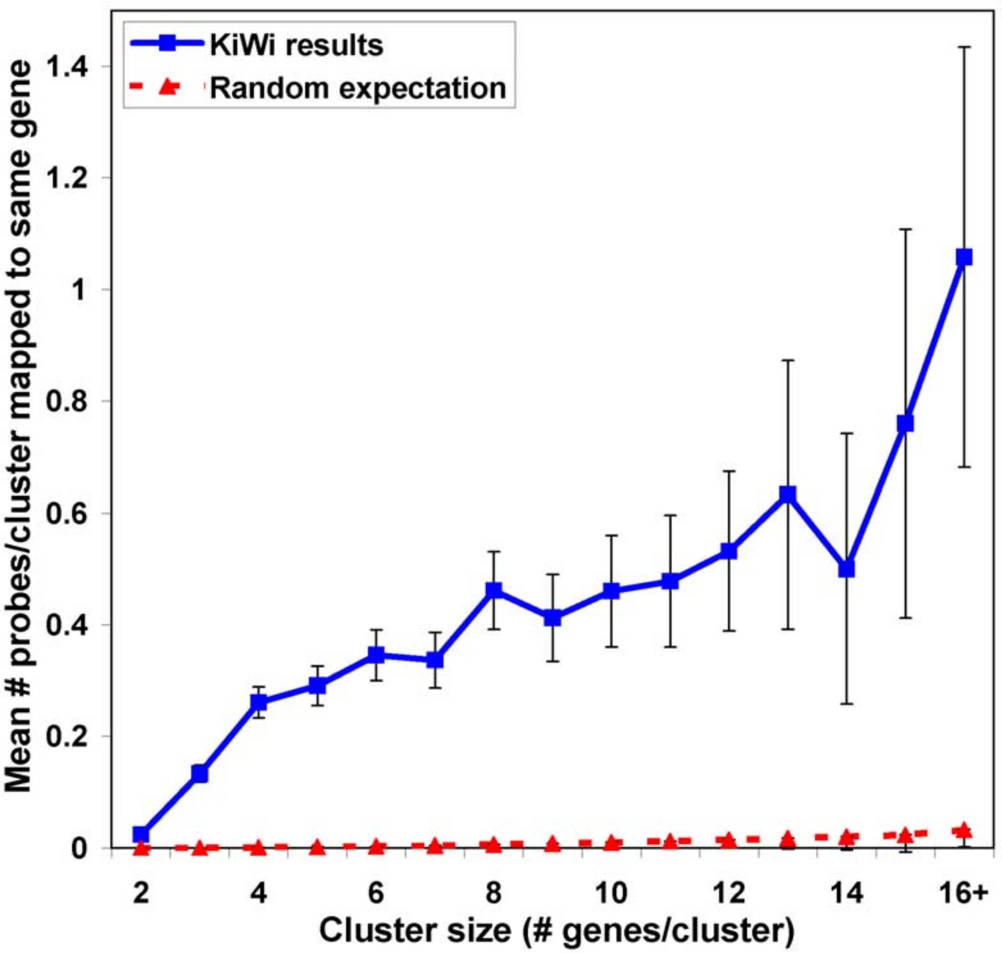
(b) Z-score for TFBS over-representation

Gao BJ, Griffith OL, Ester M, Jones SJ. 2006. KDD 2006. ACM Press. USA. 922-928.

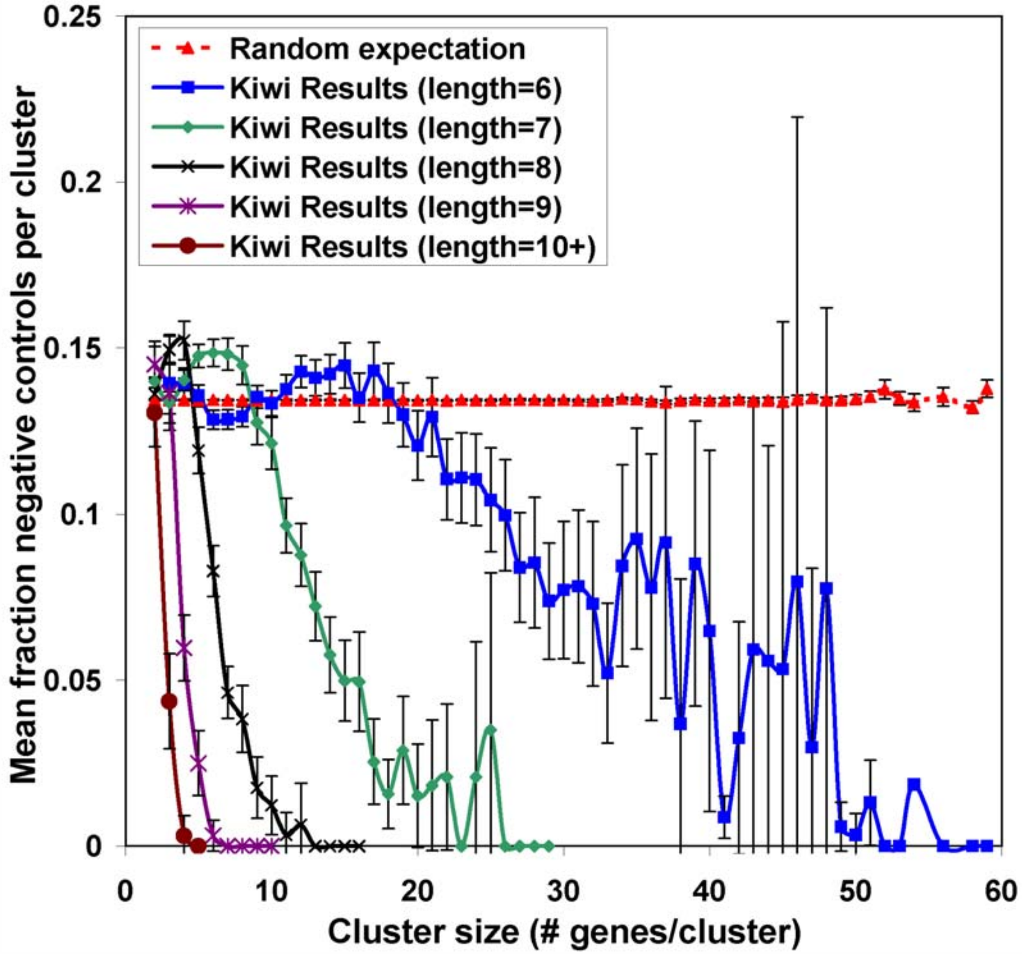
KiWi clusters share common experimental terms (e.g. cancer type)



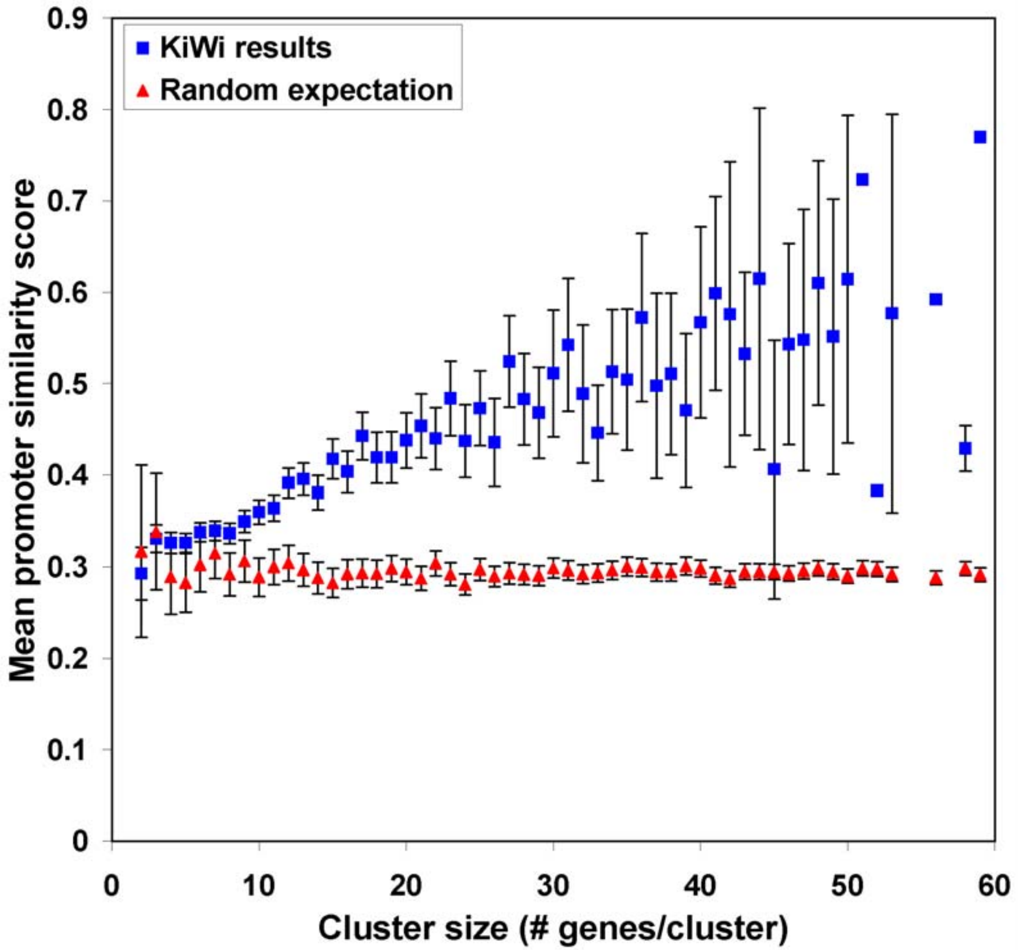
KiWi correctly clusters probes that map to the same gene



KiWi avoids ‘contamination’ by negative control sequences



KiWi groups genes with similar promoters based on de novo cisRED motif predictions



Subspace clustering: Conclusions and future work

Conclusions:

- KiWi represents the first subspace clustering algorithm capable of processing very large datasets
- KiWi successfully groups genes with common biological processes, TFBSs, and experimental annotations.

Future work:

- Paper describing KiWi implementation and biological validation.
- Develop and release more user-friendly interface.

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