Functional Context Matters: Building and Applying a New Dictionary for Human Development

Donna K. Slonim

Dept. of Computer Science, Tufts University

Dept. of Integrative Physiology and Pathobiology, Tufts University School of Medicine

Genetics Faculty, Sackler School of Graduate Biomedical Sciences

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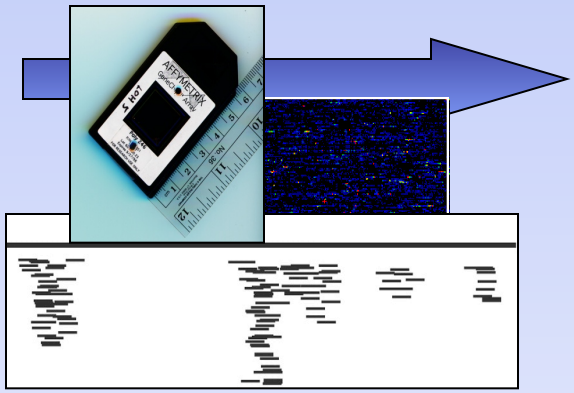
September 1, 2015

Bioinformatics for Human Development



Goals:

- Better understand normal development
- Diagnose developmental abnormalities
- Suggest novel therapies
- Discover developmental implications for adult disease

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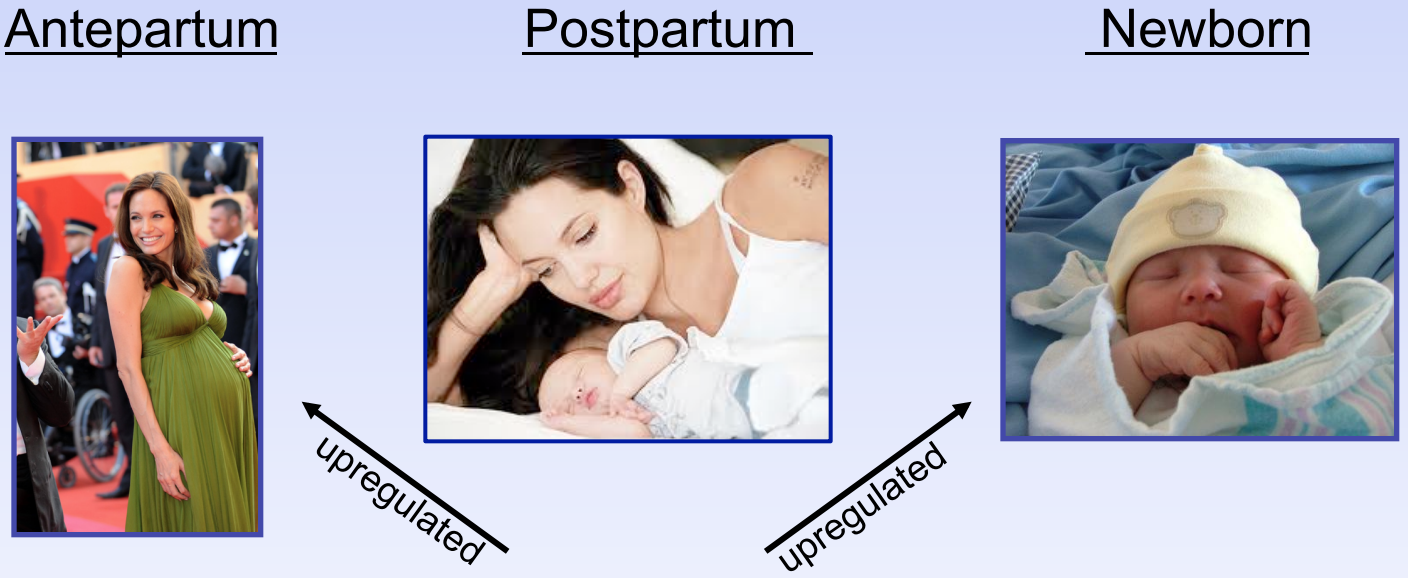
Functional Analysis of Prenatal Gene Expression: Fetal RNA in Maternal Blood

Maron, et al., *J Clin Invest* 2007

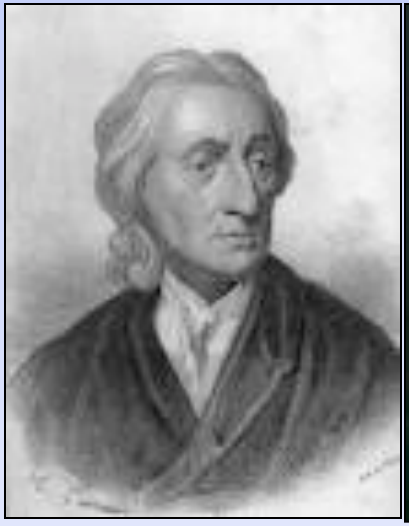
157 genes upregulated in pregnant moms and their babies, vs. postpartum moms.

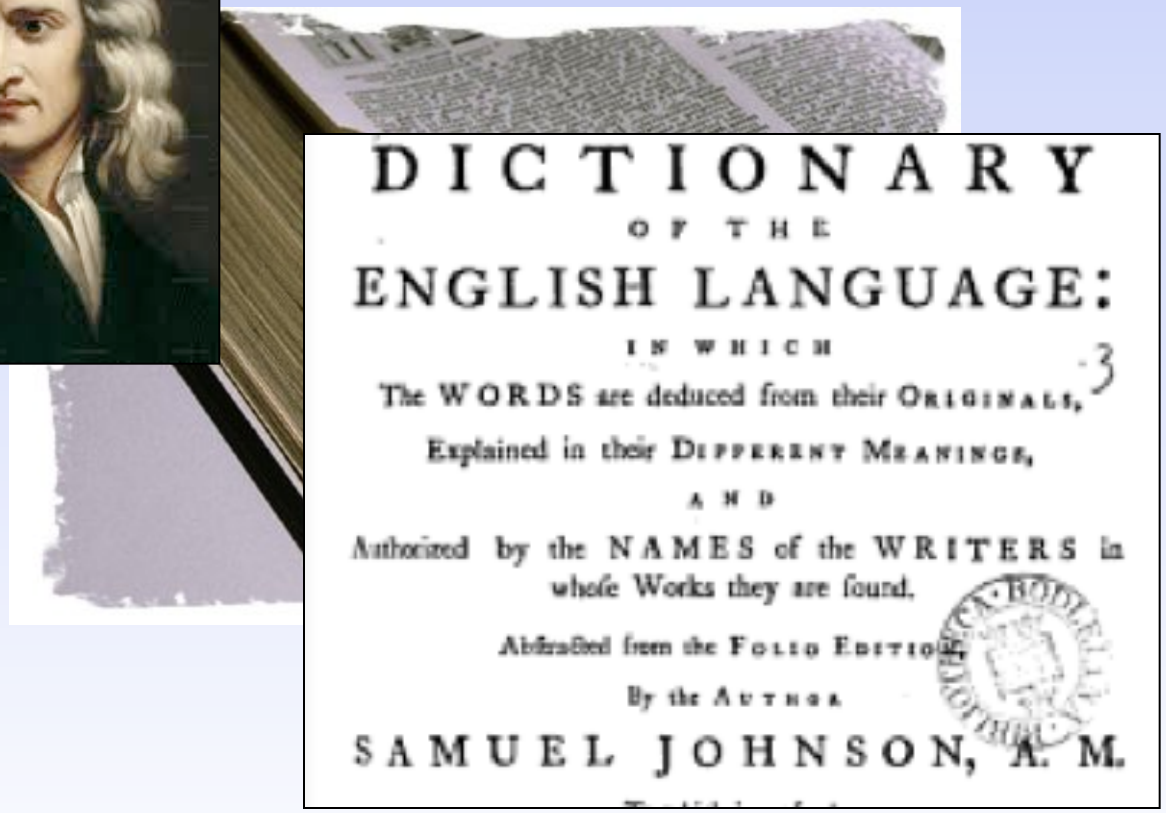


Automated functional analysis hinted at fetal origin

Evidence from manual review was much stronger. Why?

Using the Wrong Dictionary





We need to create our own dictionary.

DFLAT

Developmental FunctionaL Annotation at Tufts

Wick, et al., *BMC Bioinfo* 2014

keywords, genes, developmental processes

PubMed.gov

Manual curation

Literature-derived annotation

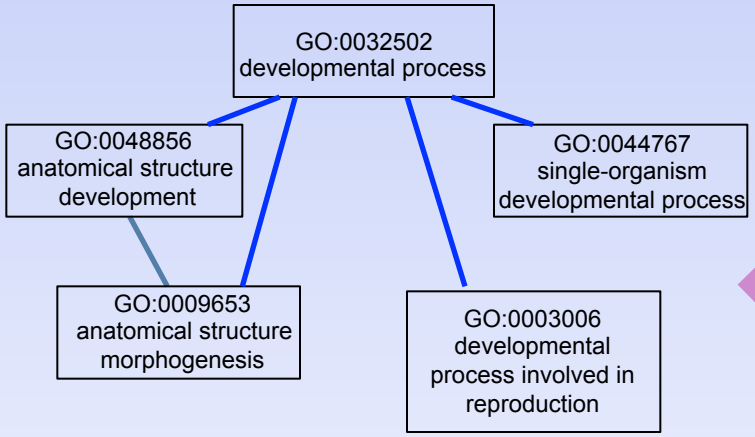
GENEONTOLOGY
Unifying Biology

GONE

DFLAT

Developmental FunctionaL Annotation at Tufts

Wick, et al., *BMC Bioinfo* 2014



Mouse developmental genes

Total: 13,344 new annotations

Human orthologs

Ortholog-derived annotation

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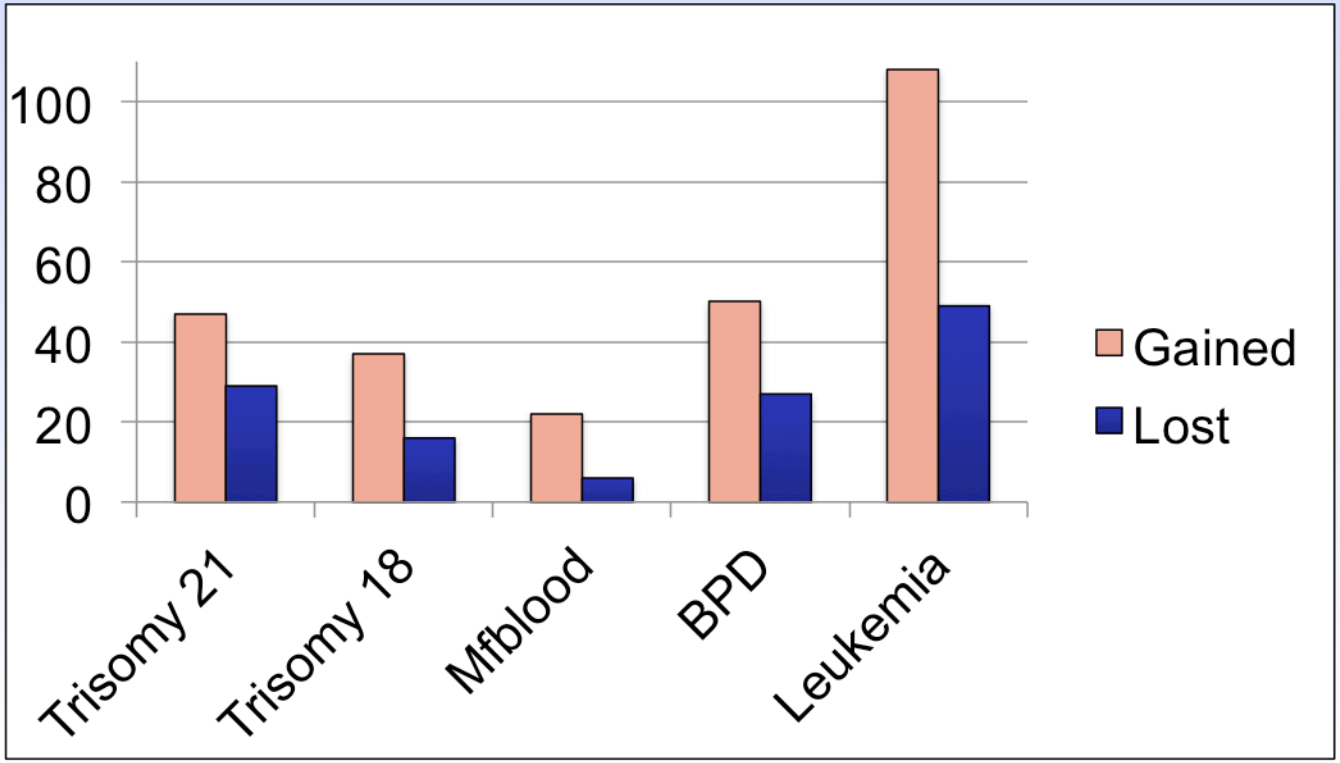
DFLAT's impact on expression analysis

GSEA with GO Biological Process terms

Significant gene sets gained/lost with DFLAT:



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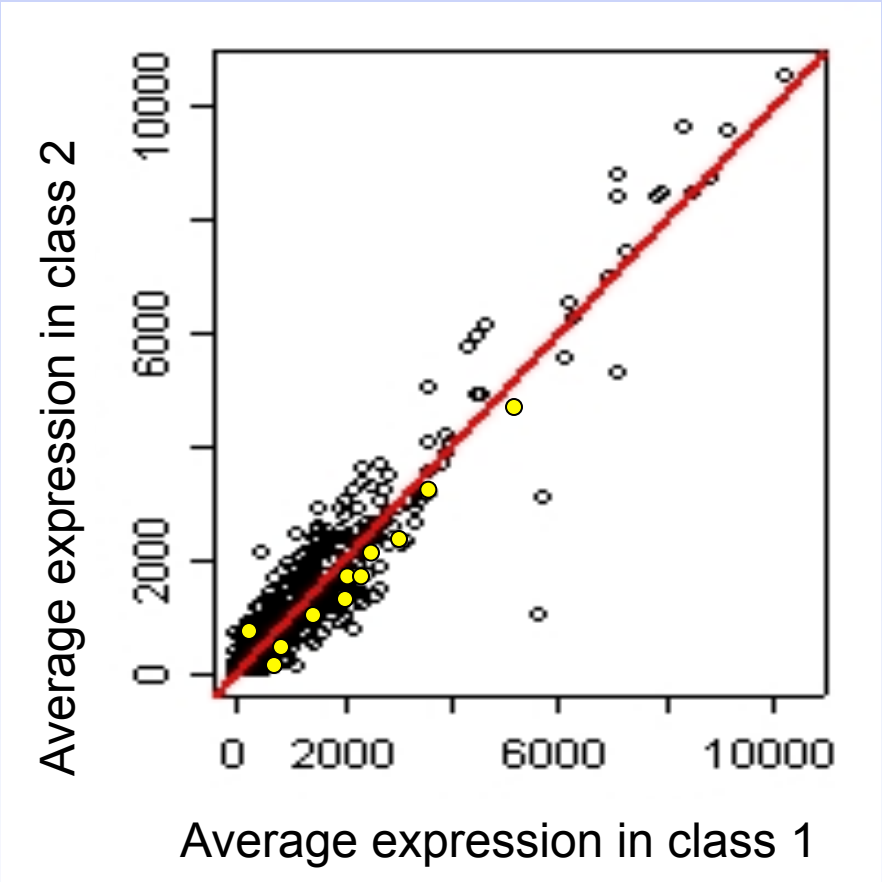
Differential expression in gene *sets*



Differences in expression may be subtle for each gene.

But, if entire set shows consistent changes, we can still detect this.

GSEA software from Broad Institute does this (as do others)

But, need to know gene sets ahead of time.

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Fetal RNA just before birth: New results with DFLAT

"I'm getting ready to feed"

"I am going to be challenged by new odors"

"I will see something soon"

"My bones and muscles are still developing"

"I am going to have to fight bacteria on my own"

"My nervous system is getting ready for me to face the world"

"I'm going to need to breathe for myself"

"Sounds and speech are going to be important to me"

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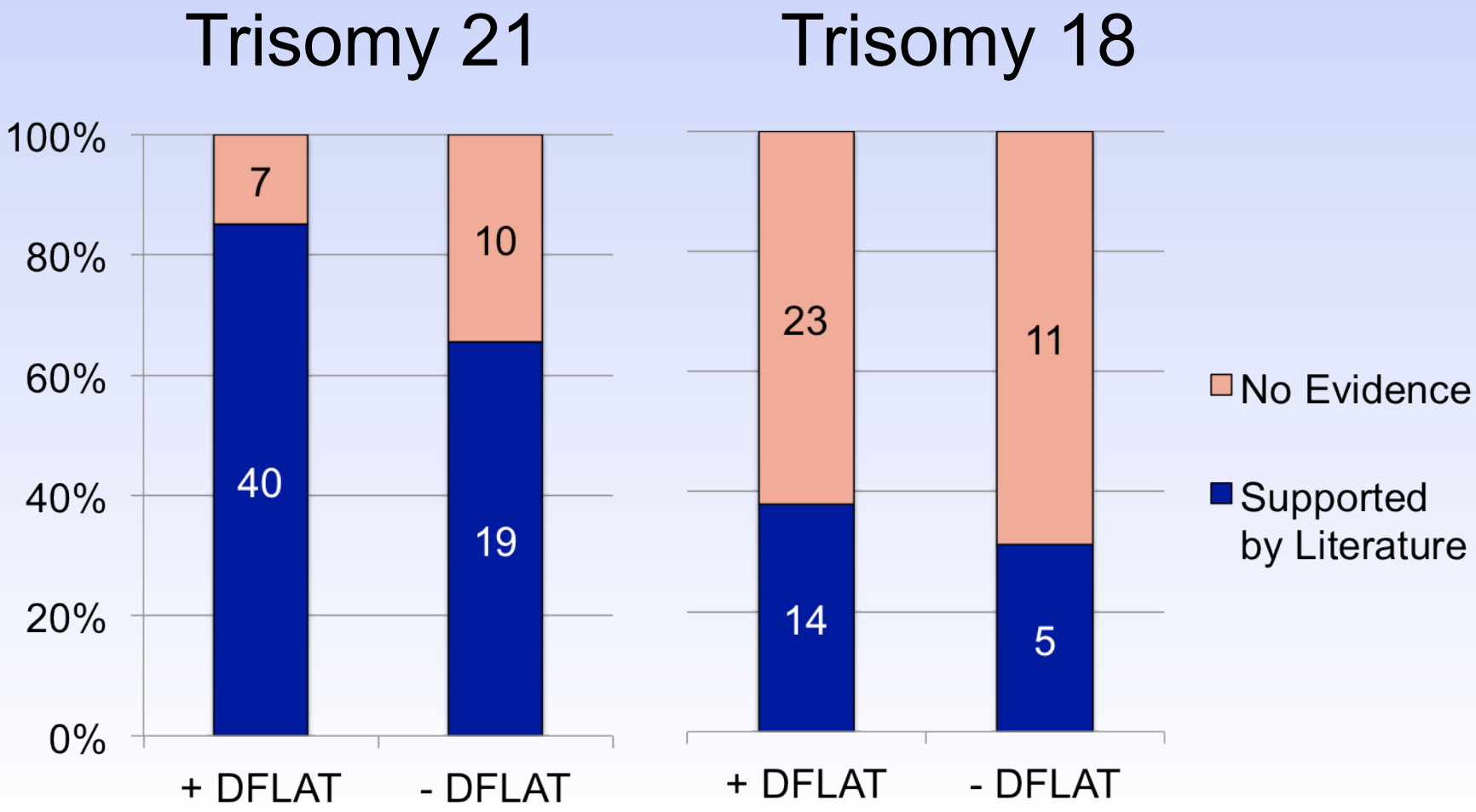
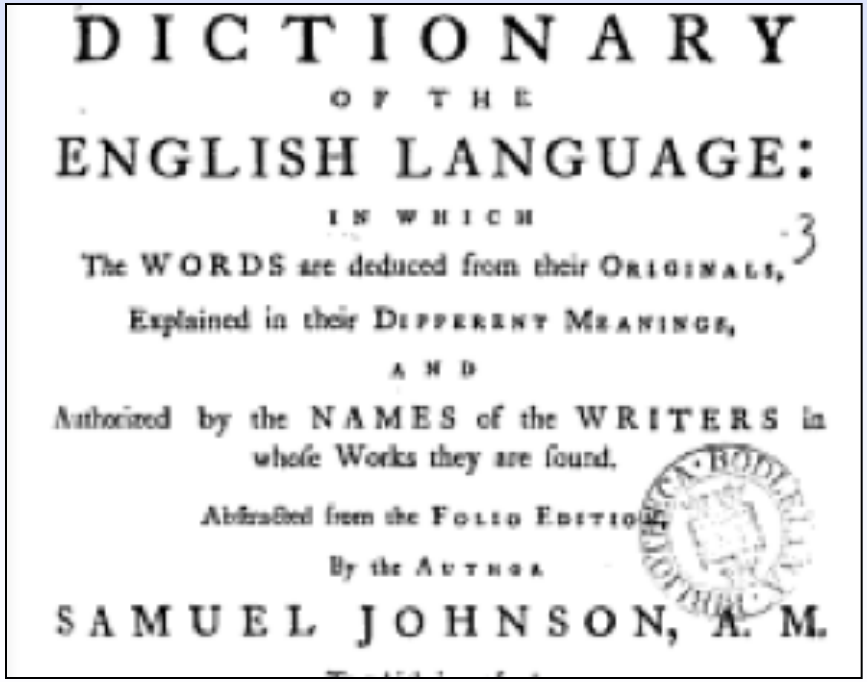
DFLAT's impact on expression analysis

Verified new functions significant ($p < 0.05$) in:



Applying the Dictionary

Characterizing Individual Developmental Anomalies



DICTIONARY

OF THE

ENGLISH LANGUAGE:

IN WHICH

The WORDS are deduced from their ORIGINALS,

Explained in their DIFFERENT MEANINGS,

AND

Authorized by the NAMES of the WRITERS in whose Works they are found.

Abridged from the FOLIO EDITION

By the AUTHOR

SAMUEL JOHNSON, A. M.

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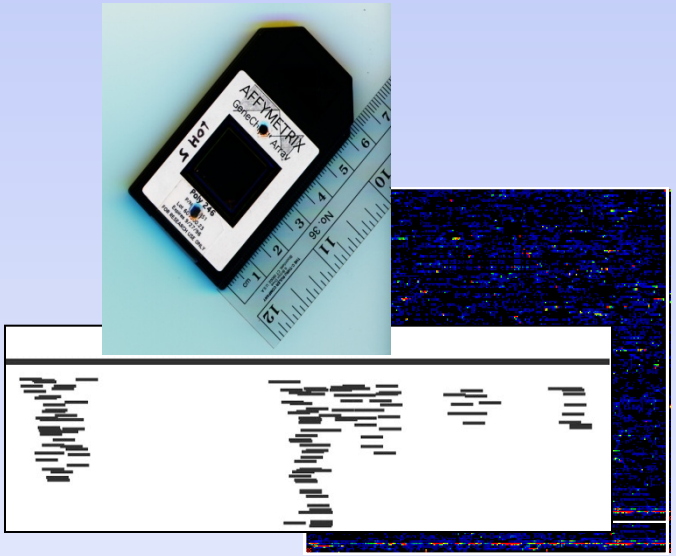
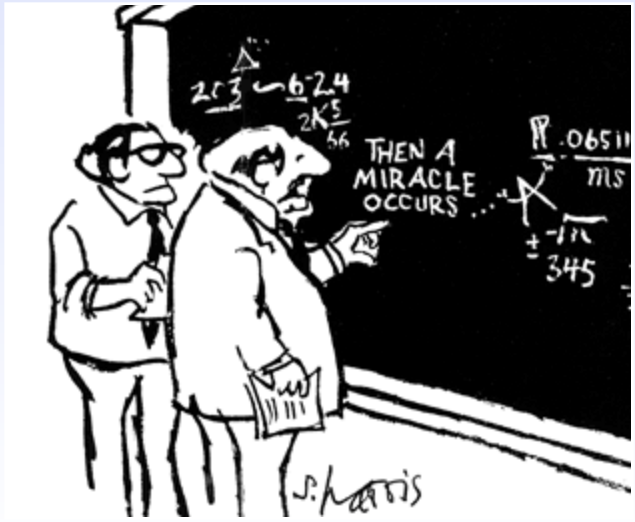
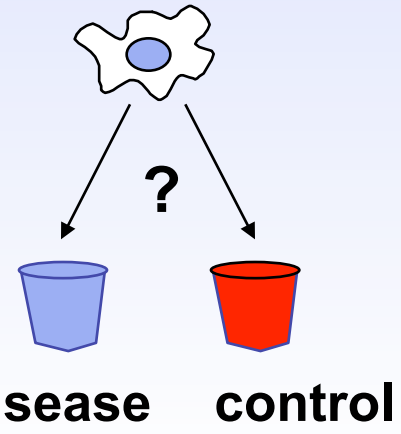
Expression Data Analysis

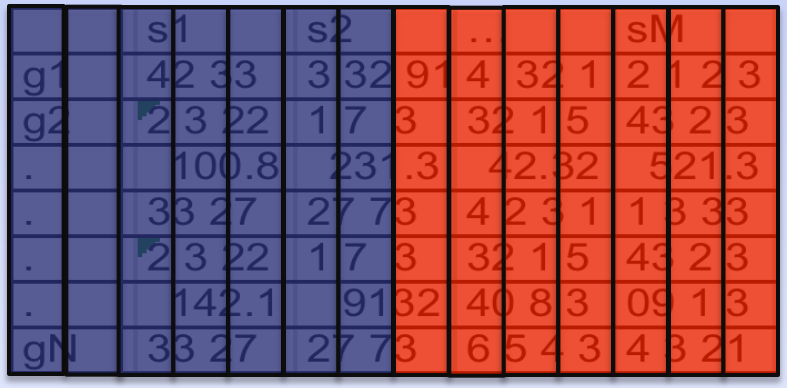


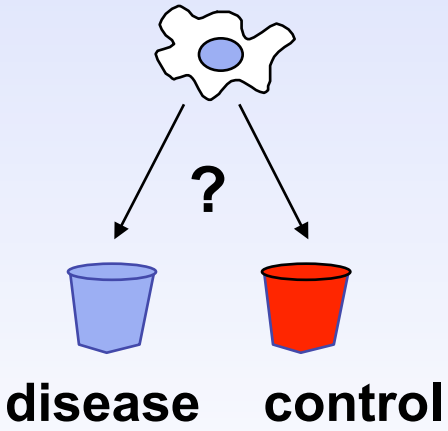
	s1	s2	…	sM
g1	3.2	23		8.2
g2	4.6	4		4.1
.	100.7	143		127
.	33	72		86
.	22.3	16		19
.	66	38		47
gN	5.3	7.2		3.7





Training Data





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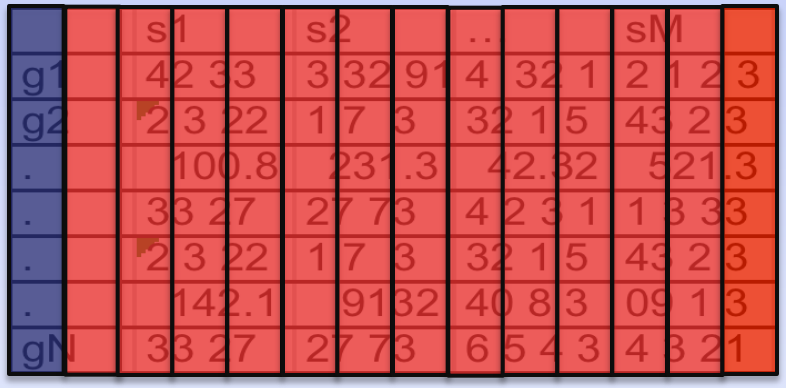
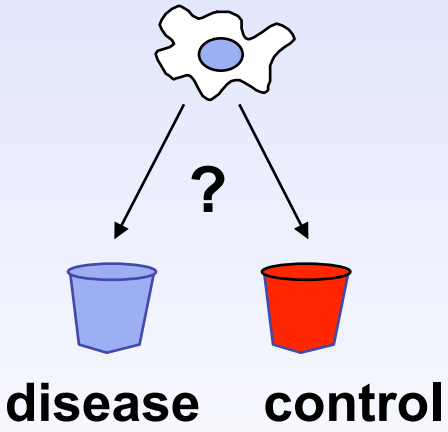
The Challenge of Rare Samples





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Anomaly Detection

Computational field of identifying unusual data points in multi-dimensional space

Training data: normal examples only

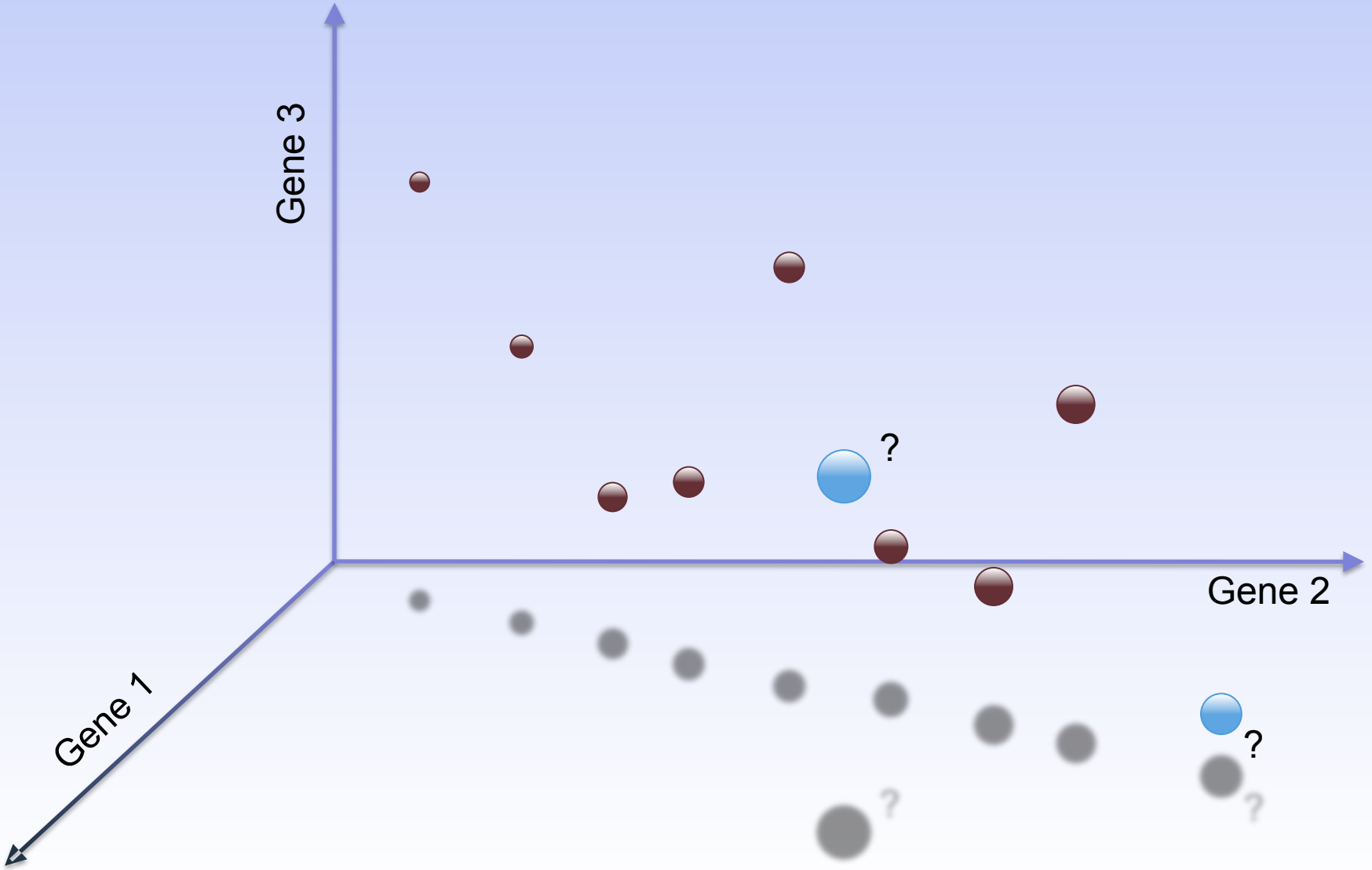
Many methods; best include:

- 1-class SVMs
- Local Outlier Factor (LOF)

But distance-based methods struggle in high-dimensional spaces

Feature Regression and Classification (FRaC)

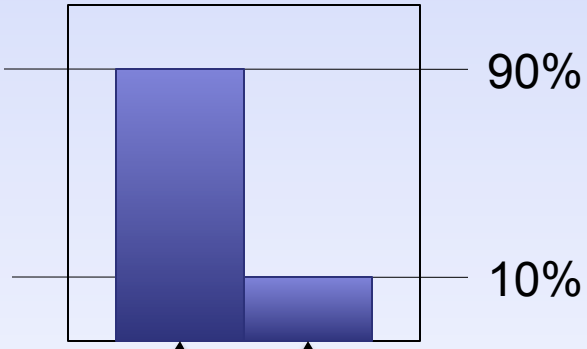
Noto, et al., *Intl Conf Data Min 2010*



Combine Predictors via Information Theory

Features (binary)	Reliability (on Training Data)	Error (on Query Data)
1	50% accuracy	misclassified
2	90% accuracy	correct
3	90% accuracy	misclassified

$$Surprisal = -log_2(p)$$



If I see this, it tells me 0.152 bits of information

If I see this, it tells me 3.32 bits of information

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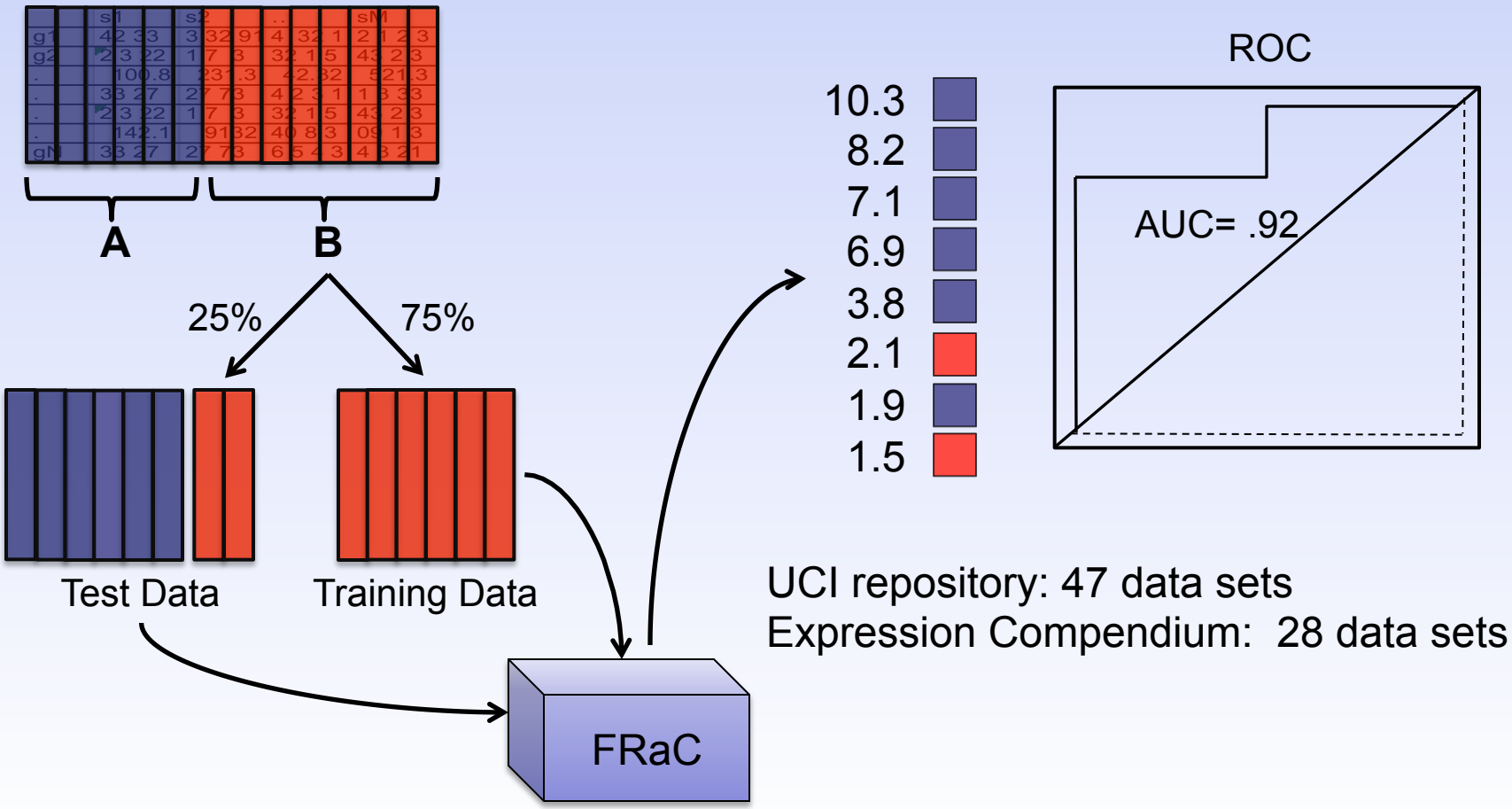
Evaluating Anomaly Detection

Create data sets from classification tasks:

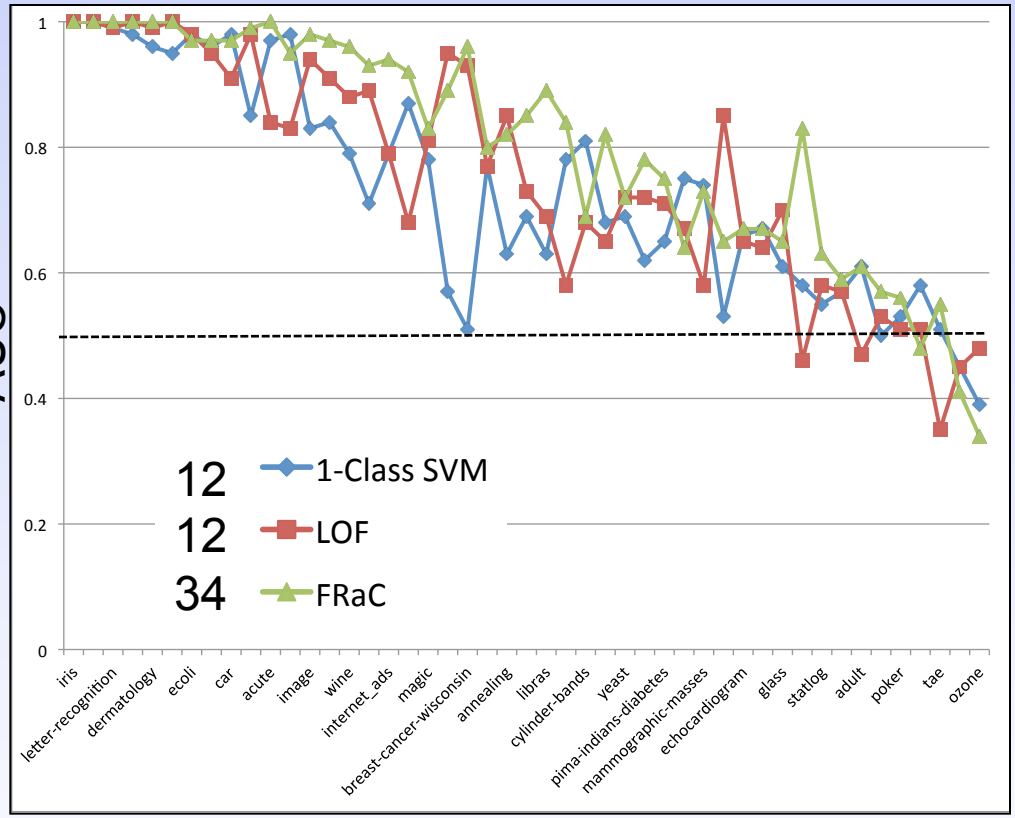


UCI repository: 47 data sets
Expression Compendium: 28 data sets

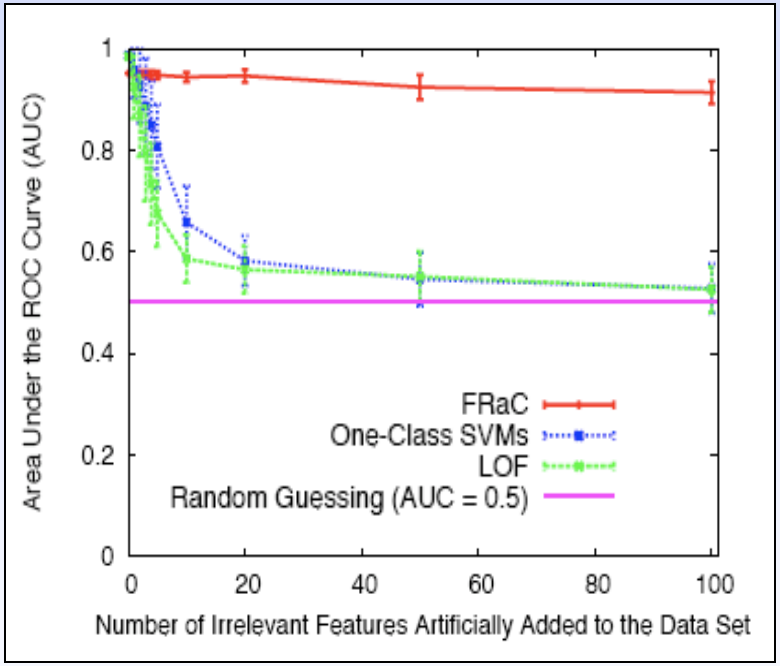
FRaC Wins on Machine Learning Data

47 UCI data sets

Noto, et al., *Data Min Knowl Disc 2012*



Much more robust to irrelevant features



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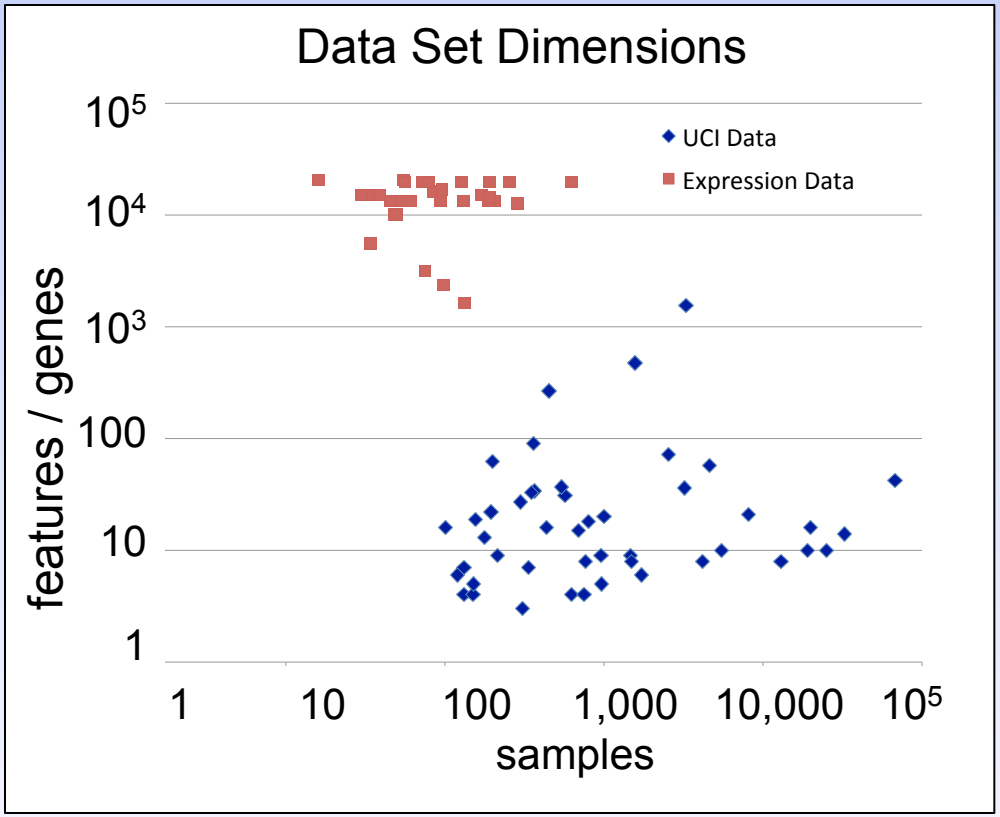
Why Genomic Problems are Harder



Dimensions

Irrelevant genes

Interpretation?

…which gene sets are anomalous?

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CSAX: Characterizing Systematic Anomalies in eXpression Data

Main Idea:

- Rank genes by FRaC surprisal
- Find enriched functions in ranked list of genes (GSEA)

But this “FRaC + enrichment” is not enough…

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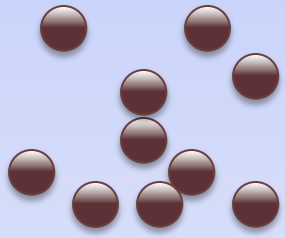
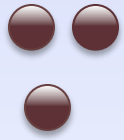
Limited Normal Training Data

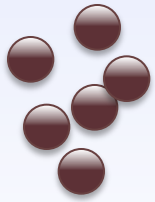
Bare minimum numbers of "normal" examples



Complex, heterogeneous high-dimensional domains



Add cross-validation:



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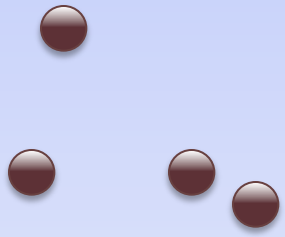

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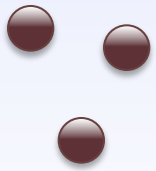

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Limited Normal Training Data

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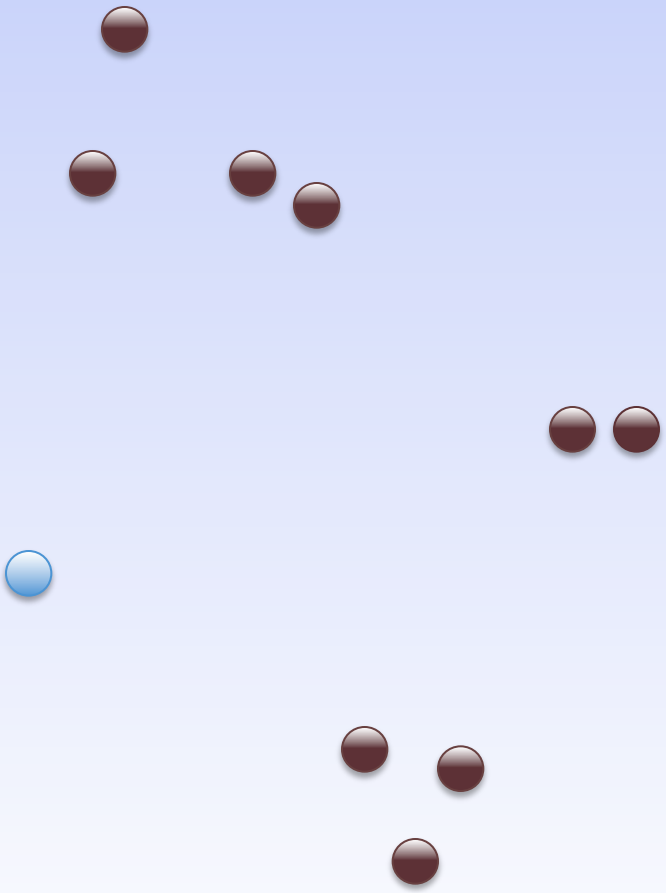
Complex, heterogeneous high-dimensional domains

Add cross-validation:



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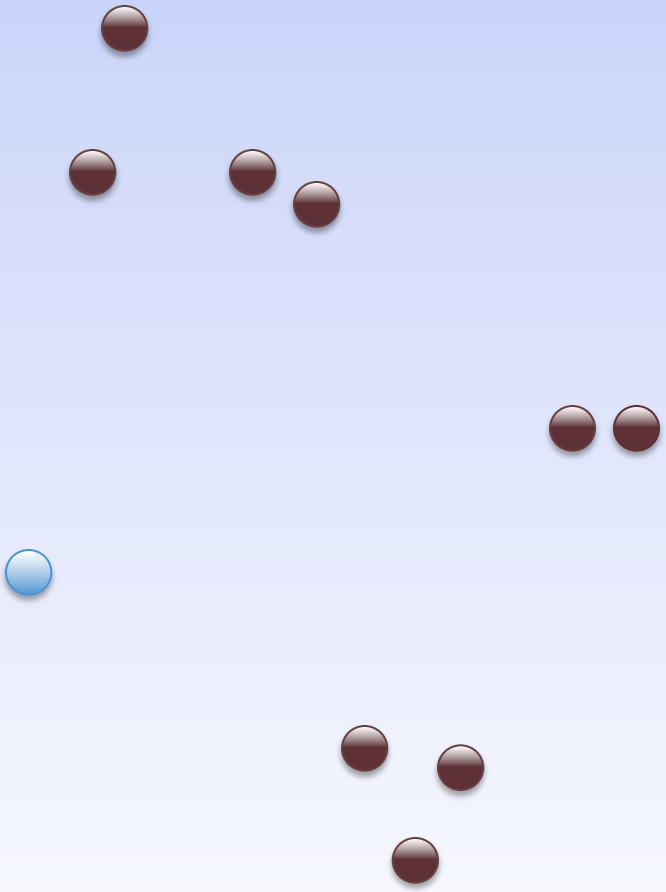
Limited Normal Training Data

Bare minimum numbers of "normal" examples

Complex, heterogeneous high-dimensional domains

Solution: bagging and weighting



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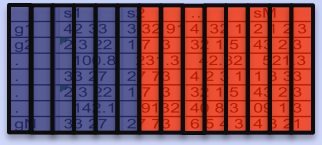
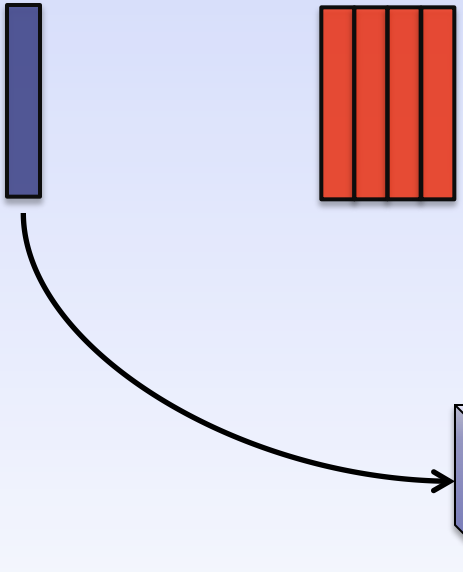
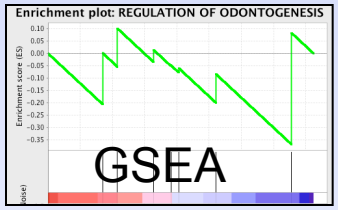


Random 50%



FRaC

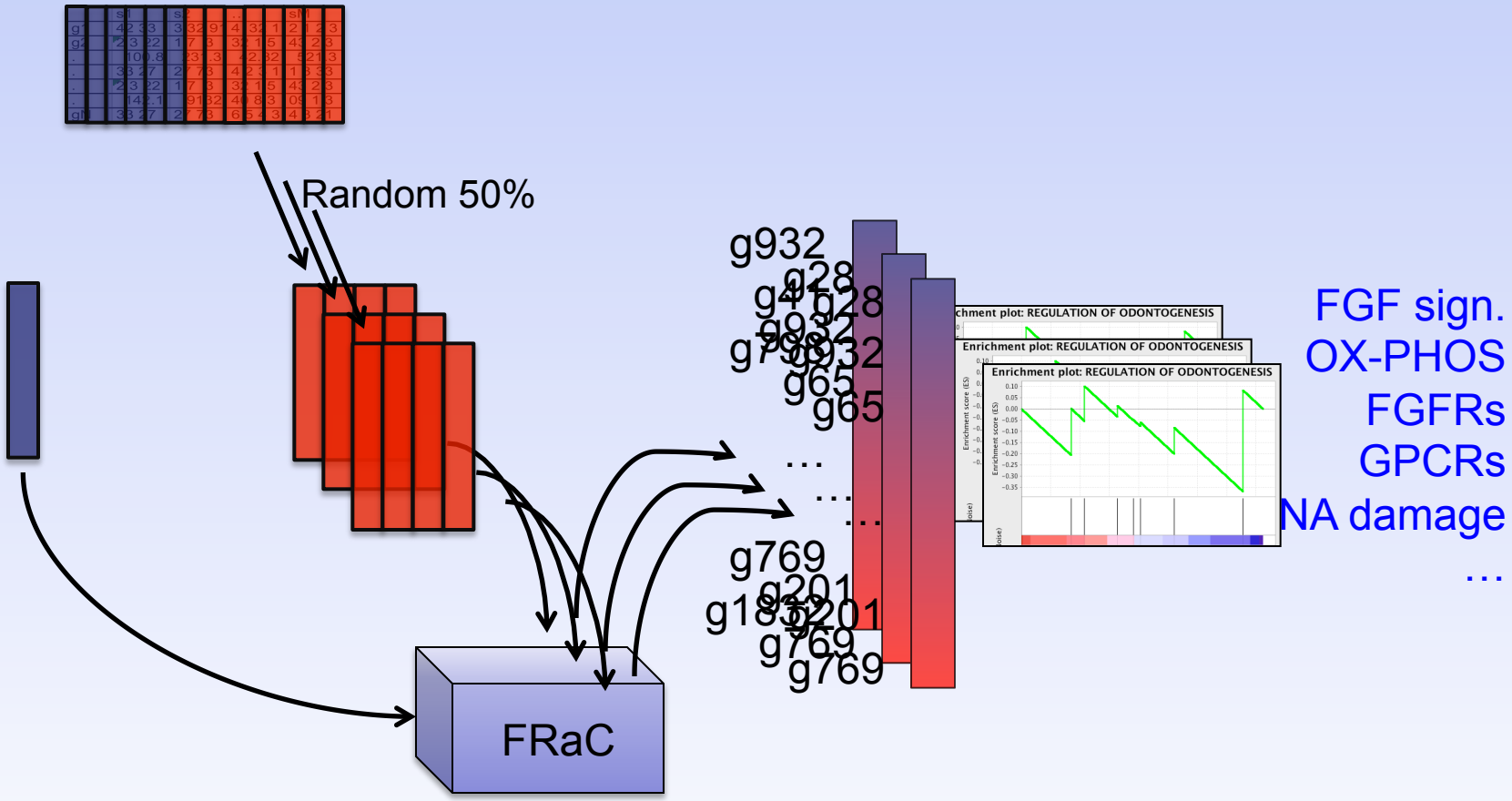
g932
g41
g798
…
g769
g1832



OX-PHOS
FGF sign.
GPCRs
MAPK path
DNA damage
…

Noto, et al., *JCB 2015*

CSAX: Characterizing Systematic Anomalies in eXpression Data



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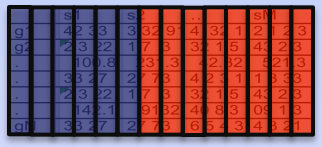
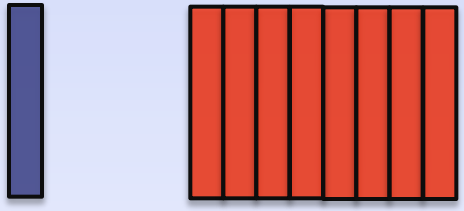
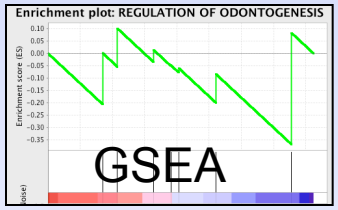




FRaC

g932
g41
g798
…
g769
g1832

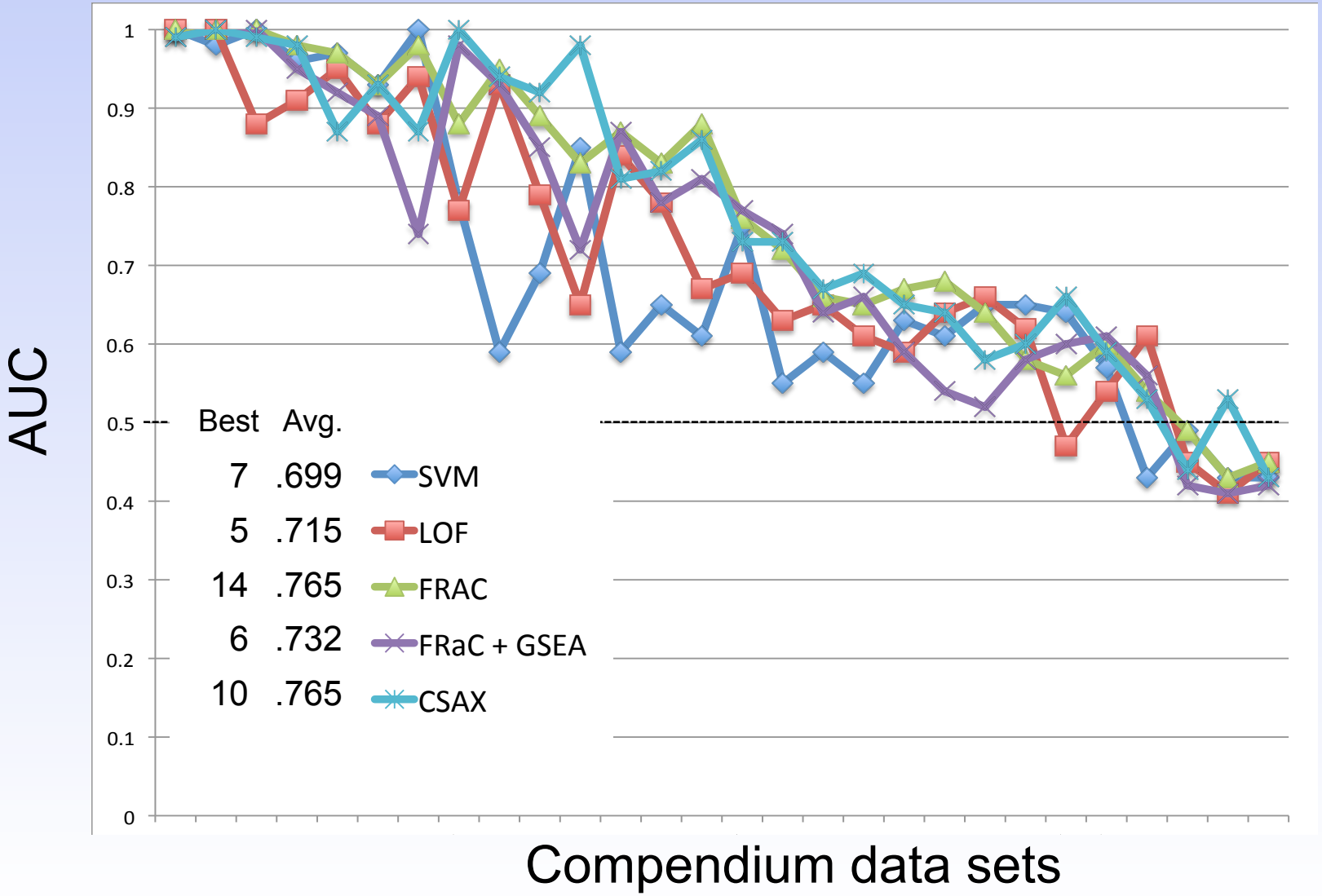


OX-PHOS
GPCRs
MAPK path
DNA damage
WNT sign.
…

Outlier score: combined enrichment scores, weighted by func. of ranks for gene sets

Noto, et al., *JCB 2015*

Outlier Detection for Expression Data



Example: impact of maternal obesity

Amniotic fluid from 17-week fetuses

Normal = mom has healthy BMI

Maternal obesity known to affect neuronal development

Top CSAX pathways (# individuals):

-axonogenesis (2)

-oxidative stress and inflammation (2)

-DNA damage response (1)

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Example: Blood from Preterm Infants

Blood from 100 infants born preterm

“Normal” = no complications during hospital stay

Complications include:

- BPD (pulmonary)
- ROP (vision)
- PVL (brain)

Pietrzky, et al., *PLoS One* 2013

Example: Blood from Preterm Infants

CSAX:

14 with periventricular leukomalacia (PVL)

calcium signaling / homeostasis (in 6 of them)

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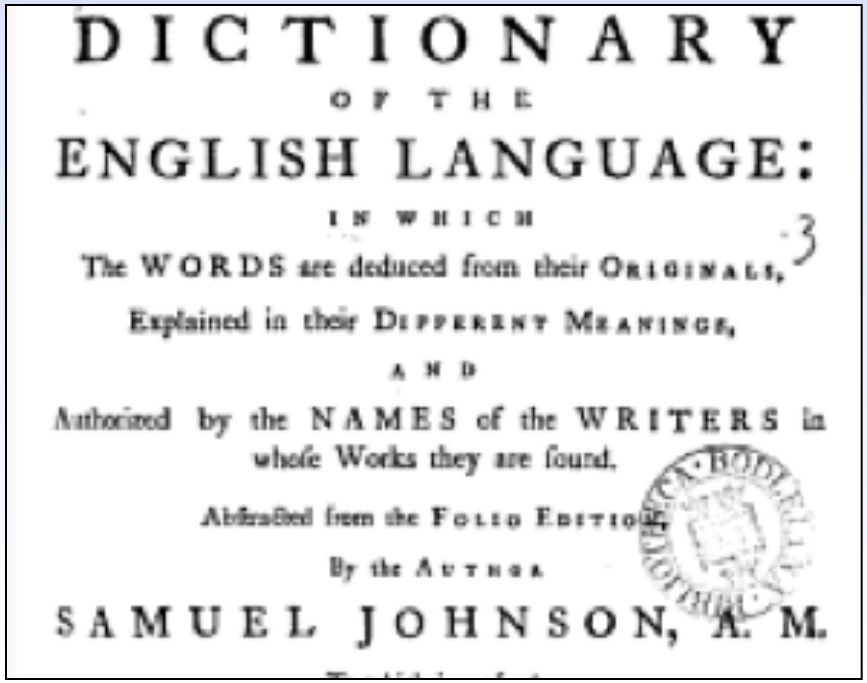
Conclusions

Gene annotation focused on relevant context helps!

Using gene sets derived from this annotation, we can characterize individual anomalies.

Progress toward precision medicine: what does it mean when n=1?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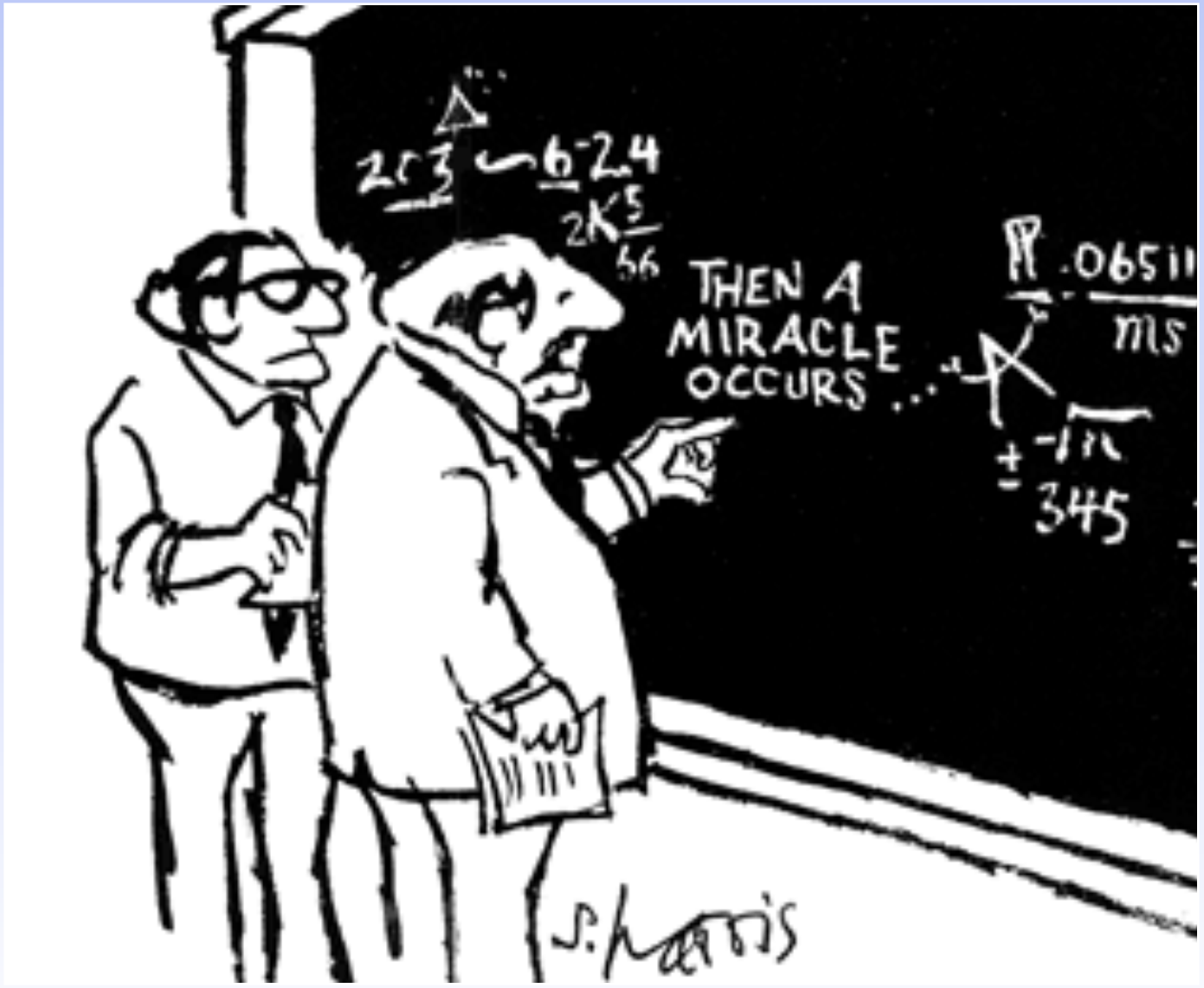
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