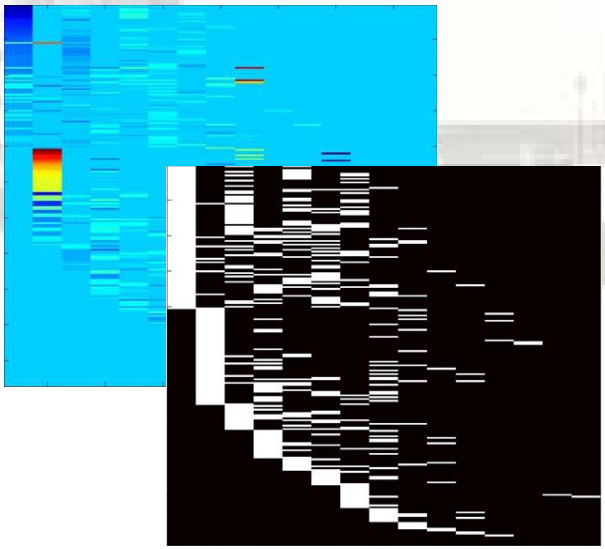
Aspects of Statistical Modelling & Data Analysis in Gene Expression Genomics



Mike West
Duke University

These slides:
www.isds.duke.edu/~mw/downloads/SemStat05

Papers, software, many links:
www.isds.duke.edu/~mw

ABS04 web site: Lecture slides, stats notes, papers, data, links:
www.isds.duke.edu/~mw/ABS04

Integrated Cancer Biology Program
icbp.genome.duke.edu

Genome Institute @ Duke
www.genome.duke.edu

#1 **Genomics, Microarrays, Data:**
Big picture

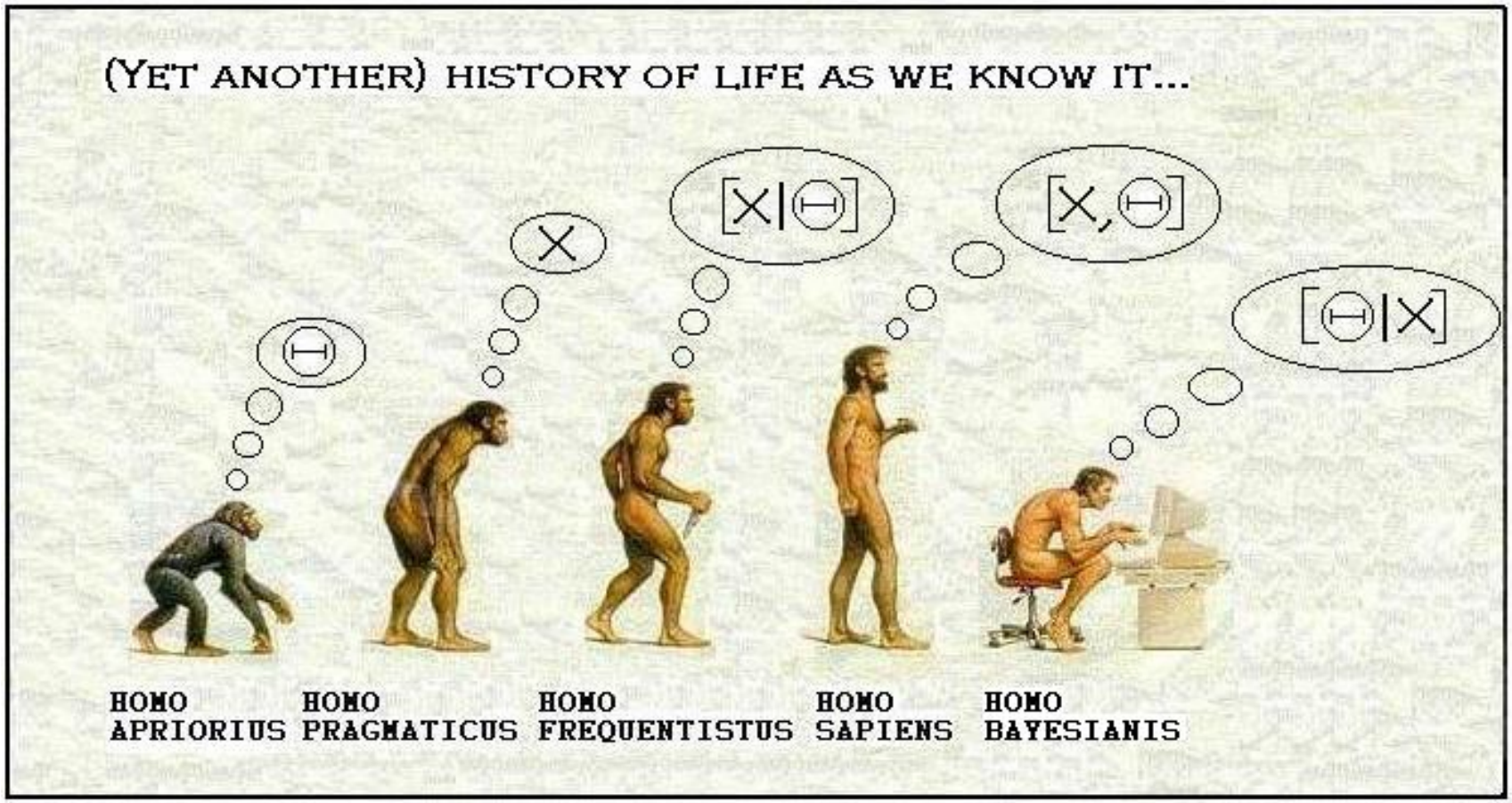
#2 **Bayesics - Regression and Shrinkage:**
Gene expression as predictors

#3 **Patterns and Factors:**
Prediction via pattern profiling

#4 **Sparse Modelling:**
Regression subset-structure uncertainty

#5 **Sparse Models and Profiling:**
Gene expression as response: Designed experiments

#6 **Sparse Models and Profiling:**
Gene expression as response: Latent factor models


(YET ANOTHER) HISTORY OF LIFE AS WE KNOW IT...
[X|Θ]
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X
Θ
HOMO APRIORIUS
HOMO PRAGMATICUS
HOMO FREQUENTISTUS
HOMO SAPIENS
HOMO BAYESIANIS

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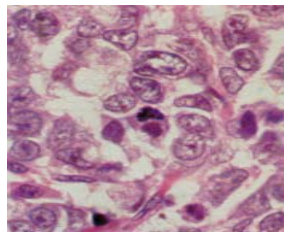
Transitions in Biology: Data and Observation

Observational science



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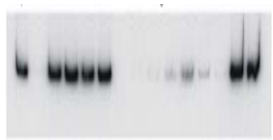
Molecular science



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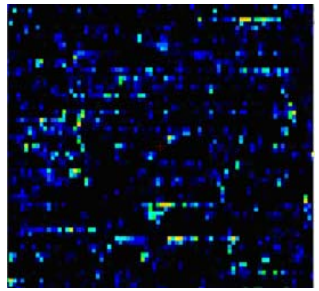
Genomic science

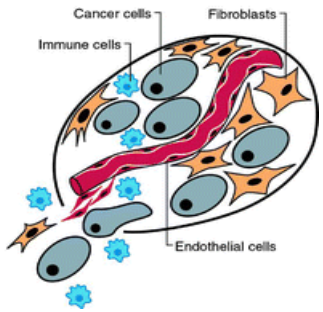


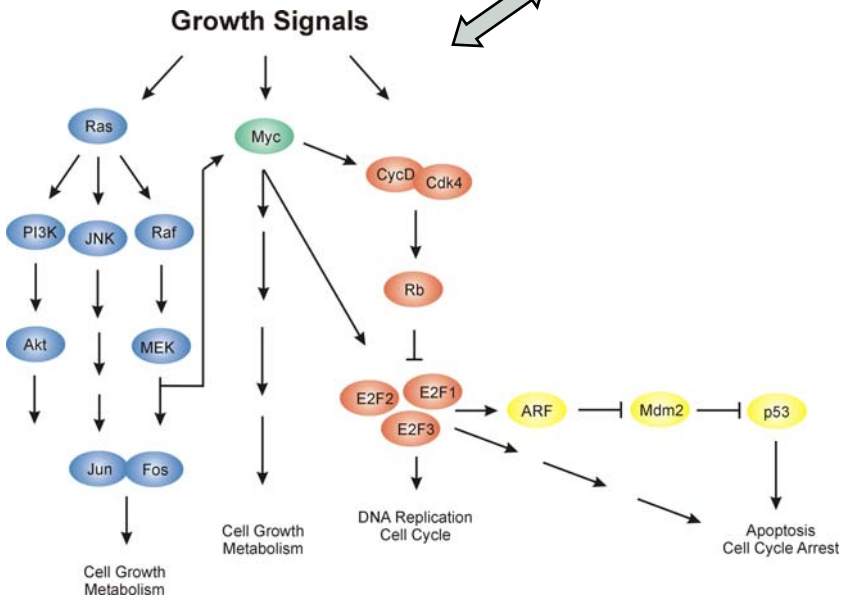
Data: Scale, Complexity –

Computational & Statistical Science

Low resolution phenotypes

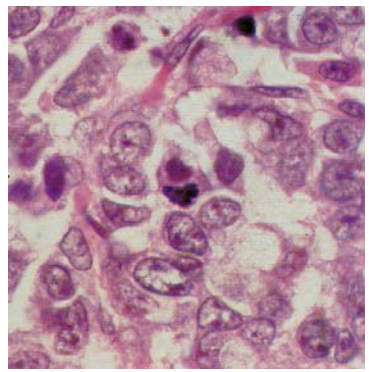
"Small worlds", small data

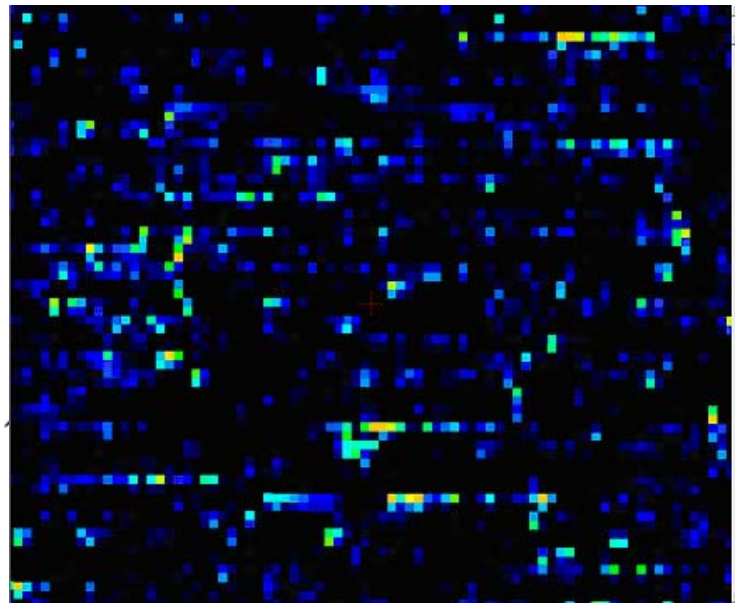




Breast cancer:

Lymph node involvement
Hormone receptor status
Tumor size
Visual assessment





Higher resolution

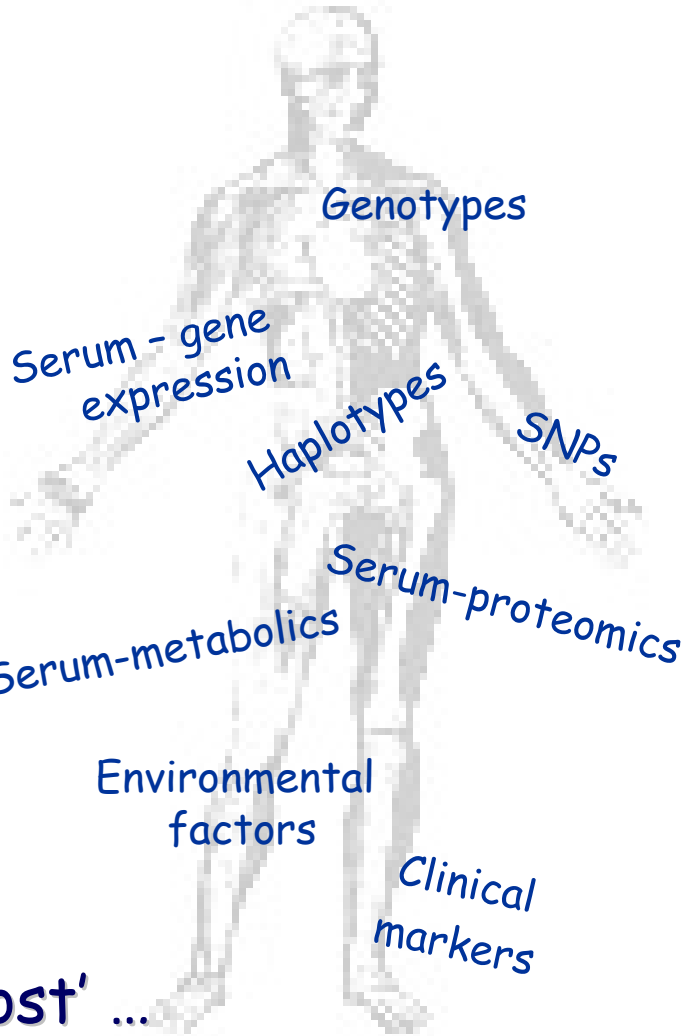
Genome scale, big data

Increased understanding

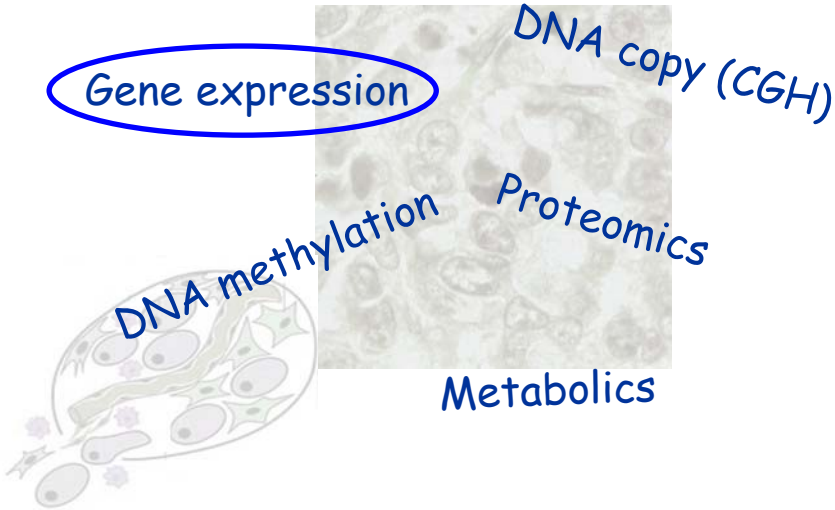
$$p(X)$$

$$p(Y|X)$$

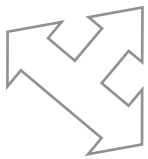
Improved prediction

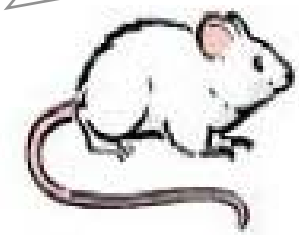


Biological/disease state …



Data from Experiment and Observation: Challenges





Translation of inferences

Gene expression profiles:
Signatures of states

Laboratory/In vitro

Laboratory/Animal models

Human Observational Studies

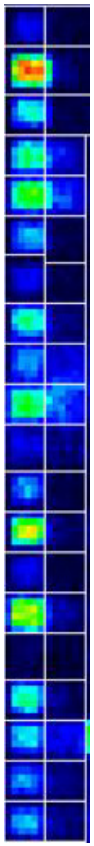
Human Clinical Studies

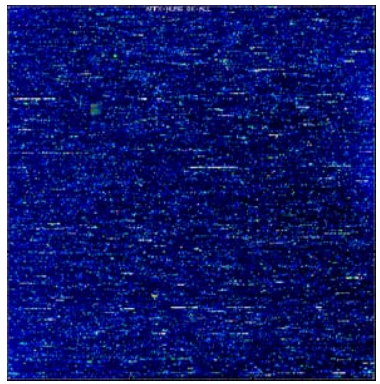
Affymetrix DNA Microarray Data

Gene probesets

Imaging/Scanning

100Mb raw data





Expression intensity estimates X+/-S

p genes, n samples

Background, noise, gross defects, …

Cross-hybridization

Sample-sample normalisation

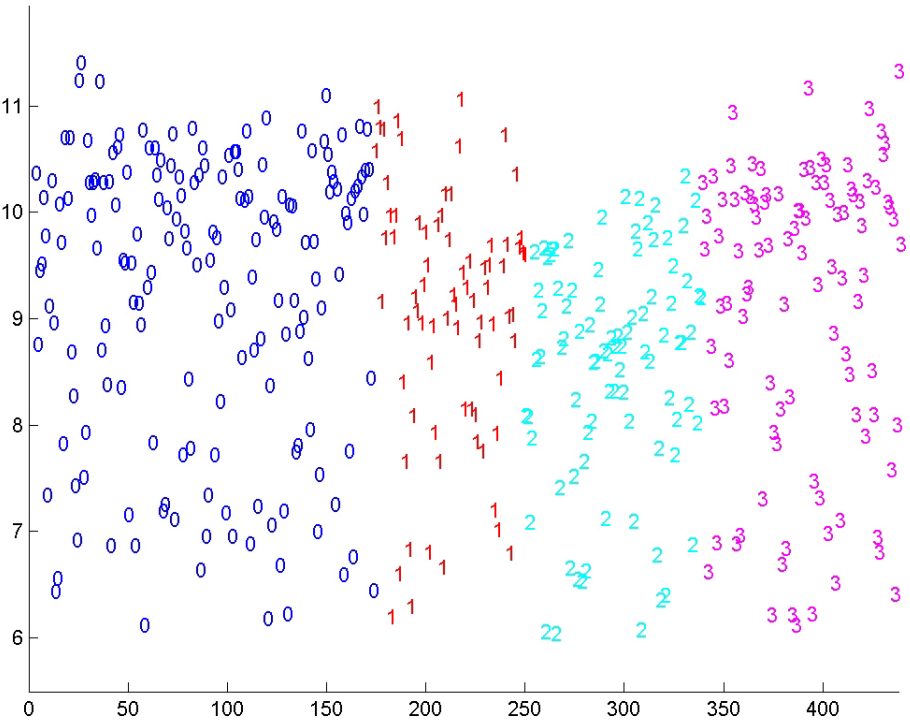
'Low level" data processing, analysis

West et al 2001

Wong & Li (dChip) 2001

Bolstad, Irizarry, Speed et al 2003a,b

RMA estimates – www.bioconductor.org



Multiple expression data sets

Multiple array technologies

Multiple species:
genome A – B mappings

Same array platform:
sample/lab/study/gene effects

Assay/batch/reagent/hybridisation sensitivities

...

Sporadic - Sparse

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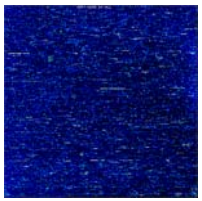
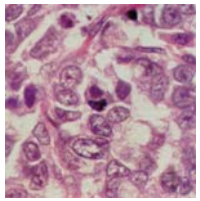
Gene expression as covariates (predictors)
Molecular phenotyping:



x



y

$p(y|x)$

- Predict aggressive vs. benign
- Disease susceptible vs. resistance
- Drug/treatment response
- Finding genes linked to response
- Patterns of association among genes
- Signatures of effect – multiple genes

$$z = H\beta + \nu, \quad \nu \sim N(0, \sigma^2 I)$$

Phenotype z

H ~ subsets of genes

LSE:

$$\hat{\beta} = B_*^{-1} H' z$$

$$B_* = H'H$$

(minimal) Bayes: Shrinkage priors

Decision theory
Regularisation - Ridge regression
Key with many predictors
Relevance of zero-mean location

Prior: $\beta | C \sim N(0, C^{-1})$

Posterior: $\beta | z, C \sim N(b, \sigma^2 B^{-1})$

Shrinkage:

$$b = B^{-1} H' z$$

$$B = \sigma^2 C + H'H$$

Degrees and Dimensions of Shrinkage

$$\beta \sim N(0, C^{-1})$$

$$C^{-1} = \tau I, \quad \tau \sim \text{InvGamma}$$

LSE as limiting case – no shrinkage: $\tau^{-1} \to 0$

Shrinks when it matters – weak/no association

Acts against over-fitting, improves stability and robustness in prediction

$$C^{-1} = \text{diag}(\tau_1, \ldots, \tau_k), \quad \tau_j \sim \text{InvGamma}$$

Multiple shrinkage

$$\beta' = (\beta_1, \ldots, \beta_k)$$

"Shrinks out" irrelevant covariates

$$\beta_j \sim N(0, \tau_j)$$

Simulate Posterior:

Iteratively resample conditional posteriors

Sample means, histograms
MC approximation of posterior

$$p(\beta|z,C) = N(b, \sigma^2 B^{-1})$$

$$p(C|z,\beta) = \prod_{j=1}^{k} p(\tau_j|\beta_j)$$

Modules in MCMC
e.g. response error variance

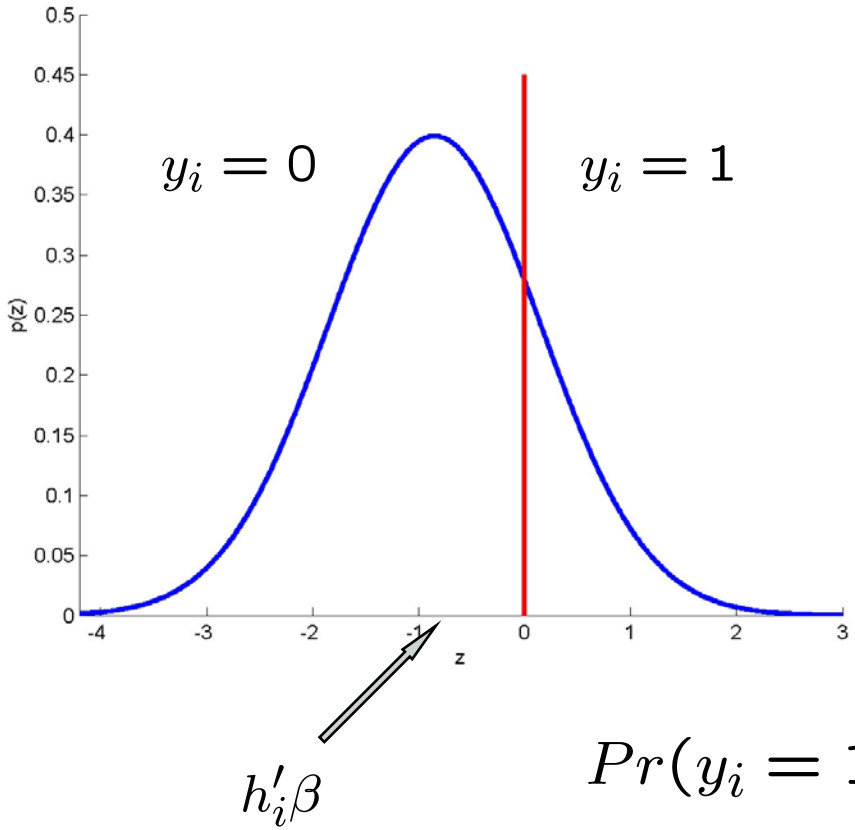
$$p(\beta|z, C, \sigma^2) = N(b, \sigma^2 B^{-1})$$

$$p(C|z, \beta, \sigma^2) = \prod_{j=1}^{k} p(\tau_j|\beta_j)$$

$$p(\sigma^2|z, \beta, C) = \text{InvGamma}$$

Binary = thresholded latent continuous

probit~normal, logit~logistic, …



$$Pr(y_i = 1) = \Phi(h_i'\beta)$$

Natural model/intepretation

Computationally nice

$$Pr(y_i = 1) = Pr(z_i > 0), \quad z_i \sim N(h_i'\beta, 1)$$

$$z = H\beta + \nu, \quad \nu \sim N(0, I)$$

Linear model if z known

Add module to impute latent z
MC samples for z
Easy summary, prediction

$$p(\beta|z,C) = N(b, B^{-1})$$

$$p(C|z,\beta) = \prod_{j=1}^{k} p(\tau_j|\beta_j)$$

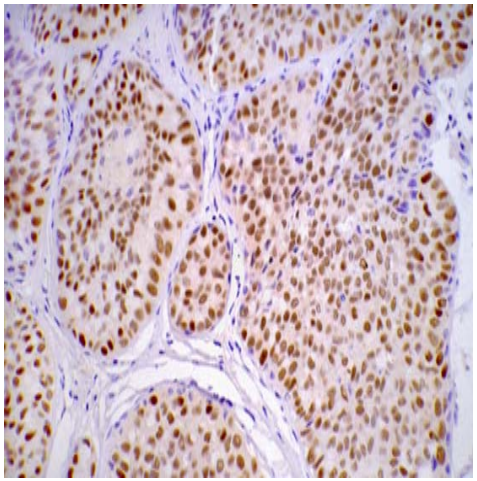
$$p(z|y,\beta) = \prod_{i=1}^{n} p(z_i|y_i,\beta)$$

y=0/1 (ER -/+)
Protein assay
Immunohistochemical staining
0/1 (0-3)

Basic Examples: Breast Cancer Data

ER – (O)Estrogen Receptor Status
HER2 hormone status
Lymph node (recurrence risk) status

Frozen tumour: Gene expression
Higher resolution
Future clinical tests: Pr(ER+)



ER positive tumour

IHC for Estrogen Receptor
(~60x magnification)

nuclei of breast epithelial cells
cytoplasm of breast epithelial cells

brown-red & pink ~ ER+

nucleii of stromal cells; collagen

(PNAS 2001 breast cancer)

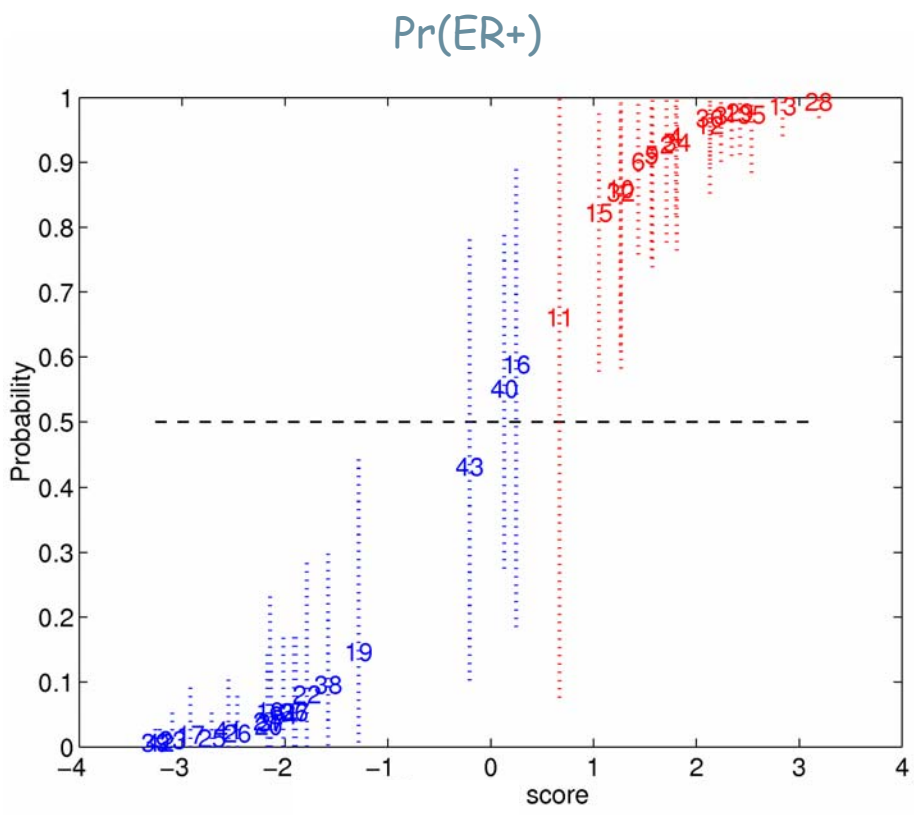
Leave-one-out Cross-Validation (CV) analysis:

"Honest" assessment of precision

Heterogeneity, small samples

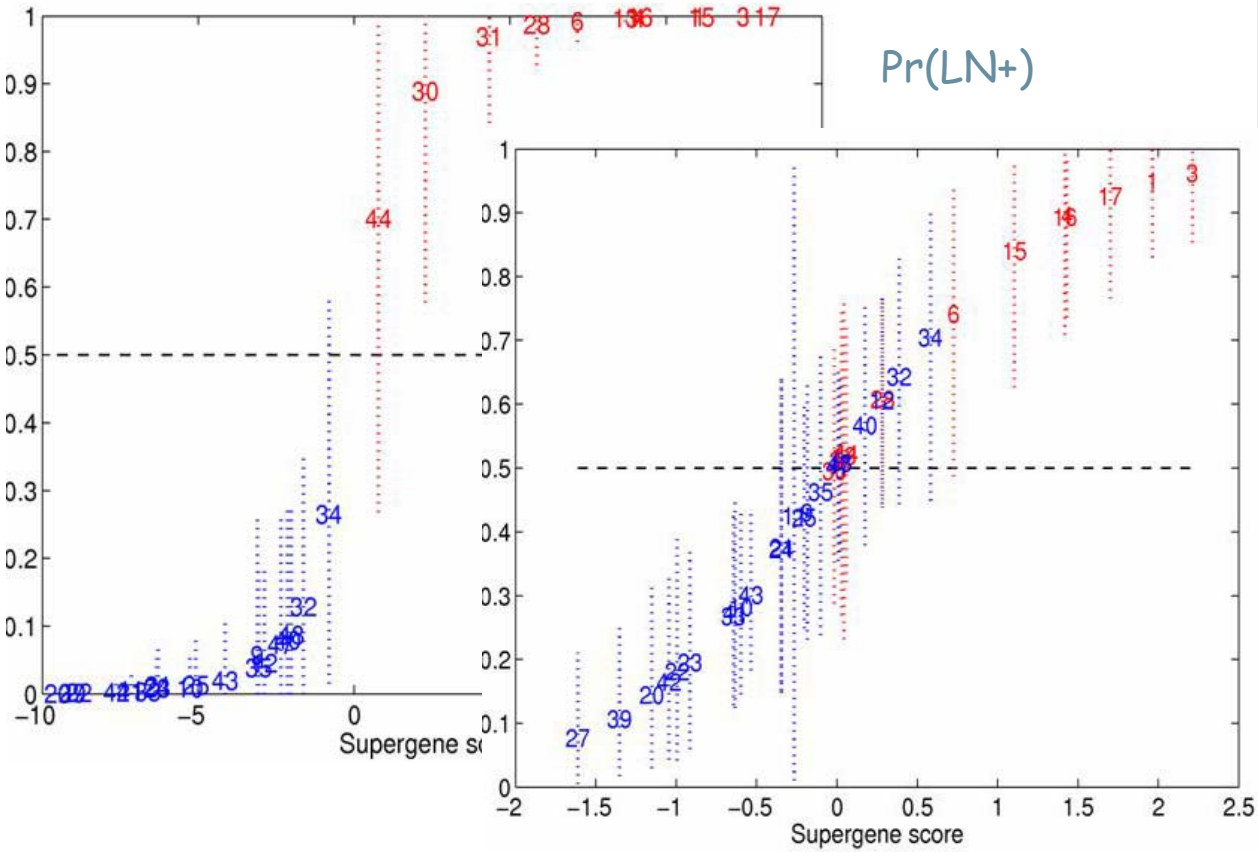
Feature/Variable selection

Critical (dominant) component of predictive assessment



Predicting lymph node status

Pre-selection of 100 genes
vs.
"Honest" CV predictions



Large p:

Small models-
Sparsity

Variable selection, Uncertainty

Complex interdependencies

Multiplicities

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Many Related Predictors: Patterns as Predictors

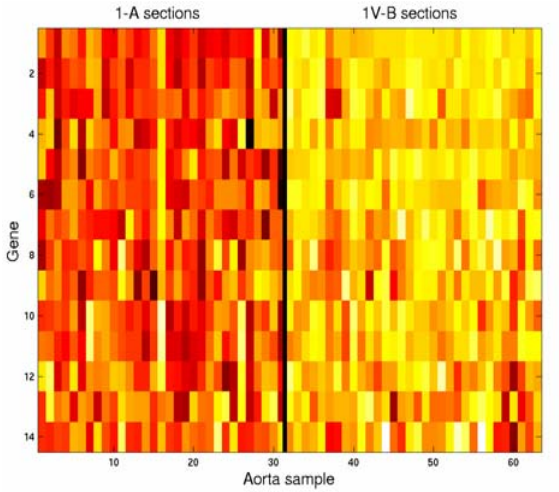
Patterns of coordinately expressed genes:

- Signatures

Metagenes

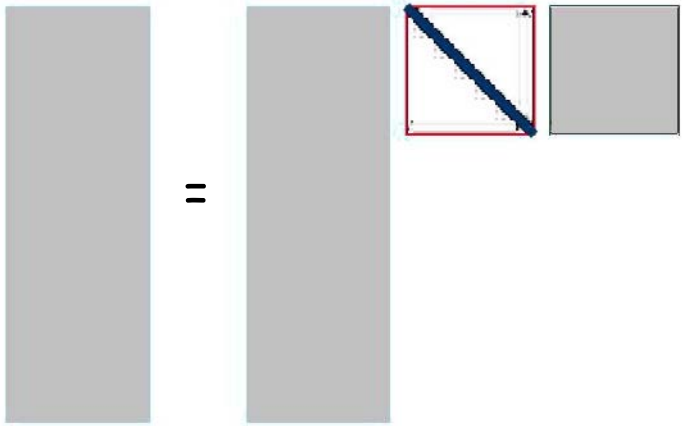
PCA, SVD of expression data

- Biologically selected gene subsets
- Trained subset selection
- Clusters



Cardiovascular disease: High/Low
(Seo, West et al 2004)

SVD: $X = ADF$



$$z = X'\beta_x + \nu$$

Genes X

$$z = F'\beta_f + \nu$$

Metagene factors F

Patterns: Factors "underlying" X are predictors

X variable set selection

p=n:
Shrinkage priors key
F variable selection

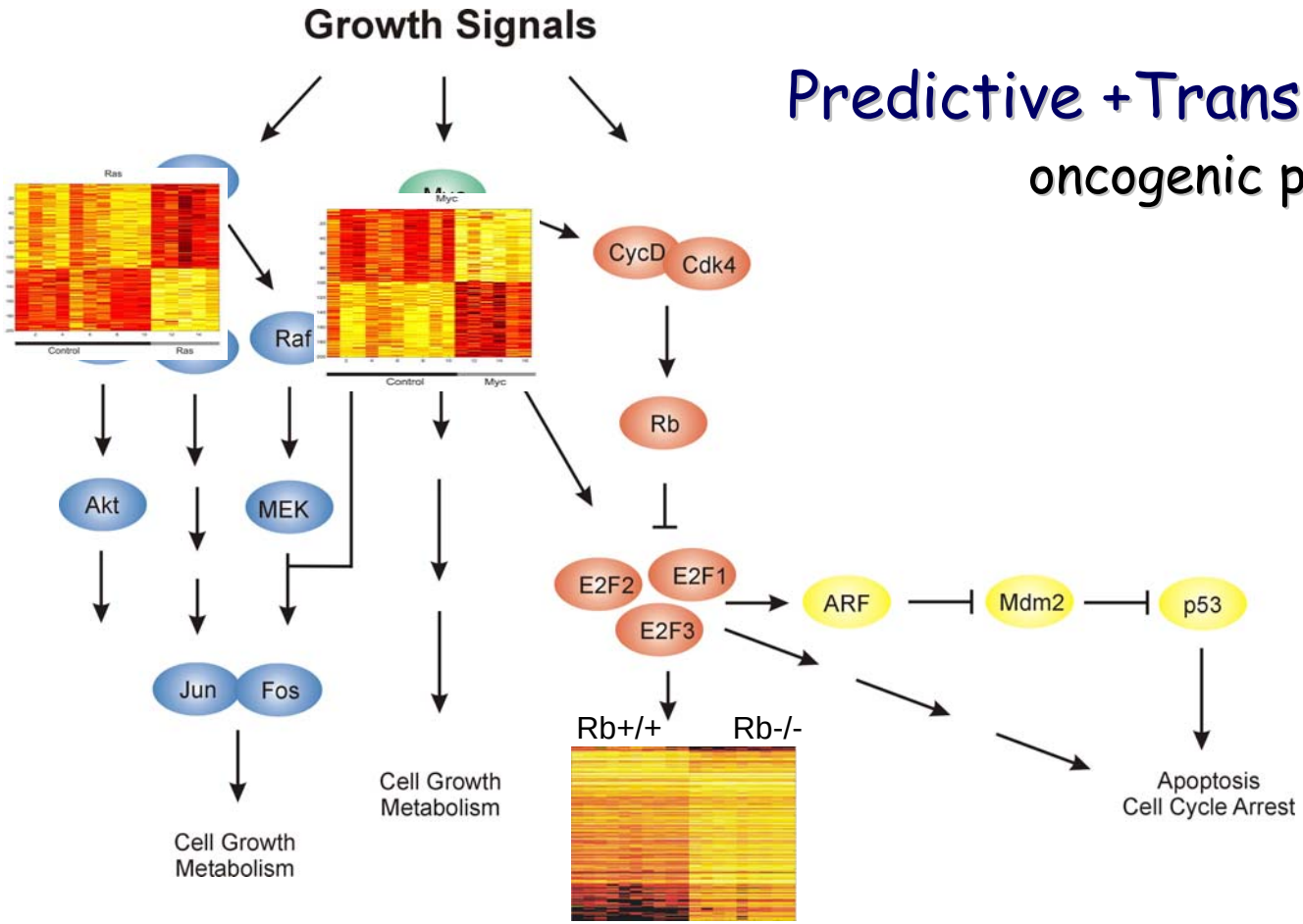
PCA: $XX' = AD^2A'$

$$\beta_f = DA'\beta_x$$

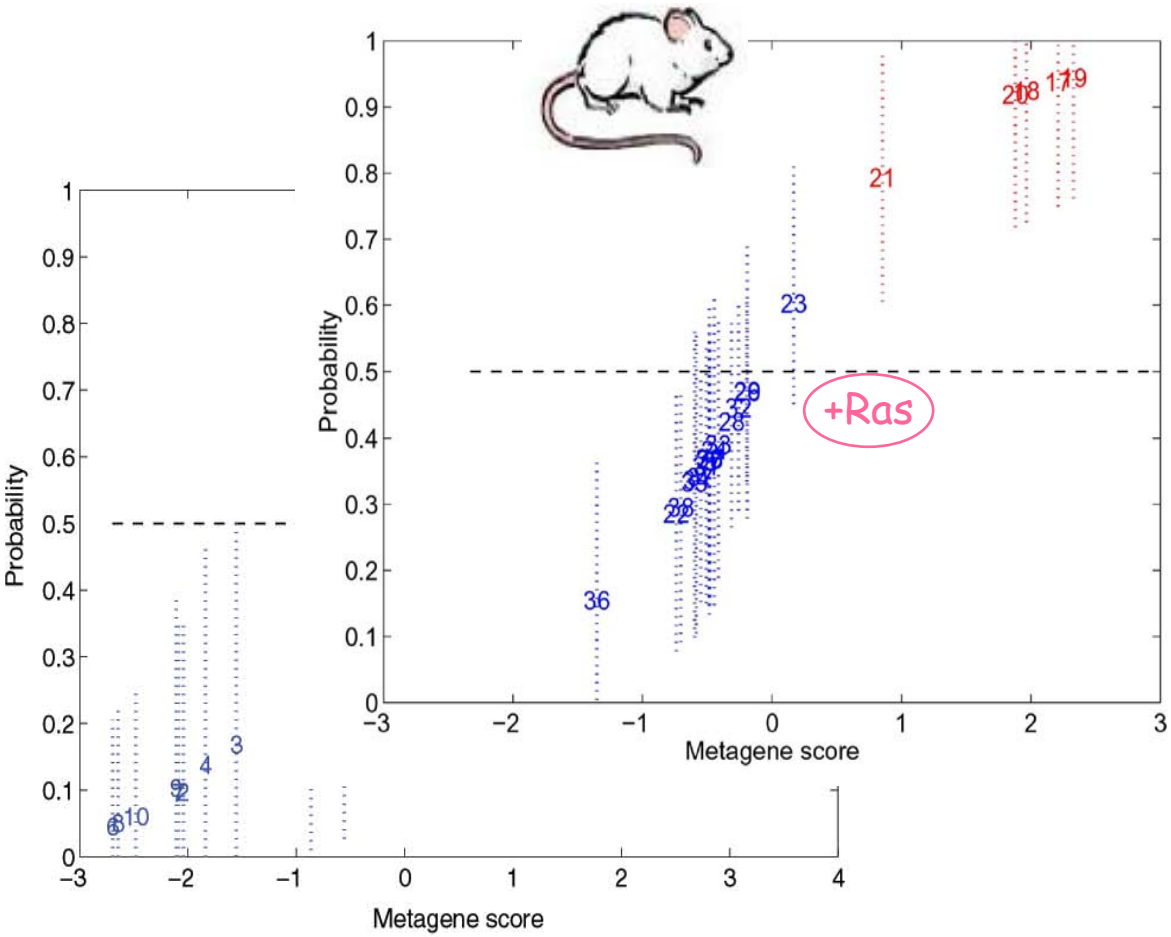
$$\dim(\beta_f) = n << p = \dim(\beta_x)$$

Metagene factor regression:
characterising genomic patterns

Predictive +Translational profiling:
oncogenic pathway deregulation



(Huang et al 03, Black et al 03)



Out-of-sample prediction

Cell line derived signatures predict differences in oncogenic activity in mouse tumours

c-Myc up-expression

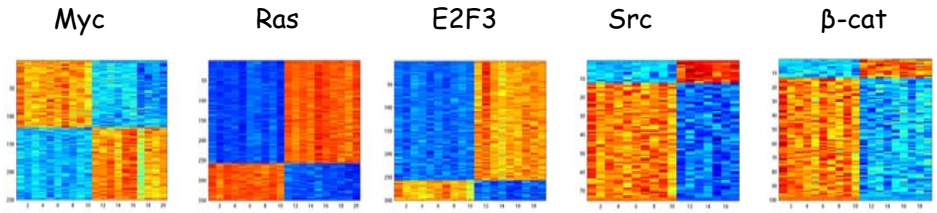
Metagene: gene subset & pattern as a predictor

(Huang et al 03, Black et al 03)

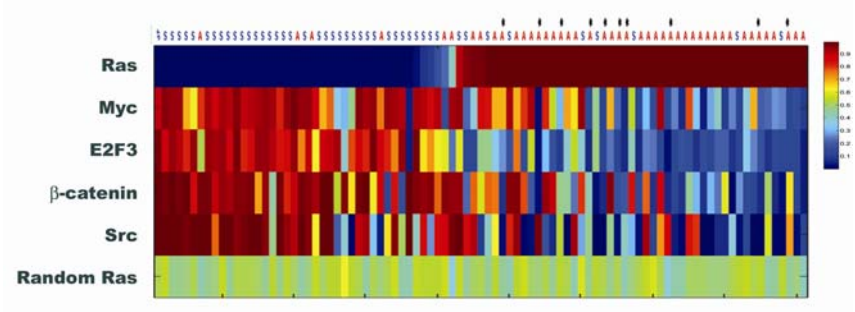
Oncogene Sub-Pathway Profiles: Translation

Single Oncogenes

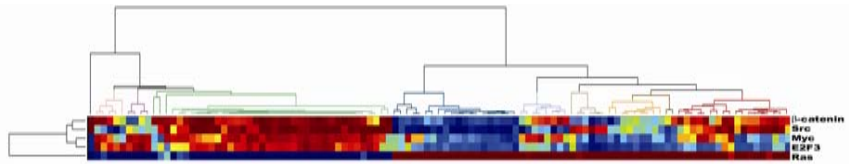
- pathway characterisation
- potential targets

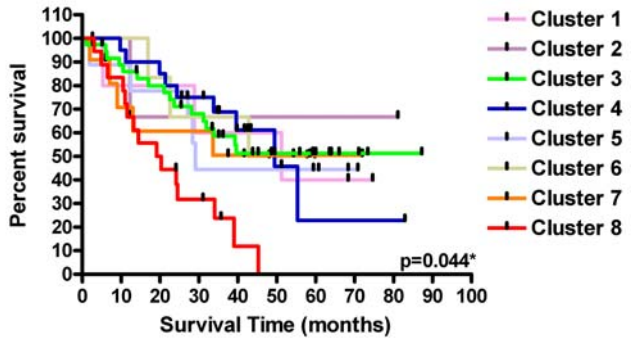


Cell lines signatures



Human lung cancers
(ovarian, breast)



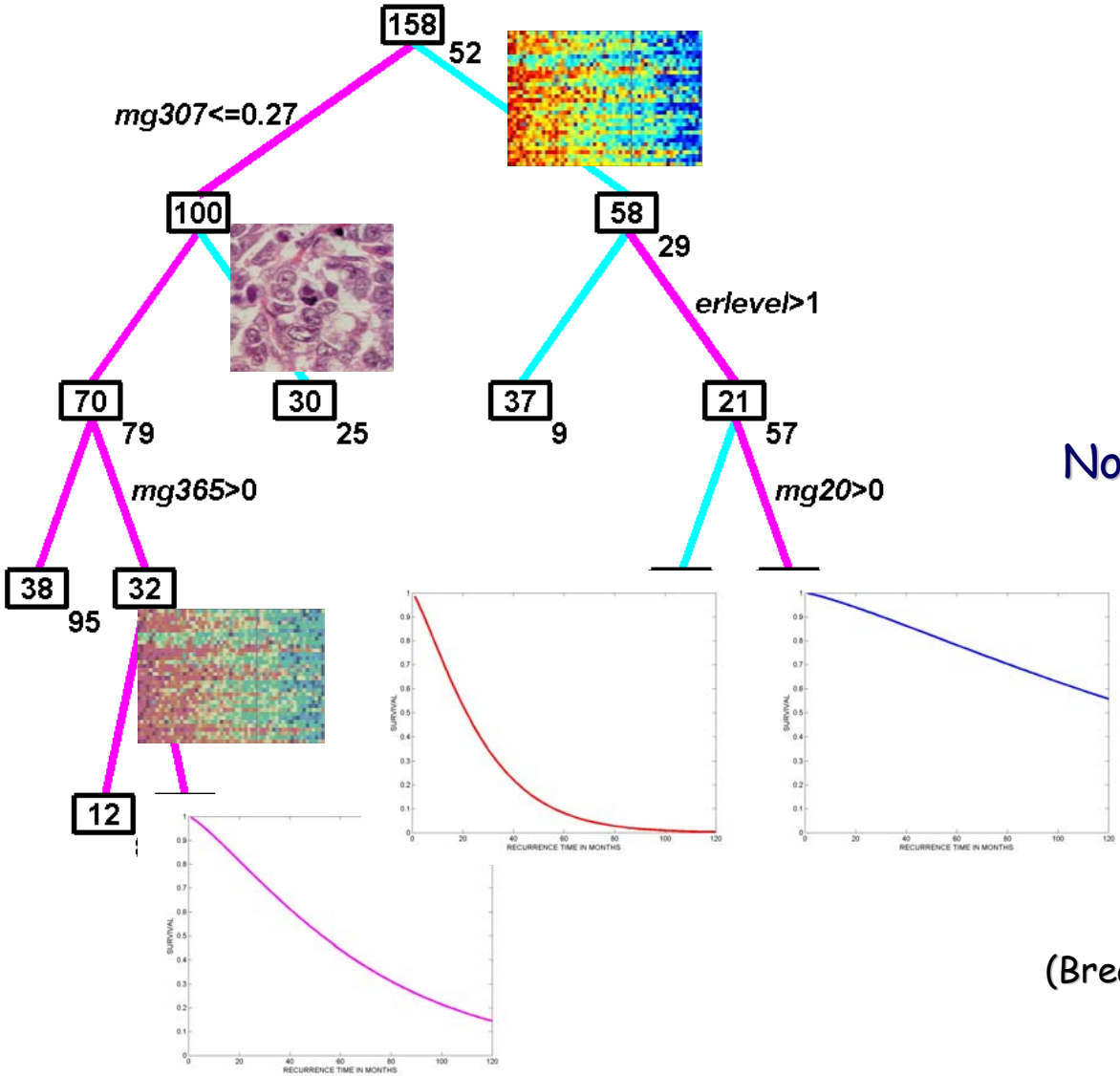


Clinical prognostic

- clinical evaluation
- therapeutic evaluation

(Bild et al 05)

Metagenes in Clinico-Genomic Prognostic Models



Genomic Medicine
Personalised Prognostics

Gene expression clustering
Metagene factors

Non-linear regressions – CART models

Integration:
non-genomic predictors

(Breast cancer – Pittman et al PNAS 04)

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Standard Sparsity Priors in Regression

$$(z_i|\beta) \sim N(h_i'\beta, \sigma^2)$$

$$\beta = \begin{pmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{pmatrix}$$

Variable inclusion uncertainty

Large p: parsimony sparsity

$$\#\{\beta_j \neq 0\} = \text{small}$$

Sparsity priors: $\beta_j \sim (1-\pi)\delta_0(\beta_j) + \pi N(\beta_j|0,\tau)$

Augment: $\gamma_j \sim Ber(\pi)$

$$\gamma = \begin{pmatrix} \gamma_1 \\ \gamma_2 \\ \vdots \\ \gamma_p \end{pmatrix}$$

MCMC computation: $p(\beta, \sigma, \gamma, \tau, \pi|Z)$

Model-based, automatic shrinkage - Simultaneous "multiple tests"

Multiple shrinkage: conservative, parsimonious
Decision theory/false discovery?
Estimation versus Decision?

$$\pi_j^* = Pr(\gamma_j = 1|Z) = Pr(\beta_j \neq 0|Z)$$

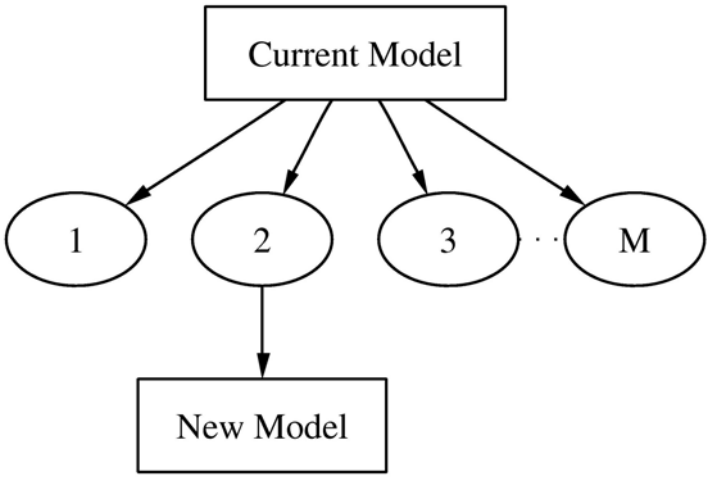
$$p(\beta_j|\beta_j \neq 0,\ Z)$$

Issues: Collinearities
Multiple related models
Computation with very large p

Model/subset probabilities:

$$Pr(\mathrm{M}_\gamma|Z)$$

(Clyde & George StatSci 04)



MCMC "local search" inspired

Good models "near" good models

Add/drop/replace variables

Move by sampling new model

Shoot out ALL neighbours:
"local proposals"

Swiftly find high probability regions of model space

Catalogue of many "good" models

Parallelisation

KEY: easily compute

$$\propto \quad Pr(\mathrm{M}_\gamma | Z)$$

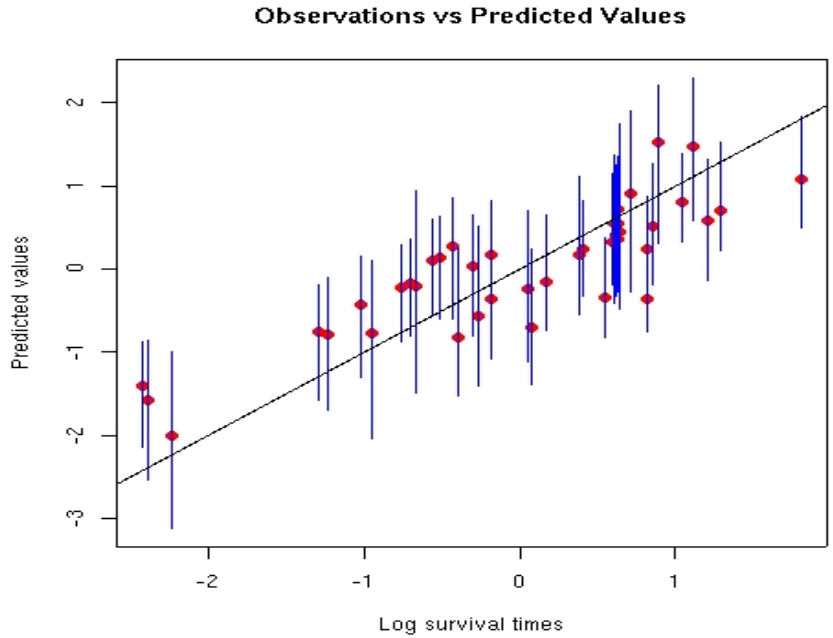
(Hans, Dobra, West 05; Rich et al 2005 – p=8400)

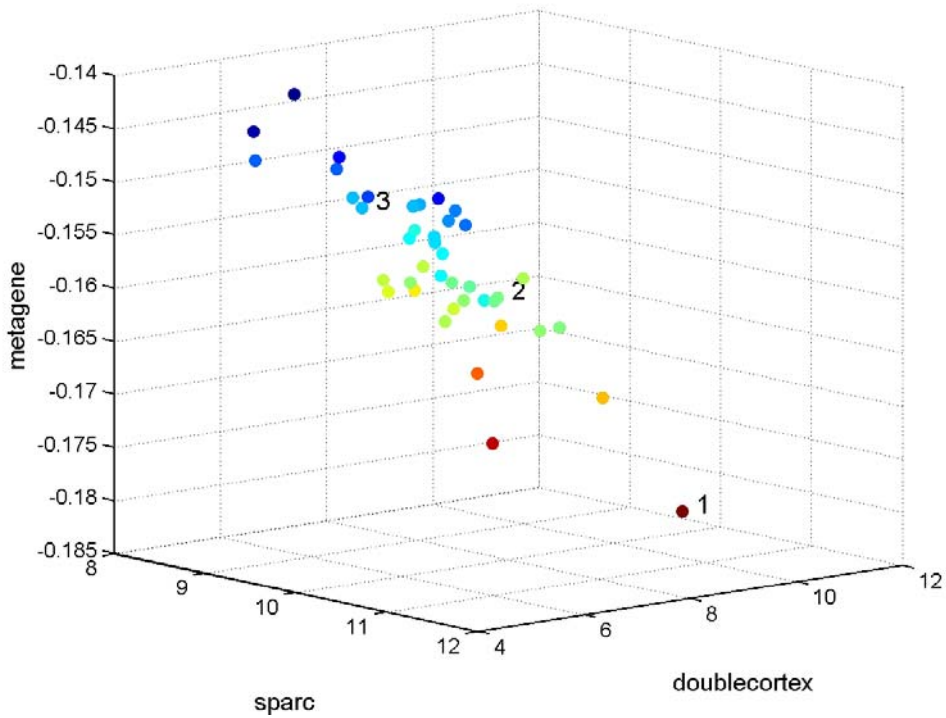
Cancer Genomics: Sparse Regressions & Prediction

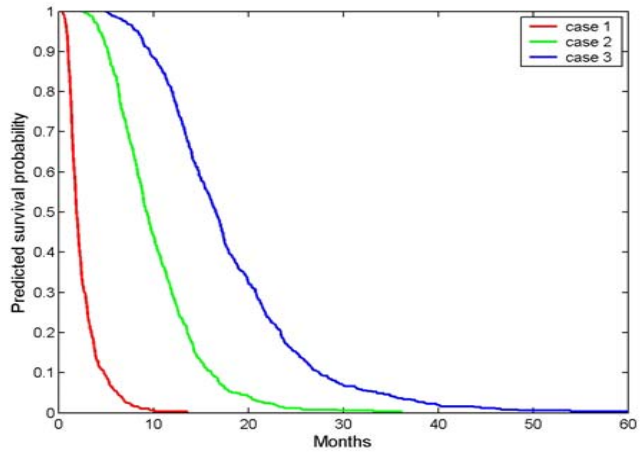
Brain cancer expression: p=8400

Survival regressions:

- multiple related 3-5 gene subsets
- key cellular motility/infiltration genes
- regression model uncertainty in prediction







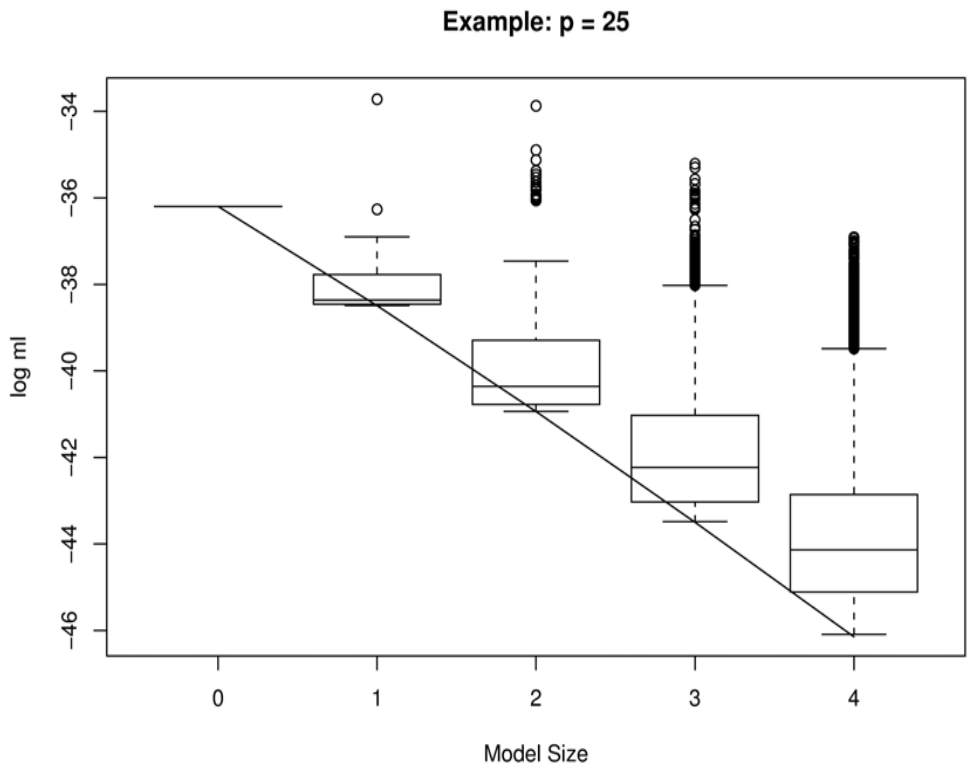
(Cancer Research, 05)

Sparsity -

Regression variable in/out probabilities

Dimension -

Implicit in Bayesian & other likelihood-based analyses (*cf.* BIC)

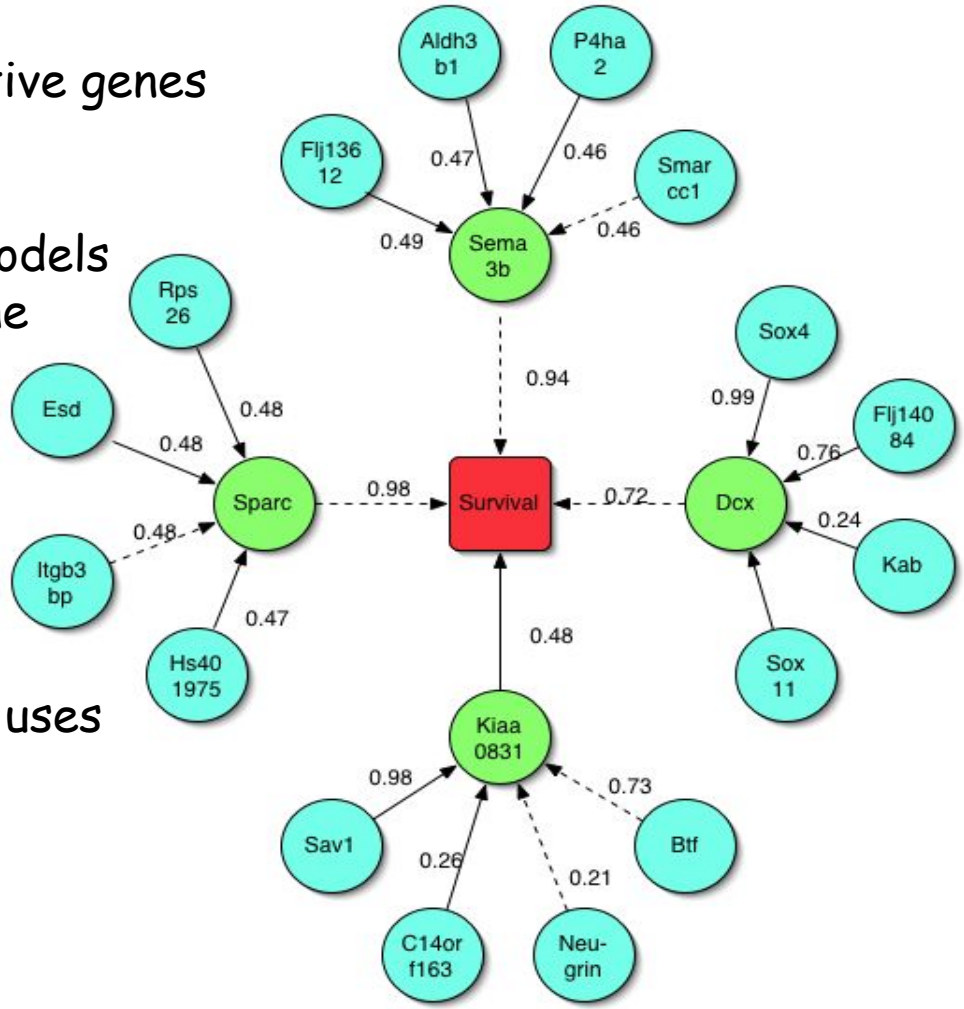


p=8400

Cascade of regression models:

- Models to predict/explain gene expression for survival predictive genes
- and so on …

Generate Directed Acyclic Graphical models (DAGs) of association patterns in gene expression

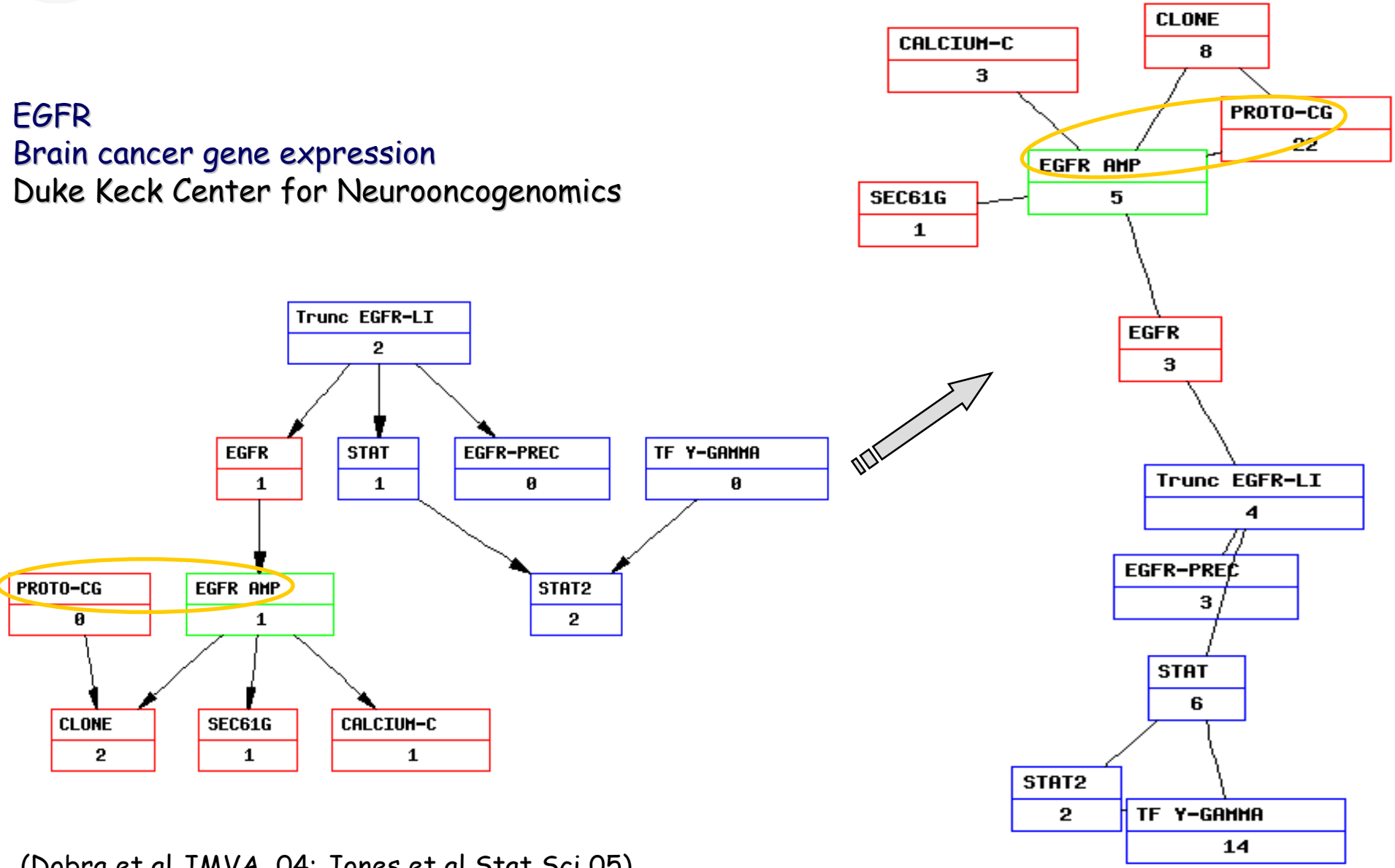


Exploratory data analysis, visualization uses

http://graphexplore.cgt.duke.edu

(Cancer Research, 05)

EGFR
Brain cancer gene expression
Duke Keck Center for Neurooncogenomics



(Dobra et al JMVA, 04; Jones et al Stat Sci 05)

These slides:
www.isds.duke.edu/~mw/downloads/SemStat05

Papers, software, many links:
www.isds.duke.edu/~mw

ABS04 web site: Lecture slides, stats notes, papers, data, links:
www.isds.duke.edu/~mw/ABS04

Integrated Cancer Biology Program
icbp.genome.duke.edu

Genome Institute @ Duke
www.genome.duke.edu