Bayesian Computing and the Incorporation of Prior Knowledge in Translational-Genomic Modeling

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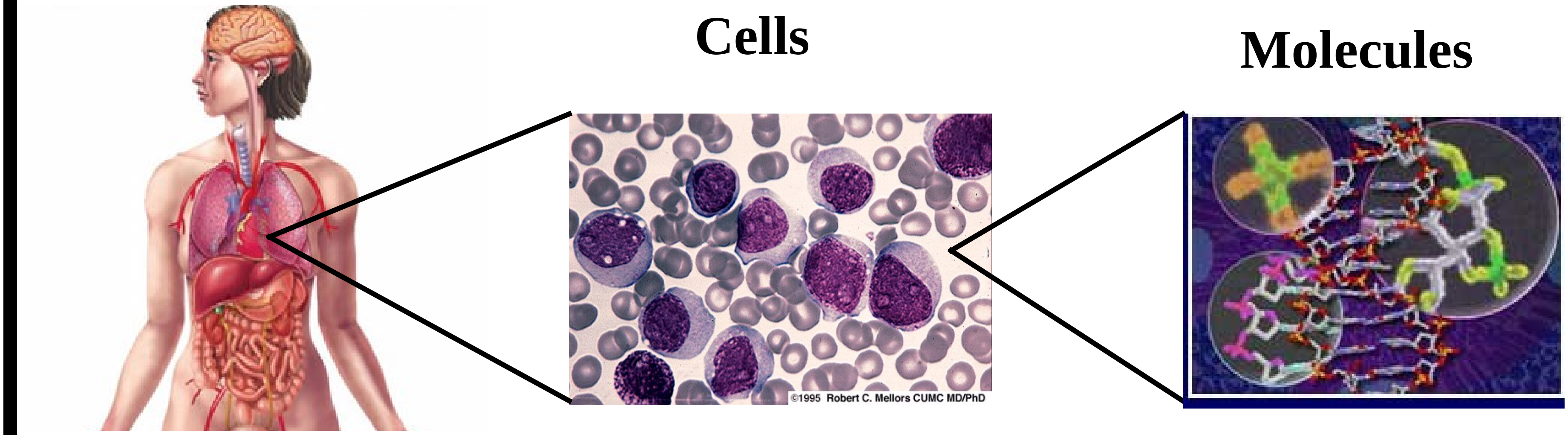
Medicine at the Right Level

- **Source of disease (ex: cancer) – molecular scale**
  - *Genes and proteins*

Organs

Cells

Molecules



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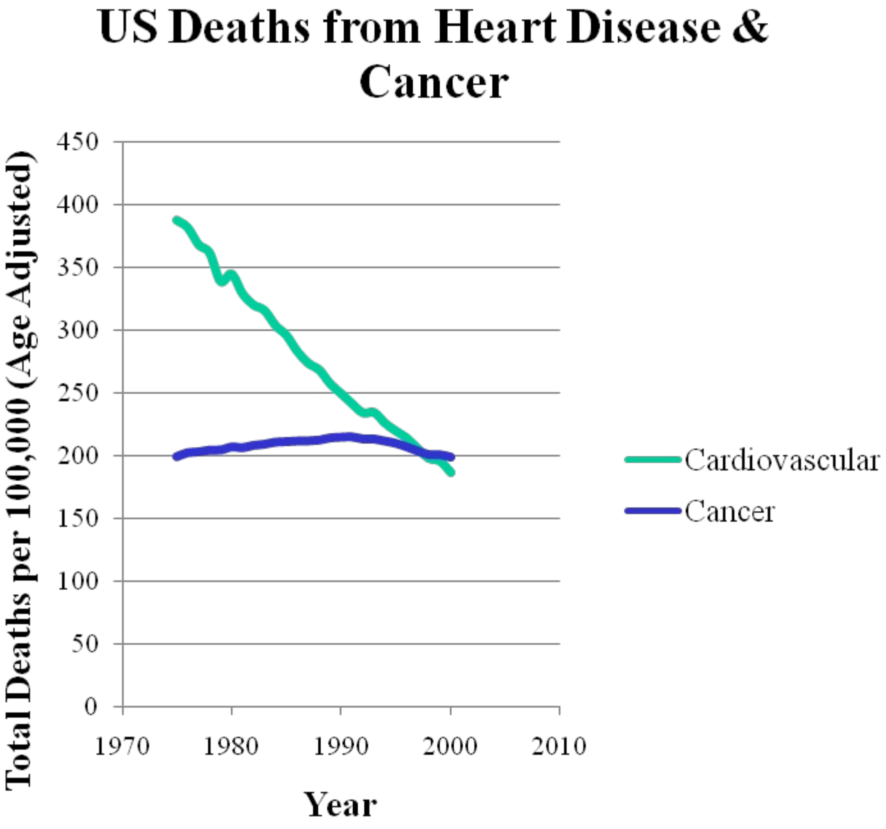
Complex Diseases

- **Most diseases do not result from a single gene product.**
- **Complex diseases require complex personalized mathematical analysis.**



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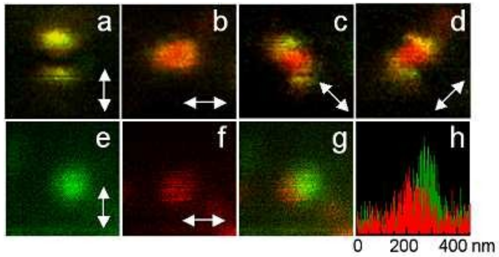
Patient-Specific Treatment

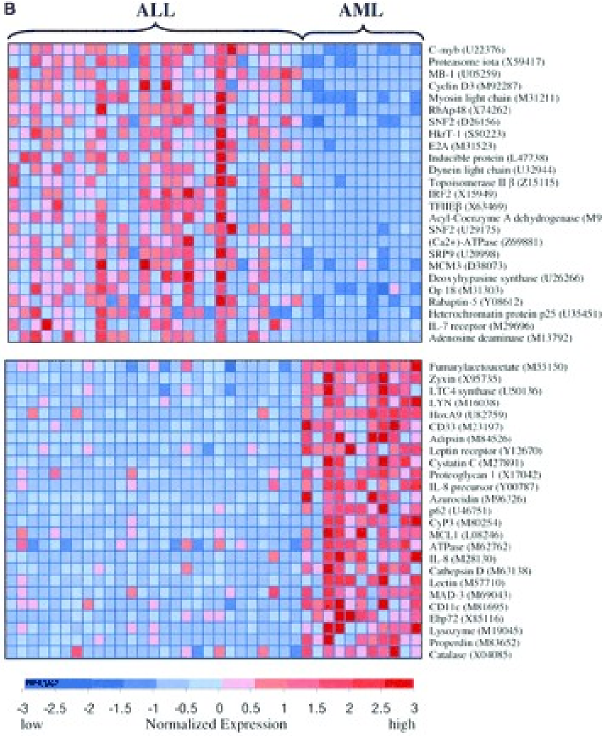
- Specificity means much higher success rate.

Nano-aspirate/biopsy

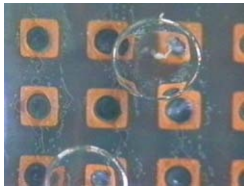
Analyze



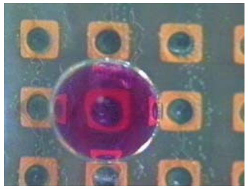
Compute



Custom drug manufacture



Nano scale chemistry lab



Enhanced disease management

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Translational Genomics

- **Genomics is the study of genes as they interact in a system that governs cell behavior.**

- **Goals of translational genomics:**
  - *Screen for key genes and gene families that explain specific cellular phenotypes (disease).*
  - *Use genomic signals to classify disease on a molecular level.*
  - *Mathematically model dynamical system behavior to derive therapeutic strategies to alter undesirable behavior.*

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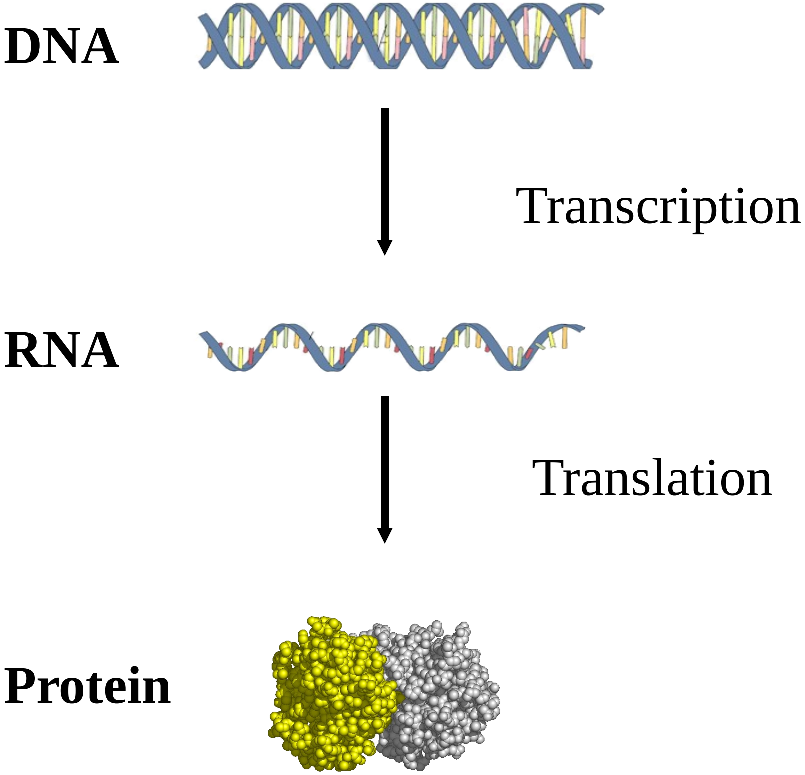
Central Dogma of Molecular Biology



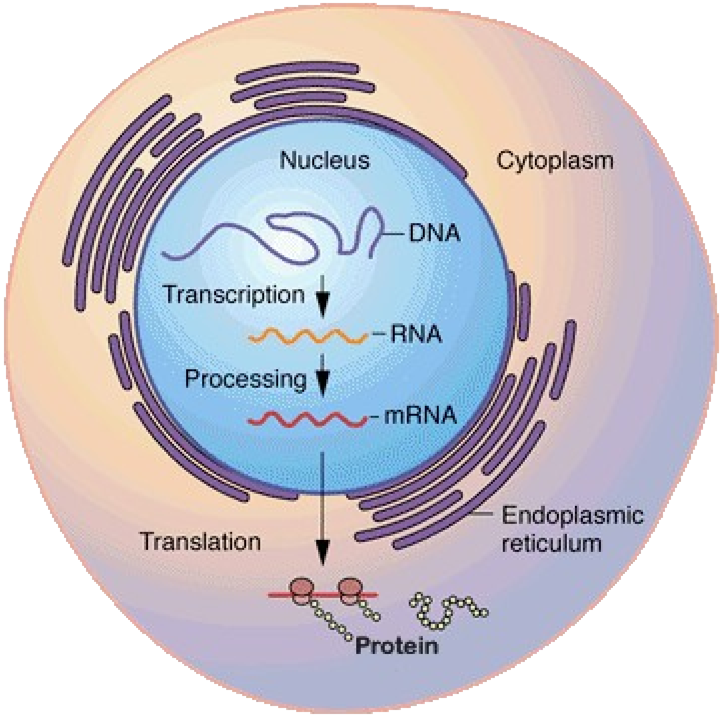
DNA

Transcription

RNA

Translation

Protein



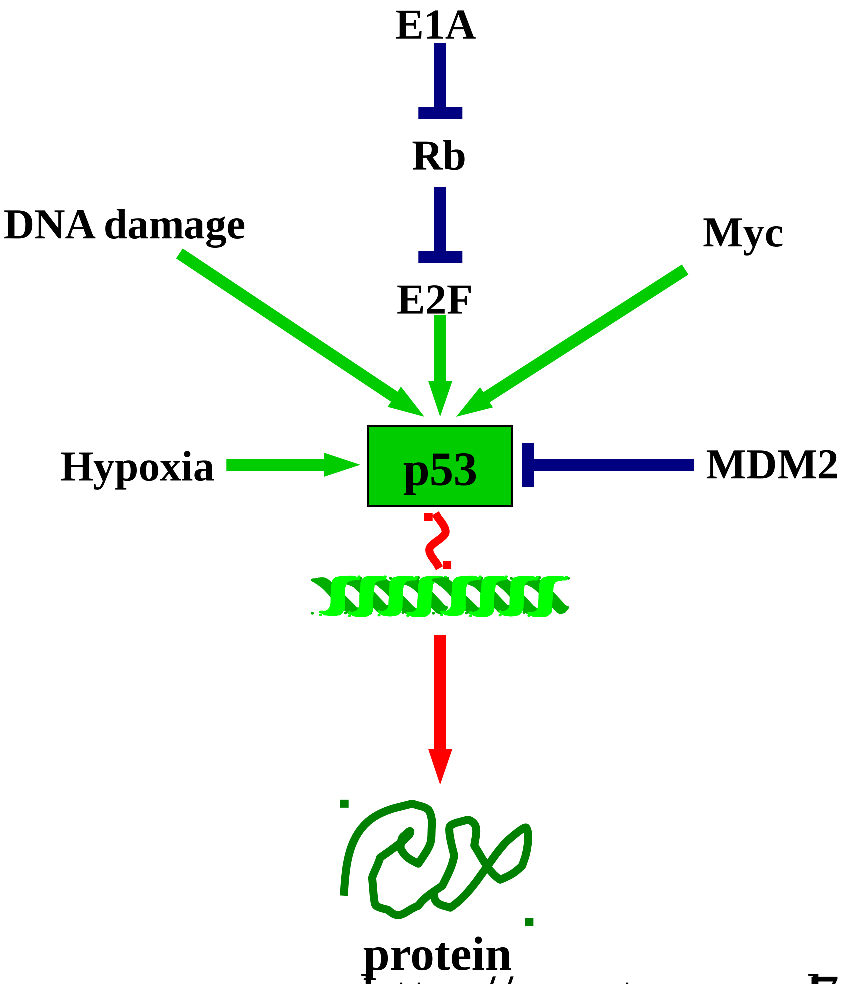
Gene Regulation

Gene expression
the process by which gene products (proteins) are made

Gene regulatory controls

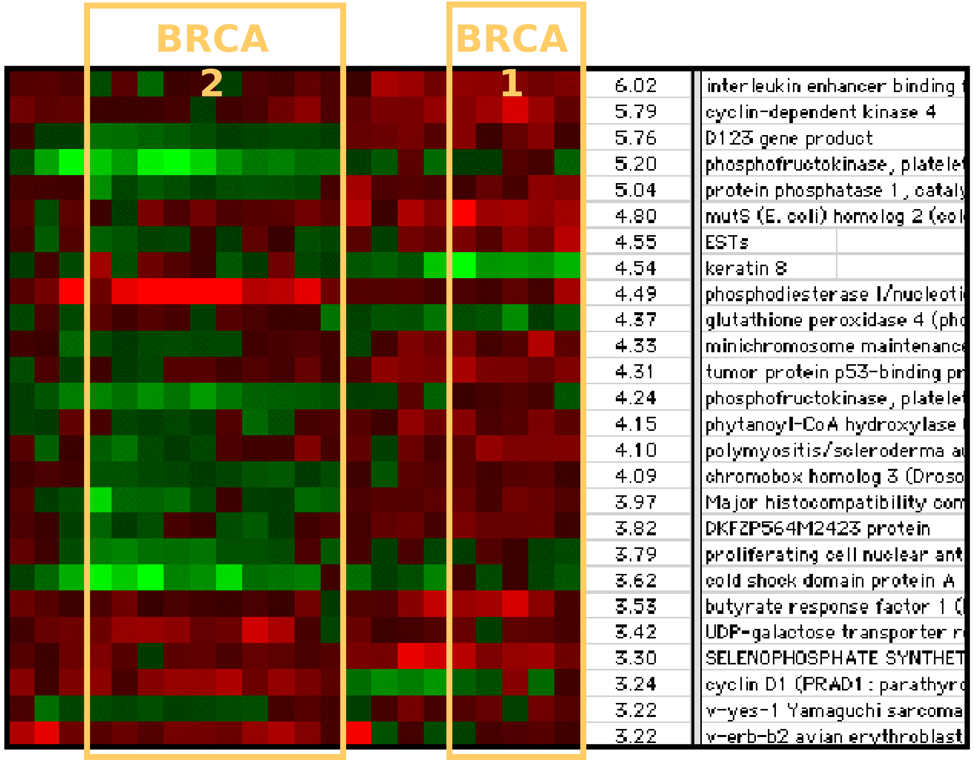
transcription

translation



Genomic Classification of Disease

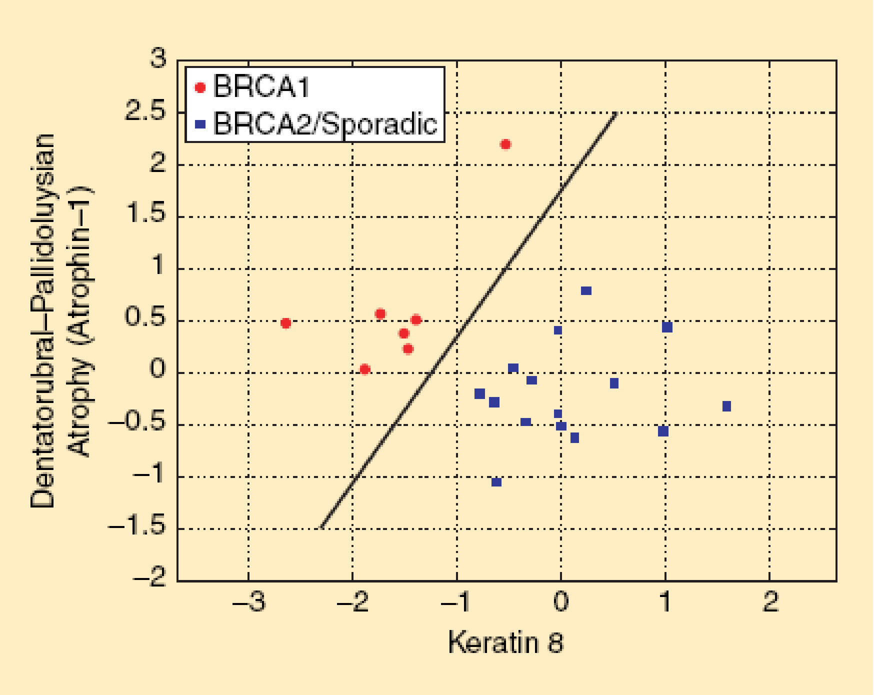
- **Abundance of RNA is measured for each gene (gene-expression microarray, RNA-Seq).**
- **A rule is used to train a classifier from the data.**



6.02	interleukin enhancer binding f
5.79	cyclin-dependent kinase 4
5.76	D123 gene product
5.20	phosphofructokinase, platelet
5.04	protein phosphatase 1, cataly
4.80	mutS (E. coli) homolog 2 (col
4.55	ESTs
4.54	keratin 8
4.49	phosphodiesterase I/nucleoti
4.37	glutathione peroxidase 4 (pho
4.33	minichromosome maintenance
4.31	tumor protein p53-binding pr
4.24	phosphofructokinase, platelet
4.15	phytanoyl-CoA hydroxylase
4.10	polymyositis/scleroderma au
4.09	chromobox homolog 3 (Droso
3.97	Major histocompatibility com
3.82	DKFZP564M2423 protein
3.79	proliferating cell nuclear ant
3.62	cold shock domain protein A
3.53	butyrate response factor 1 (
3.42	UDP-galactose transporter r
3.30	SELENOPHOSPHATE SYNTHET
3.24	cyclin D1 (PRAD1: parathyro
3.22	v-yes-1 Yamaguchi sarcoma
3.22	v-erb-b2 avian erythroblast

Classification of Hereditary Breast Cancer

- Classifier discriminates types of breast cancer using two-gene signature.
- If treatment for BRCA1 and BRCA2 differ, then early detection is critical.

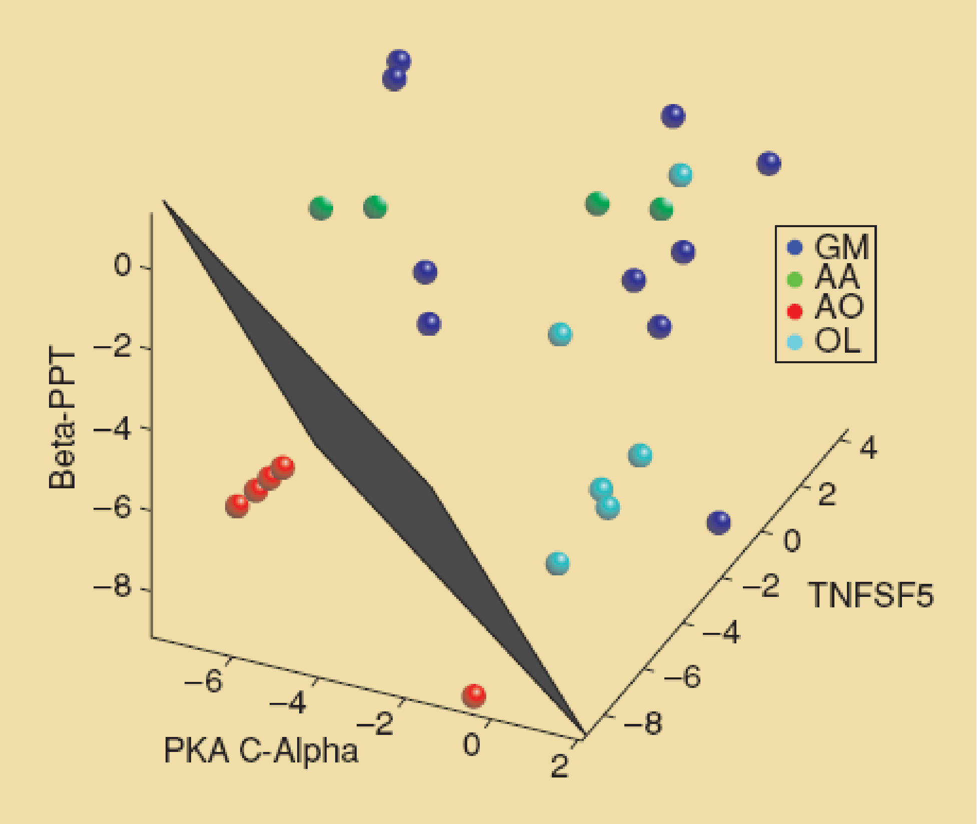


Glioma Application

- Data from four types of glioma: OL, GM, AO, AA
- Find small gene sets to separate each type from others.
- Small sample: 25 patients.

3-Gene Glioma Classification

- 3-gene linear discrimination for anaplastic oligodendroglioma from others.



A Huge Challenge

- **Janet Woodcock (Director, Center for Drug Evaluation and Research, FDA): [As much as 75 percent of published biomarker associations are not replicable] "This poses a huge challenge for industry in biomarker identification and diagnostics development."**

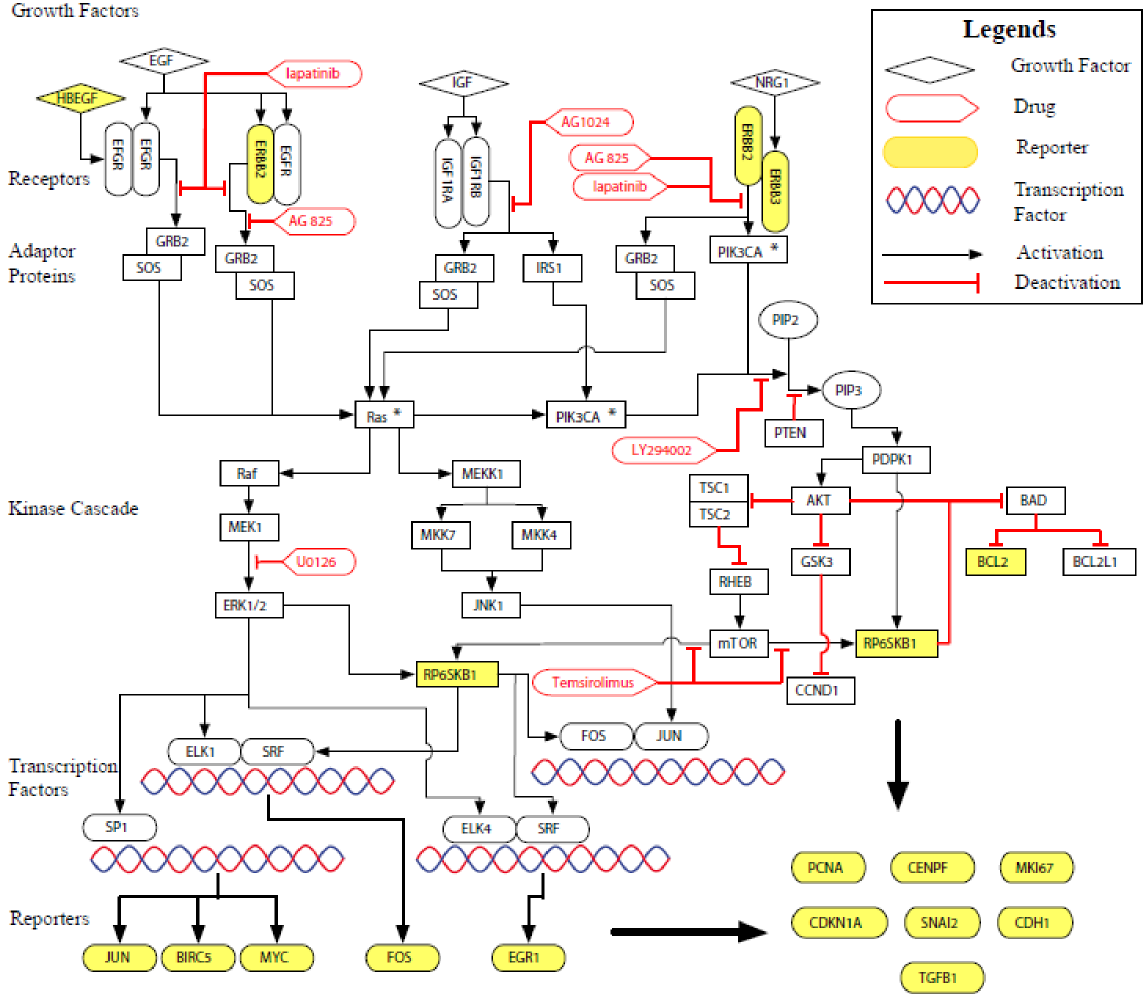
Small Samples Don’t Work

- There are tens of thousands of genes and a small number of replicates, usually less than 100 – Big data can be very small data.
- If the sample is large (many replicates), then the data can be split into training (classifier design) and testing (error estimation).
- Small data sets cannot be split because there would be insufficient data for both training and testing.
- Vain hope train and test on the same data.
  - *This results in poor error estimation – not reproducible.*

Bayesian Classification

- **Integrate prior (existing) biological with new data to design a classifier and estimate the error.**
  - *If one had full knowledge of the system, one would derive the optimal classifier need no data.*
  - *Partial knowledge constraints the space of classifiers, thereby allowing more efficient use of the data.*
- **Obstacles:**
  - *Mathematically much more difficult.*
  - *Computationally much more difficult: involves high-dimensional Markov-chain-Monte-Carlo computational integrations and complex optimizations to incorporate prior knowledge.*

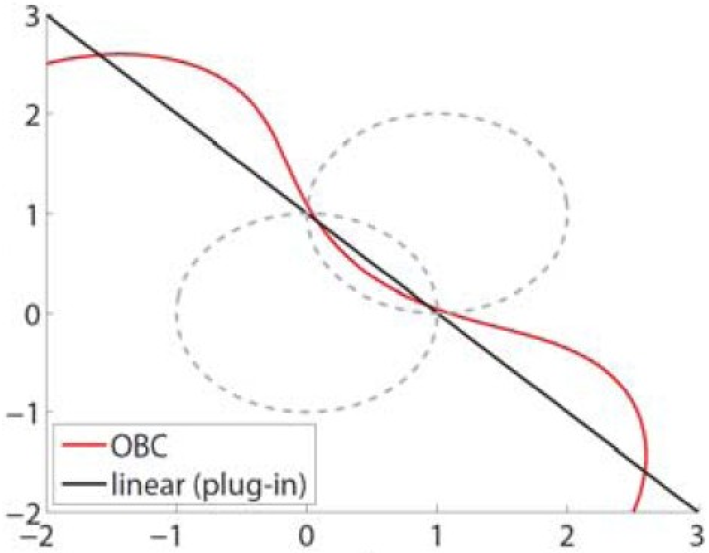
Growth Factor (GF) Signaling Pathways



- Biochemical pathways constrain the feature-label distribution.
- Key problem: Transform pathways into usable prior knowledge.

OBC for Gaussian Model

- **Polynomial Optimal Bayesian Classifier (red line)**
  - *Dotted lines are level curves for the densities corresponding to the average means and covariance matrix.*
  - *Black solid line is linear classifier corresponding to the optimal classifier for the average mean and covariance matrix.*



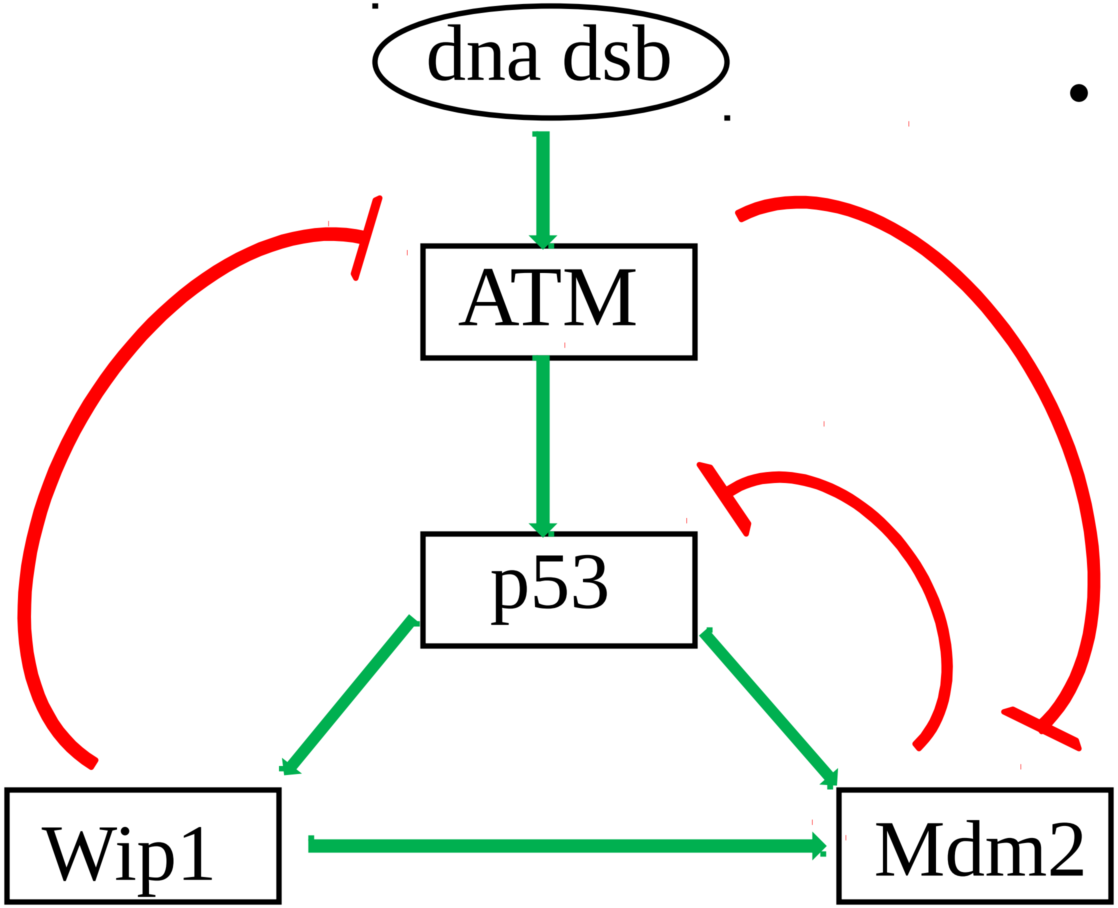
Control of Gene Networks

- The therapeutic problem is to model a gene regulatory network and then find an optimal treatment strategy.
  - Consider an external control variable and a cost function depending on desired outcome.
  - Minimize the cost function by a sequence of control actions over time – control policy (drugs).
  - Design optimal treatment regime to drive the system away from undesirable states.
- Problem 1: Infer network from data.
- Problem 2: Mathematically derive optimal controller.

A p53 Network

- Consider the DNA double strand break repair pathways involving the tumor suppressor gene p53.
- p53 is a master guardian gene tightly controlling various activities like cell cycle progression, senescence and apoptosis.
- Mutation in p53 is observed in 30% - 50% of common human cancers.
- We consider 4 genes: ATM, p53, Mdm2, Wip1.

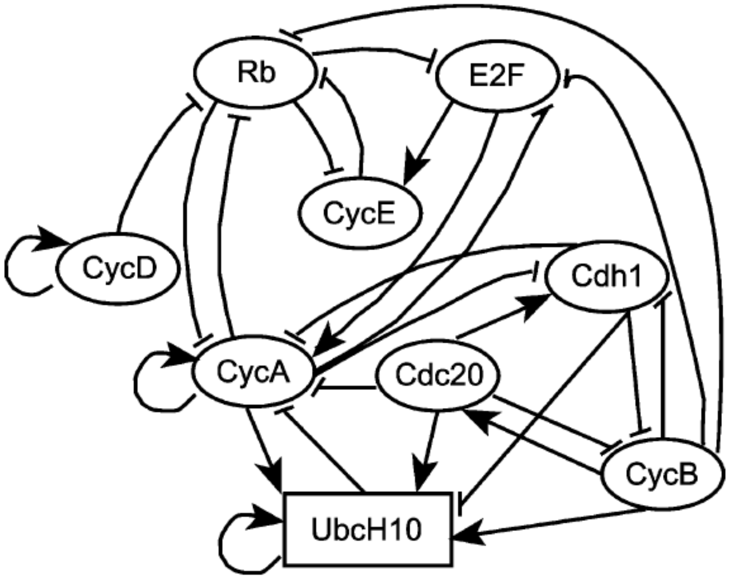
ATM-p53-Mdm2-Wip1 Pathways



- dna_dsb refers to DNA damage.

Mutated Mammalian Cell Cycle PBN

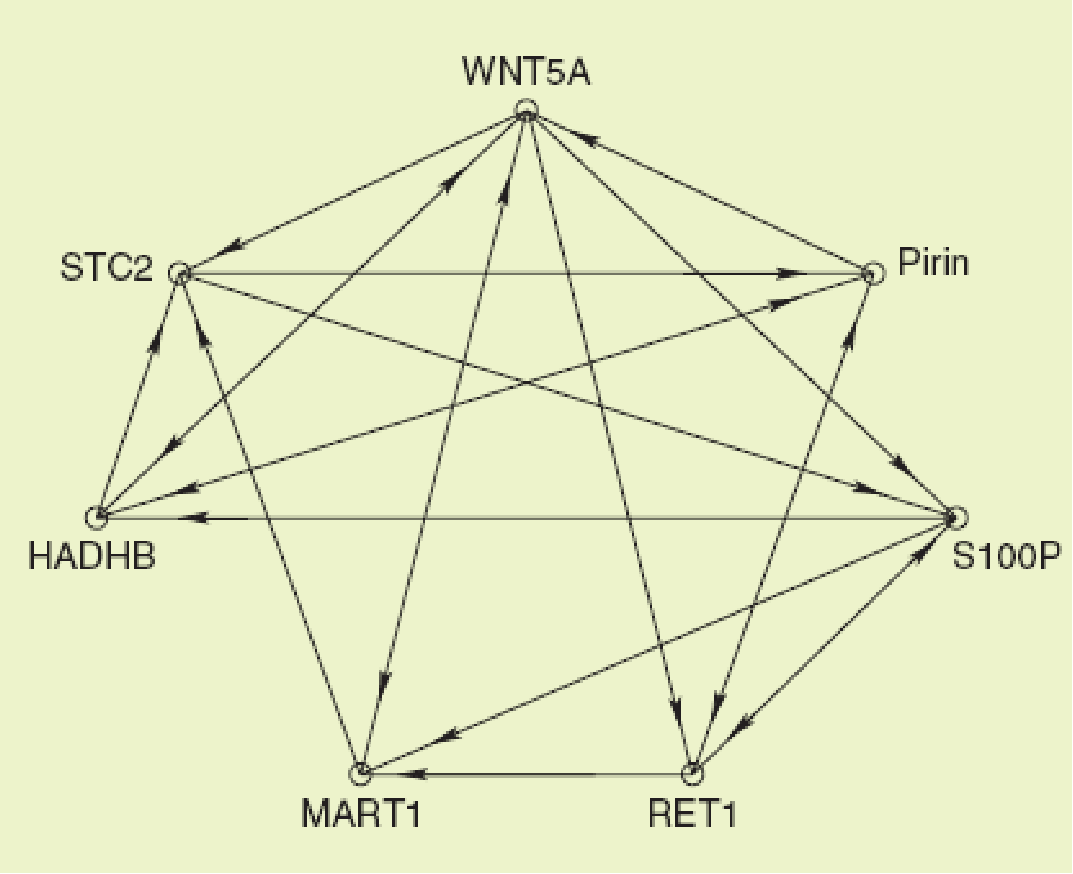
- **If CycD and Rb are simultaneously down-regulated, then the cell cycles in the absence of any growth factor.**
- **Intervention tries to stop simultaneous down regulation.**



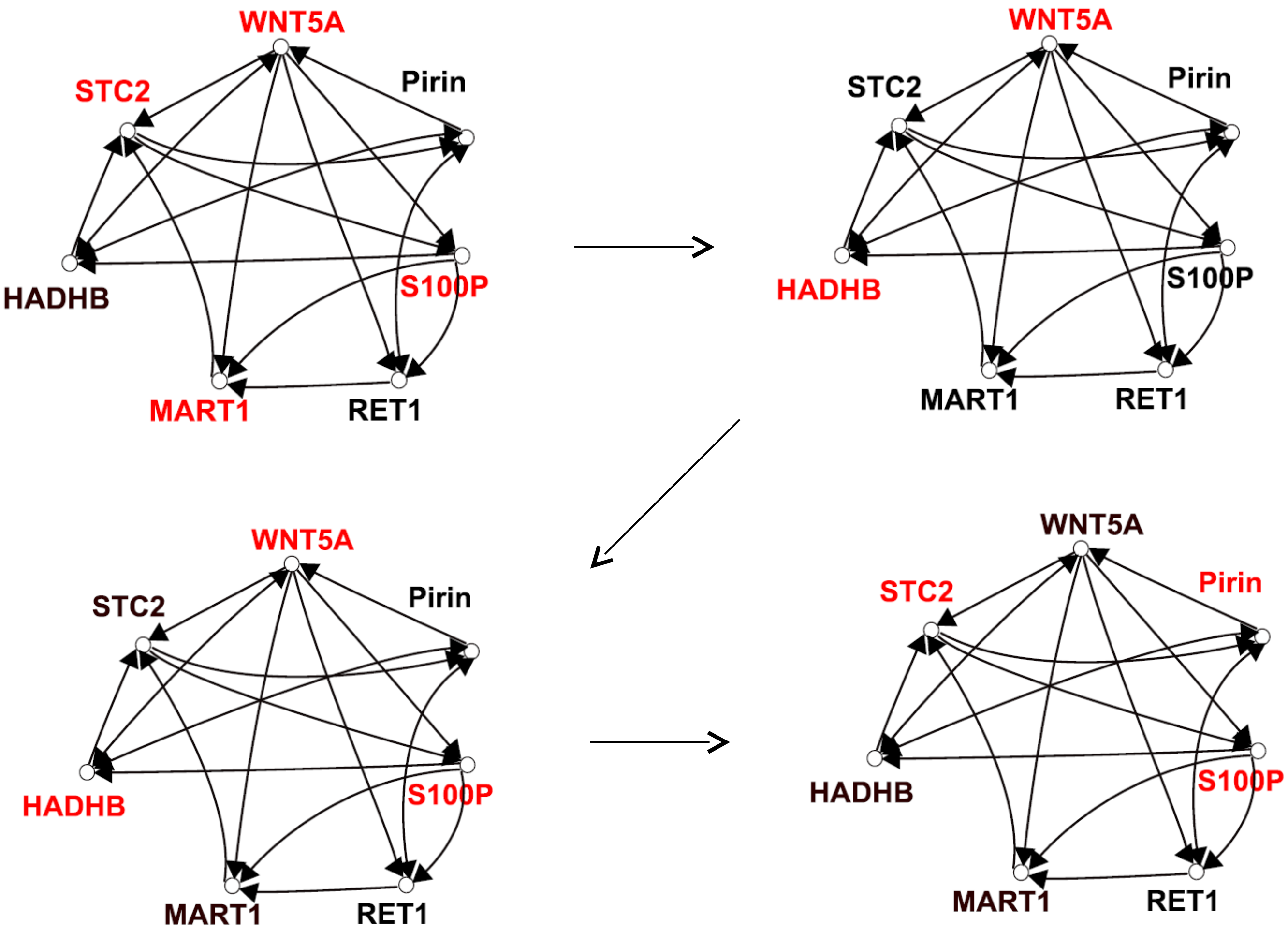
Product	Predictors
CycD	Input
Rb	$(\overline{\mathrm{CycD}} \wedge \overline{\mathrm{CycE}} \wedge \overline{\mathrm{CycA}} \wedge \overline{\mathrm{CycB}})$
E2F	$(\overline{\mathrm{Rb}} \wedge \overline{\mathrm{CycA}} \wedge \overline{\mathrm{CycB}})$
CycE	$(\mathrm{E2F} \wedge \overline{\mathrm{Rb}})$
CycA	$(\mathrm{E2F} \wedge \overline{\mathrm{Rb}} \wedge \overline{\mathrm{Cdc20}} \wedge (\overline{\mathrm{Cdh1} \wedge \mathrm{Ubc}})) \vee (\mathrm{CycA} \wedge \overline{\mathrm{Rb}} \wedge \overline{\mathrm{Cdc20}} \wedge \overline{(\mathrm{Cdh1} \wedge \mathrm{Ubc}}))$
Cdc20	CycB
Cdh1	$(\overline{\mathrm{CycA}} \wedge \overline{\mathrm{CycB}}) \vee (\mathrm{Cdc20})$
Ubc	$(\overline{\mathrm{Cdh1}}) \vee (\mathrm{Cdh1} \wedge \mathrm{Ubc} \wedge (\mathrm{Cdc20} \vee \mathrm{CycA} \vee \mathrm{CycB}))$
CycB	$(\overline{\mathrm{Cdc20}} \wedge \overline{\mathrm{Cdh1}})$

WNT5A Network

- **Up-regulated WNT5A associated with increased metastasis.**
- **Cost function penalizes WNT5A being up-regulated.**
- **Optimal control policy with Pirin as control gene.**



Sample Trajectory



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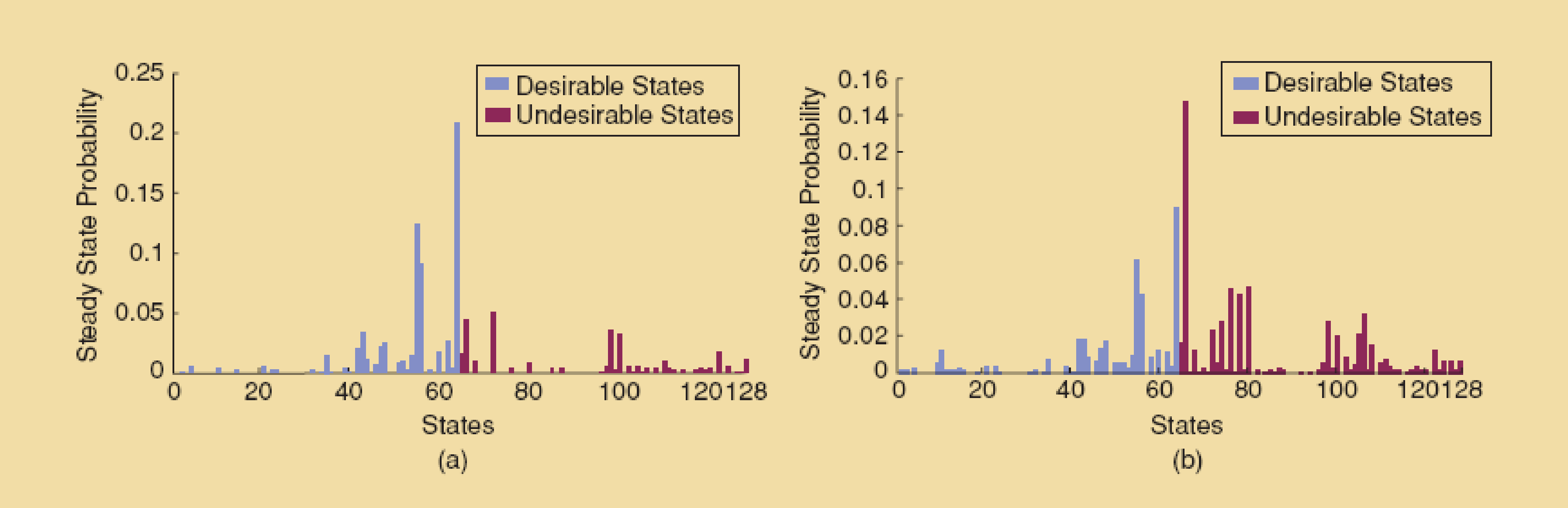
Shift of Steady-State Distribution



- **Optimal (infinite horizon) control with pirin has shifted the steady-state distribution to states with WNT5A down-regulated: (a) with control; (b) without control.**

Bayesian Control

- **Network models are uncertaint owing to insufficient data and natural regulatory variability among cells.**
- **Bayesian control: design a control policy that has best average performance across an uncertainty class of networks.**
- **Computational issues:**
  - *Assuming a given network, a common design method is dynamic programming, which suffers from the "curse of dimensionality."*
  - *Bayesian control is much more computational owing to a huge search space and difficult optimizations – much research is necessary.*