DEPARTMENT OF CHEMICAL AND BIOMOLECULAR ENGINEERING & INSTITUTE FOR GENOMIC BIOLOGY

University of Illinois at Urbana-Champaign

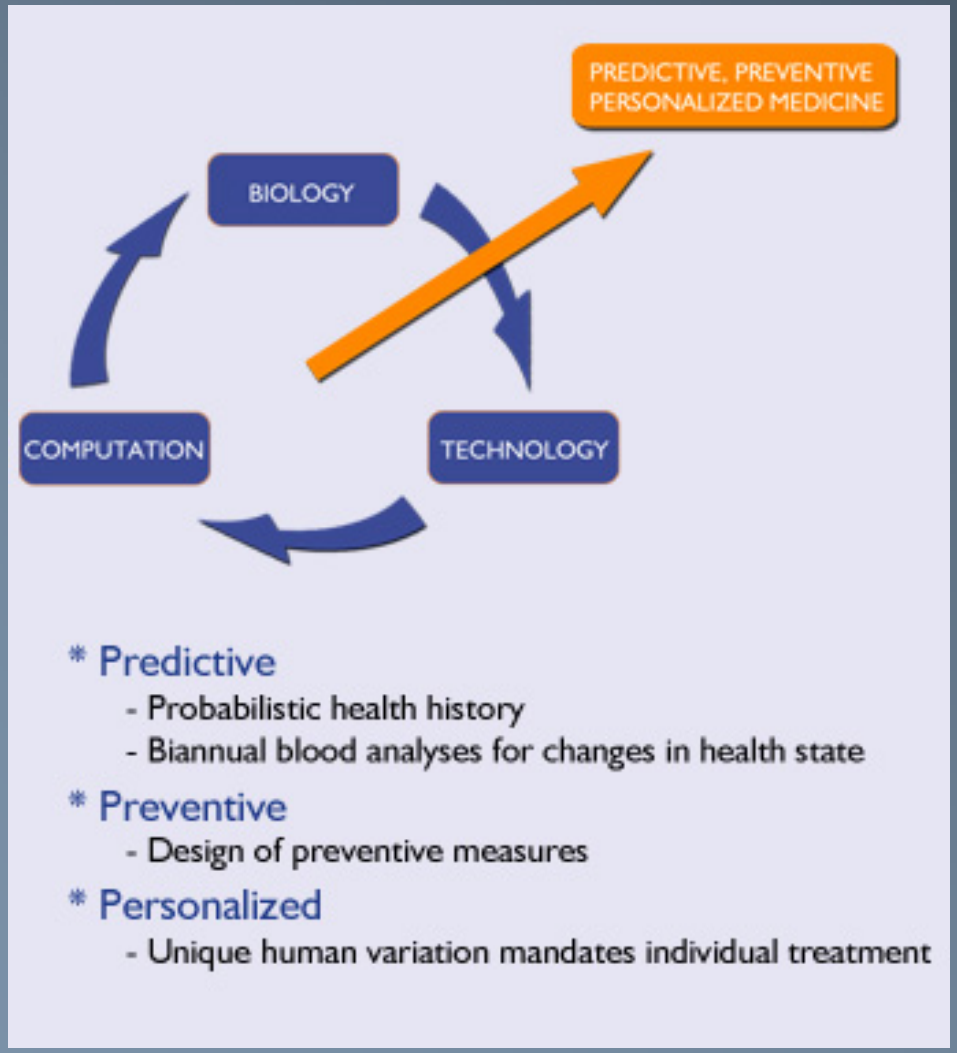
Computational Challenges for Systems Biology and Personalized Medicine

Nathan D. Price

Frontiers of Extreme Computing

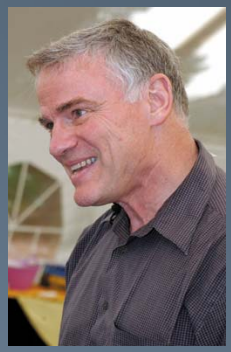
Oct 23, 2007

Revolution in Biology and Medicine



"The Human Genome Project has Catalyzed two paradigm changes in contemporary biology and medicine—
systems biology and predictive, preventive and personalized medicine. " – Lee Hood

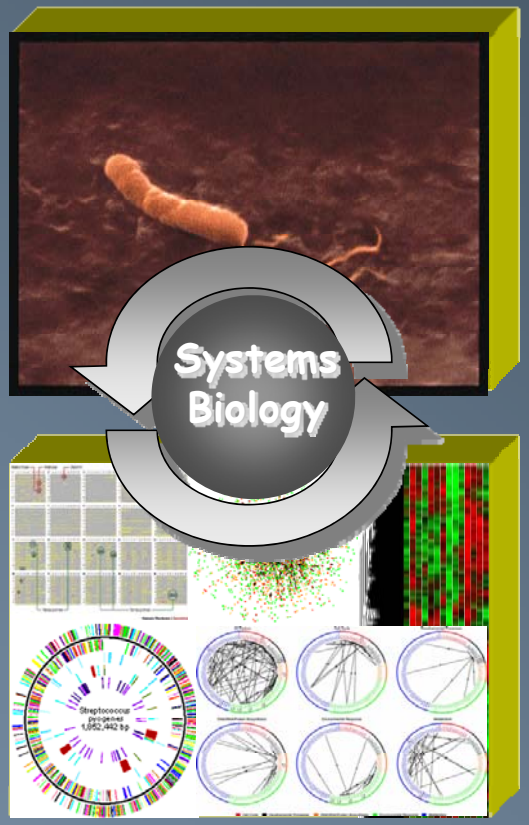
Acknowledgement
Lee Hood
Institute for Systems Biology



Systems Biology

High-Throughput Data Generation (Genome Sequencing, DNA Arrays, Proteomics, Metabolomics)

Data-rich



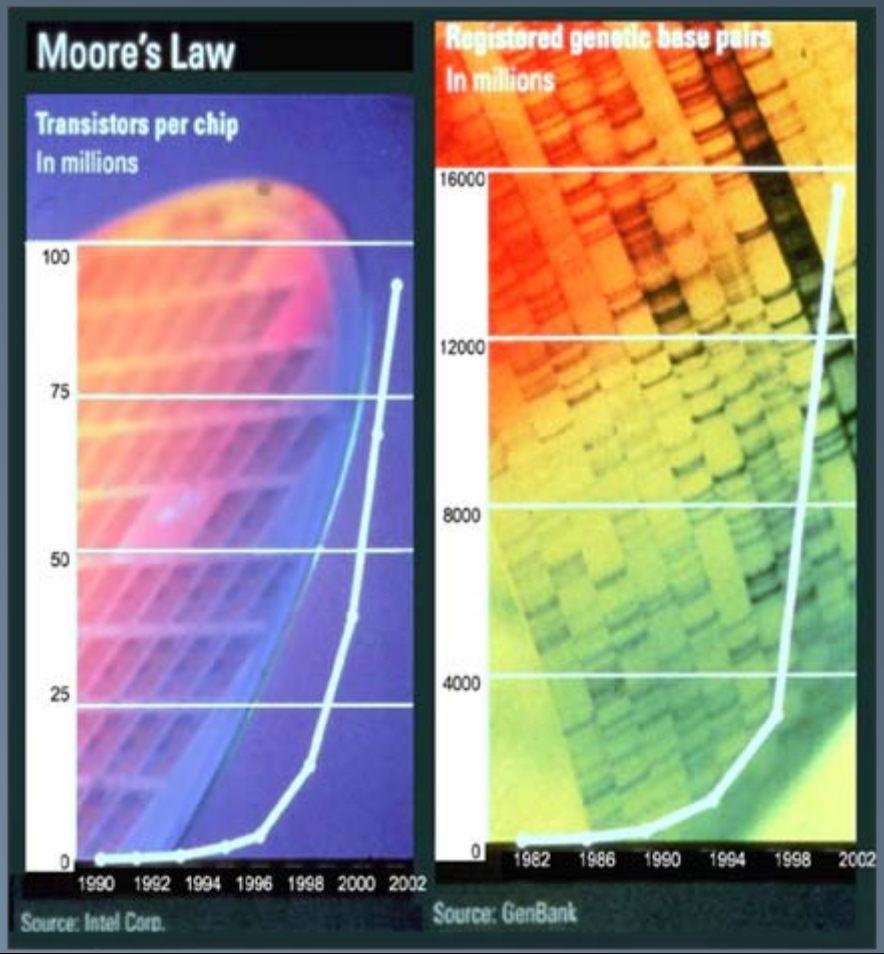
Bioinformatics (Computation, Engineering, Systems Science, Modeling, Simulation)

Data-poor

Systems biology challenge: *Utilize high-throughput technologies to drive large scale biological and medical discovery*

The Exponential Rise in Computation Power and Biological Data: The Fuel of the Biomedical Revolution

- The harnessing of the (exponentially increasing) biological data through the use of (exponentially increasing) computational capabilities will revolutionize biology and medicine
- For given problems, one or the other may be limiting, and this can change in the future depending on how the problem constraints grow in each dimension, and the rate of growth of each



Computational Challenges in Systems Biology

- How to fully decipher the (digital) information content of the genome
- How to do all-vs-all comparisons of 1000s of genomes (or more)
- How to extract protein and gene regulatory networks from 1 & 2
- How to integrate multiple high-throughout data types dependably
- How to visualize & explore large-scale, multi-dimensional data
- How to convert static network maps into dynamic mathematical models
- How to predict protein function *ab initio*
- How to identify signatures for cellular states (e.g. healthy vs. diseased)
- How to build hierarchical models across multiple scales of time & space
- How to reduce complex multi-dimensional models to underlying principles
- Text searching to bring the literature and experimental data together

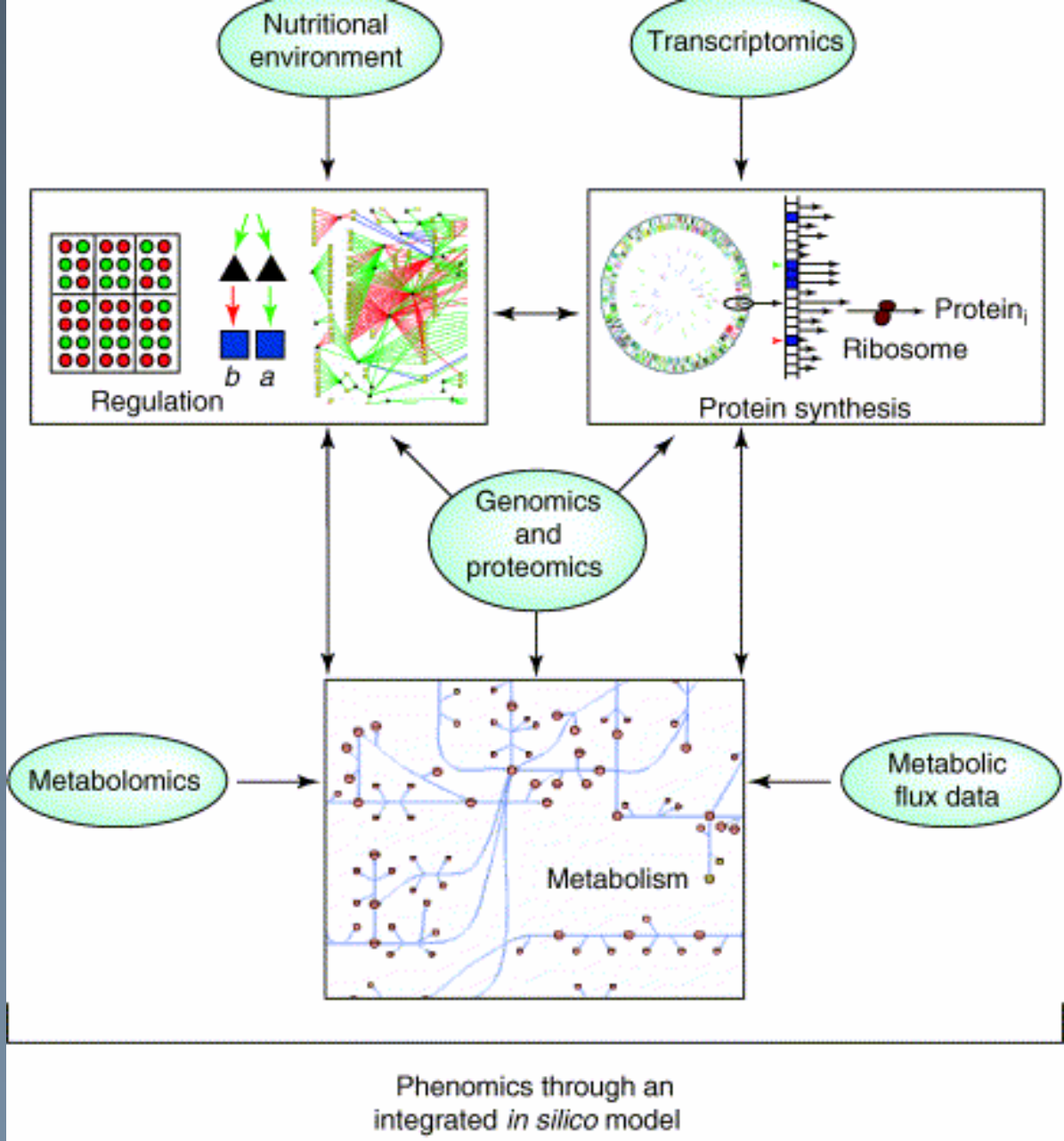
Hood, L. et al, *Science*, 2004

Scales in Biology with Computational Opportunities

- Protein folding
- Detailed molecular simulations
- Cell-scale simulation
- Cell-cell interactions
- Microbial communities
- Ecosystem

Integrating Heterogeneous Biological Data through Cell-Scale Computational Models

Whole cell simulation represents an exascale computing challenge



Phenomics through an integrated *in silico* model

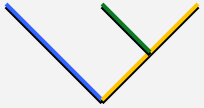
Price et al, *Trends in Biotechnology*, 2003

Biochemical Reaction Networks

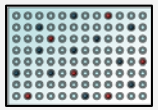
Statistical Influence Networks

Data Sources

Phylogenetic Data



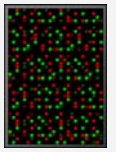
Physiological Data



Literature

PubMed

Genome Annotation

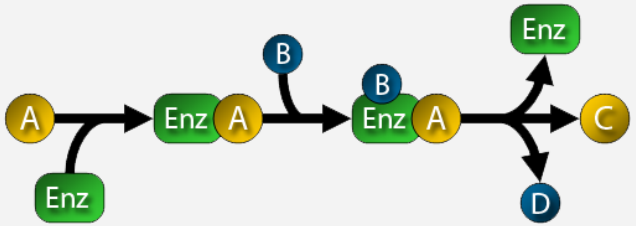


Interactomics

More detail (biochemistry, etc.)

Less detail

Reaction Stoichiometry

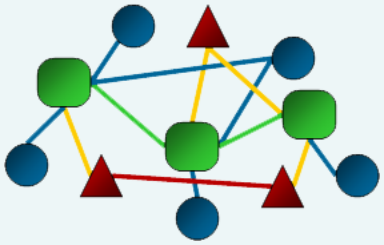


	Enz	A	Enz-A	B	Enz-A-B	C	D
Rxn. 1	-1	-1	+1	0	0	0	0
Rxn. 2	0	0	-1	-1	+1	0	0
Rxn. 3	+1	0	0	0	-1	+1	+1

Integrated Network Data

- Transcriptomics →
- Proteomics →
- Metabolomics →

Interaction Networks

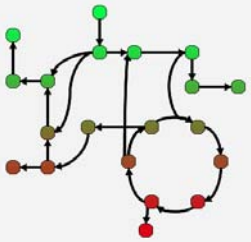


Protein-Metabolite
Protein-Protein
DNA-Protein
DNA-DNA

Application of Constraints

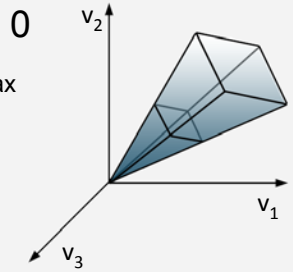
Network Inference

Constraint-Based Model



$S \cdot v = 0$

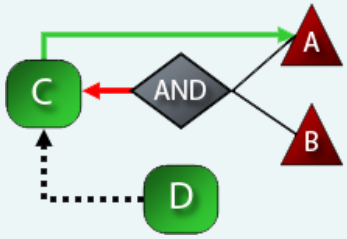
$v \le v_{max}$



Mathematical Model

Statistical Influence Network

$C = f(A,B,D)$

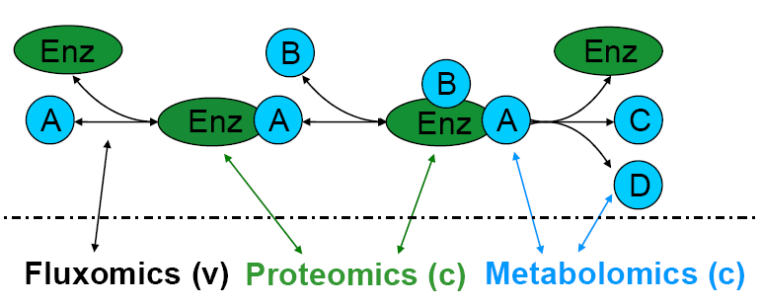


Activation
Inhibition
Indirect

Eddy, JA, and Price, ND, *Encyclopedia of complexity and systems science* (In press)

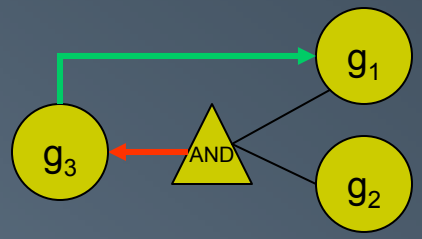
Two types of biological network models

Biochemical Reaction Networks



1) Directly mechanistic
2) Require significant knowledge of the system
3) Broadly applicable where biochemistry is known
4) Laws of physics and chemistry can be directly applied
5) Relate more closely to phenotype (i.e. fluxes)
6) Once reconstructed from biochemical data, network not likely to change (other than additional reactions)

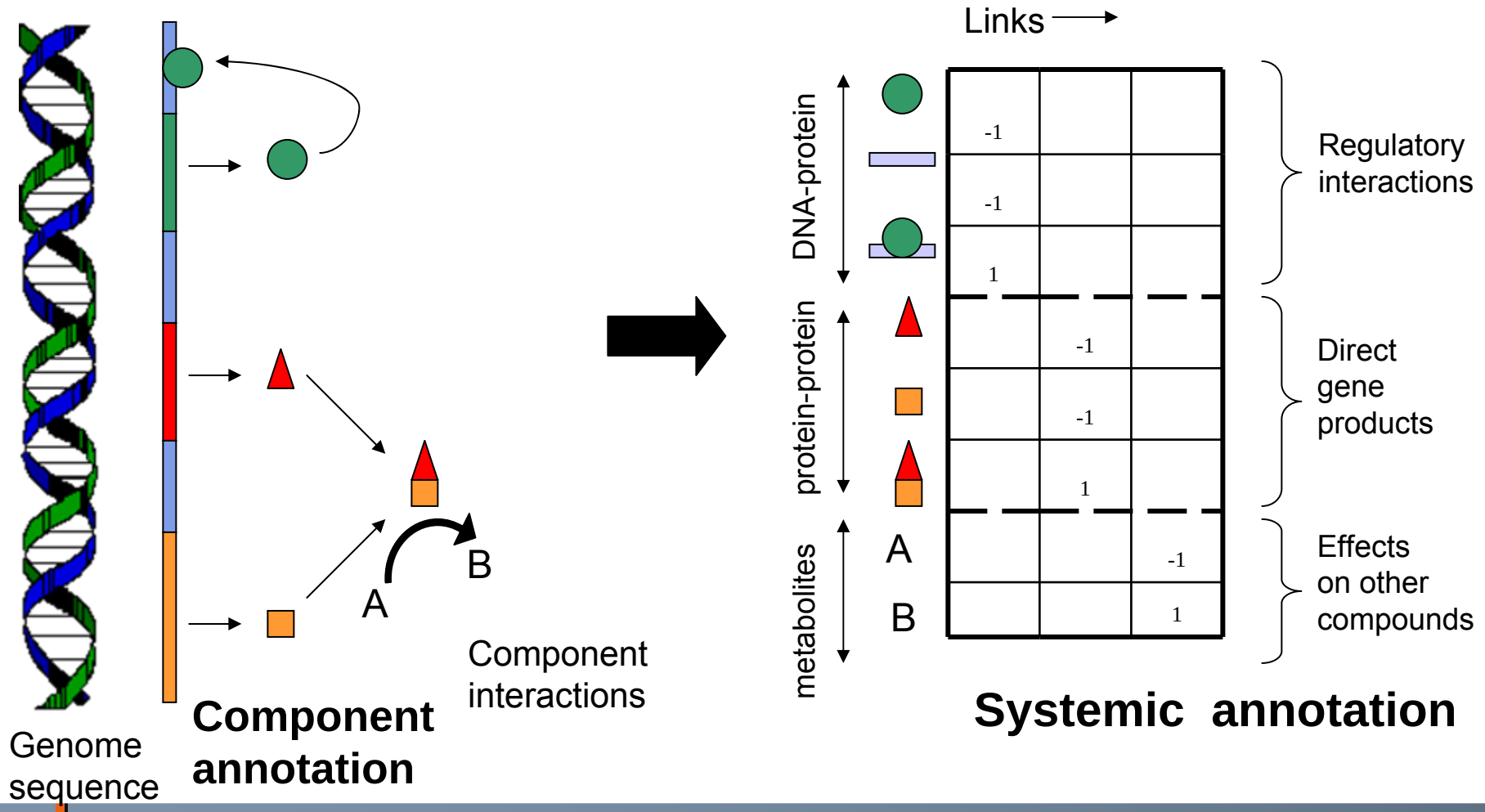
Statistical Influence Networks



1) Not generally mechanistic
2) Can be applied without needing prior knowledge (although can be incorporated)
3) Broadly applicable without knowledge of biochemistry
4) Physico-chemical laws typically not applicable/applied
5) Relate more directly to high-throughput data (i.e. transcriptomes)
6) Additional data can lead to significant network rewiring

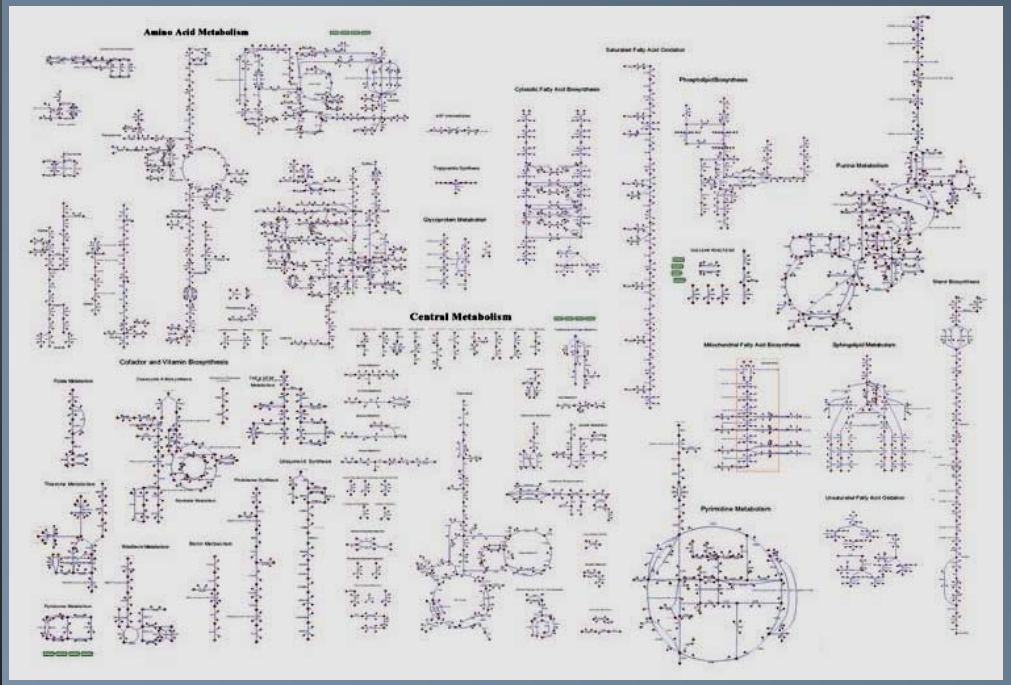
Price, N.D., and Shmulevich, I., *Current Opinion in Biotechnology*, 2007

From Component to Systemic Annotation of Genomes



Palsson, *Nature Biotechnology*, 2004

Mathematical Representation of a Biochemical Network



Stoichiometric Matrix

reaction

metabolite →

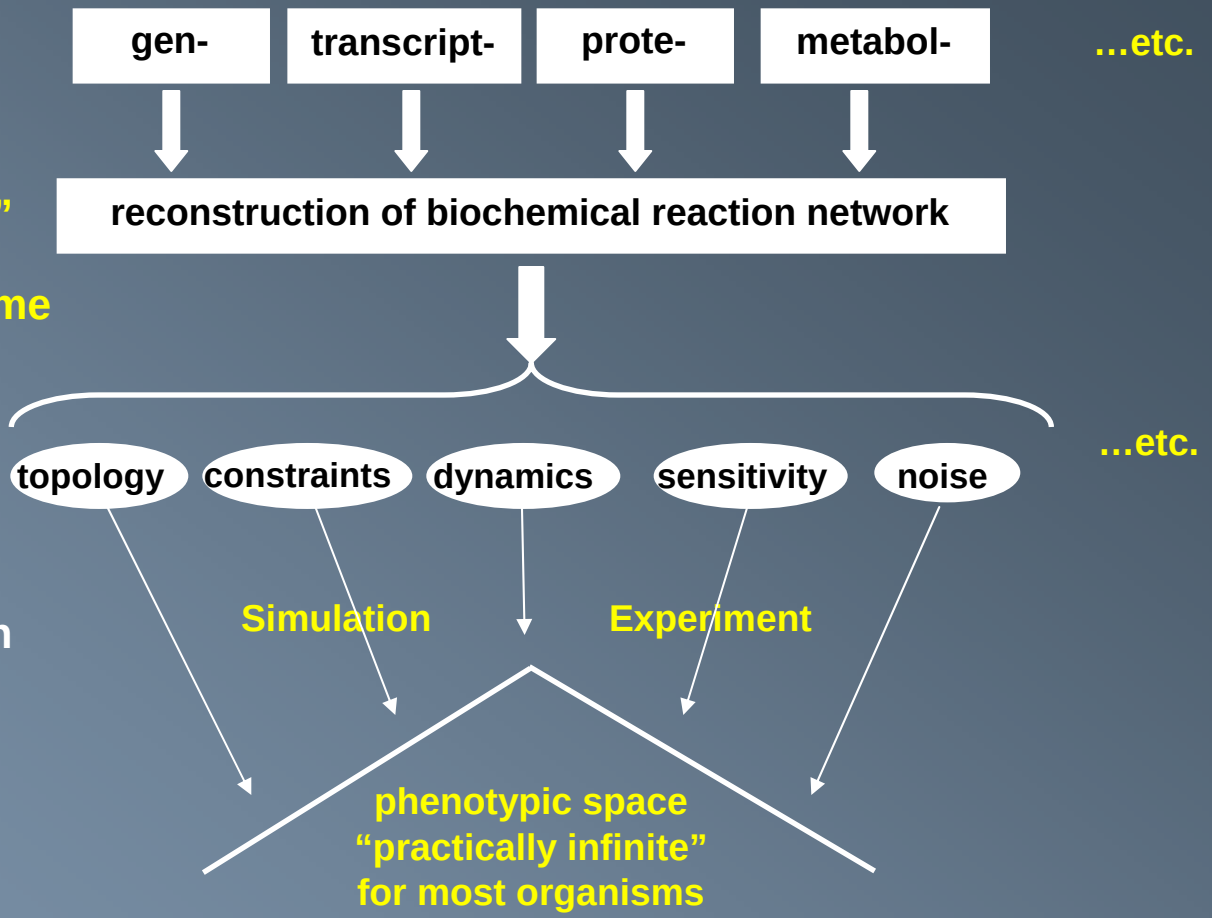
$$S = \begin{pmatrix} -1 & 0 & -1 & 0 & -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 1 & 1 & -1 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \end{pmatrix}$$

With the network represented in matrix form, the tools of linear algebra, linear programming, and convex analysis are available.

The Systems Biology Process

The role of reconstruction

1. **Components**
   Plurality of omics
2. **Reconstruction**
   "Systemic annotation"
   one set of reactions
   arising from the genome
3. ***in silico* modeling**
   plurality of methods
4. **Hypothesis generation and testing**
   -CHiP-Chip
   -Fluxomics

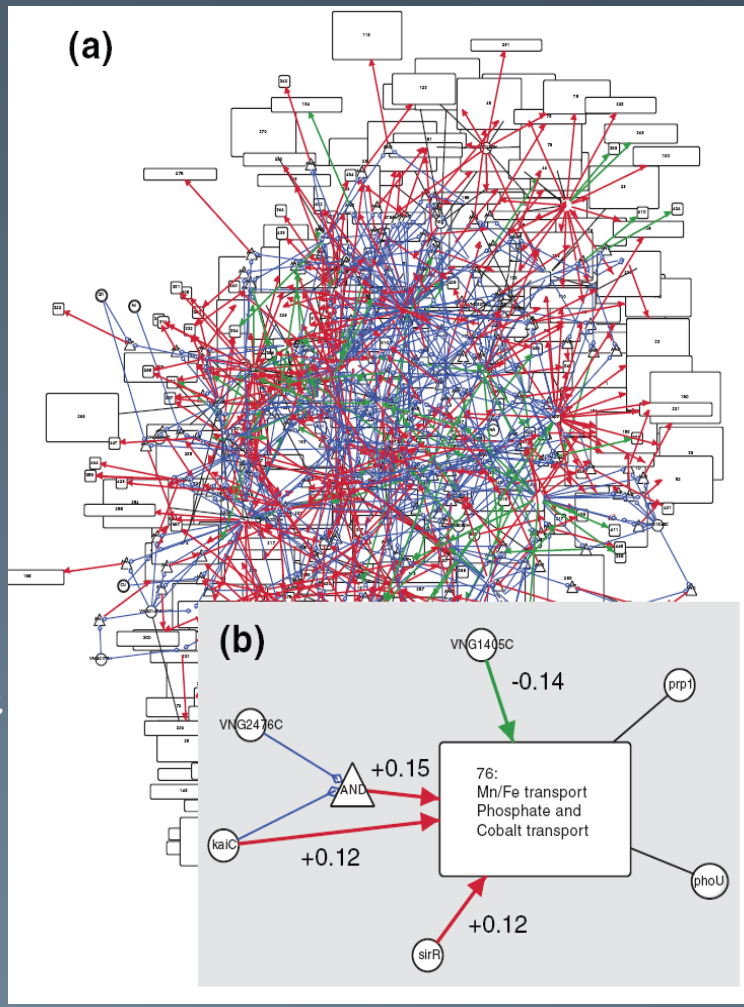


Computational challenges for biochemical network reconstruction

- Automated reconstructions of cellular networks in detail from genomes (e.g. Rick Steven's SEED)
- Can it be extended to forming computable networks?
- Can experimental data (e.g. knockout lethality data) be used as input as well
- Are their limits to the algorithmic nature of the problem?
- Is automated text mining a necessary component? (probably)
- Given inputs of genome, biochemical characterizations, knockout lethality, probabilistic inference, can a predictive computable network be generated? (Seems the answer should be YES)
- Also, can probabilistic metabolic networks be generated and shown to be useful (similar in ideas to Shmulevich's Probabilistic Boolean Networks)
- Reconstruction of dynamic models (would require sequence to kinetics computational capabilities

Computational challenges for statistical inference networks

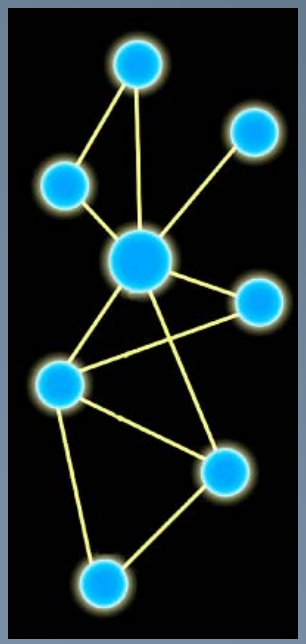
- Network inference at the genome-scale
  - Currently, this is done by bi-clustering before network inference can be done
  - Largest models currently work with hundreds of variables, but what is needed is thousands to tens of thousands
  - Is an interplay between computational and data limitations
- Enabling computation of genome-scale networks with feedback
  - For example, current models predict gene expression s given TF expression
- Integrating heterogeneous data types
  - E.g. linking proteome and transcriptome



Bonneau et al, *Genome Biology* (2006)

Beyond Genome-Scale Networks to Whole Cell Simulators

- Adding spatial component to models will require greatly increased computational power (and data generation)
- Simulation of physical properties of molecular machines



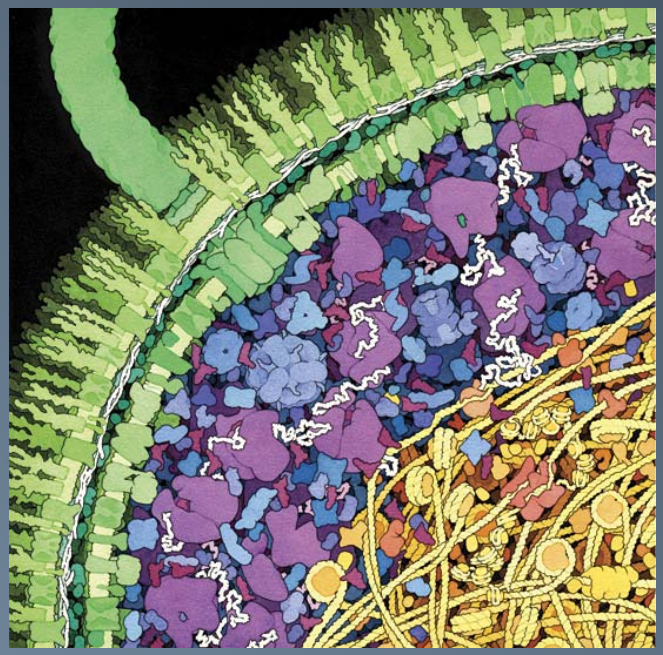


Image by David Goodsell

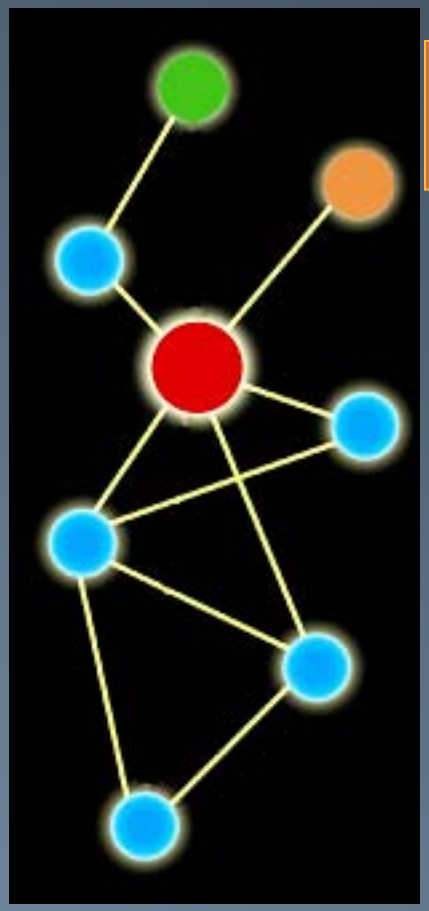
COMPUTATIONAL CHALLENGES FOR PERSONALIZED MEDICINE

INSTITUTE FOR GENOMIC BIOLOGY
University of Illinois at Urbana-Champaign

DEPARTMENT OF CHEMICAL AND BIOMOLECULAR ENGINEERING

Systems View of Disease

- Diseases are the result of one or more perturbed biomolecular networks
- These perturbations lead to differences in the abundance of biomolecules (e.g. mRNA, proteins, metabolites)
- These changes can then be measured and used for molecular diagnostics of disease
- Thus, reporters of the state of these networks are available, if we can learn to read the signals



dynamics of pathophysiology

diagnosis

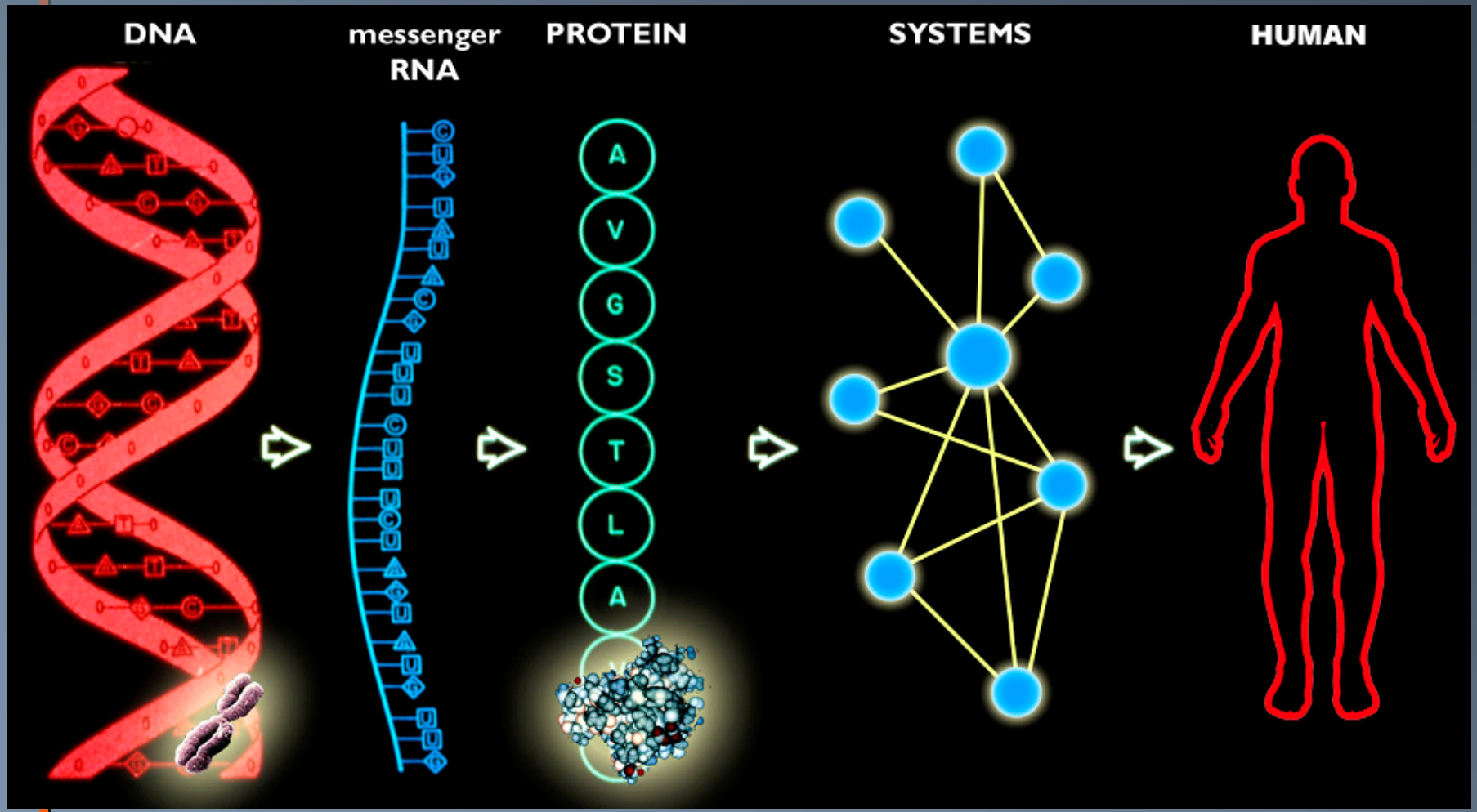
therapy

prevention

Foundational Data for Personalized and Predictive Medicine

- Individual Genome Sequences
  - Two people sequenced so far
    - James Watson: Co-discoverer of structure of DNA
    - J. Craig Venter – One of pioneers leading human genome sequencing
  - Will provide personalized information for each patient
  - Will provide probabilistic health futures
- Blood Diagnostics
  - 1000s of individual measurements
  - Patterns will be used to read out a current heath state
  - Taken repeatedly over the lifetime of a patient
    - Thus, patient can act as their own 'control' when changes from previous norms emerge
  - Represents the interplay between the digital information of the genome and the interactions with the environment throughout the lifetime of the patient

Example Types of Biological Information



Computational Challenges of Systems Medicine

- The $1000 genome will mean that eventually we can have genome sequences for at least hundreds of thousands of individuals
- Diseases, such as cancer, are multi-genic and influenced by a variety of environmental factors
- Thus, we will need to mine this data to identify diagnostic patterns that will guide therapy choice
- Computational challenges associated with the high-combinatorics of personalized medicine are enormous

Computational Challenges for Personalized Medicine Diagnostics

- Thus, we can imagine that to identify powerful diagnostics, we will need to:
  - Link genome sequence data to patient records and blood diagnostic measurements (current and over time)
  - Search for patterns requiring mutations in multiple points in the genome, requiring a number of environmental factors (hopefully linked through previous studies to the blood) etc.
- There are 6 Billion bases in the human genome, each of which could, in theory, be involved in disease (the actual number may be much lower, though)
- Most diseases are multi-geneic – current thought is that cancers results from ~6 mutations that are different in each case – even within what are considered the same cancer – and that symptoms can be non-existant from subsets of these mutations
- The combinatorics of these problems leads quickly into very large search space where full enumeration will not be possible – and thus advanced computation with efficient approximate search strategies will be needed

Tracking perturbed networks through molecular signals in blood

- By learning to track network perturbations through blood measurements, the blood will become a novel means for studying human biology and medicine, including:
  - Normal physiology
  - Virtually all diseases
  - Development
- However, we are not currently at the point we can do this in higher organisms.
- To develop this vision in full will require
  - Models of each cell type in body
  - Models of secretion patterns in vivo
  - Computational separation of signal from multiple sources in the blood

Moving Beyond Diagnostics to Therapy Discovery

- To truly understand and be able to control multi-geneic diseases, we must be able to model the effects of these mutations on systems
- This requires personalized computational models for personalized medicine
- Eventually, we would like to have human disease simulators that, given a genome and then supplemented over time with additional information (e.g. blood diagnostics) from interaction with the environment, could predict therapies and provide the possibililty to actually fix disease states.
- There is a huge information barrier (in addition to experimental) that will require huge amounts of computation to realize

Conclusions

- Systems Biology presents a myriad of computational challenges that must be met, including simulation at the level of molecules, pathways, cells, communities, and ecosystems.
  - Today, I focused primarily on challenges for simulating genome-scale networks in cells
- The future of systems medicine clearly will require large investments in increasing computational power in order to harness the amount of information that will be available for each patient – VASTLY greater than it is today.

Contact Information

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www.igb.uiuc.edu/labs/price/home.html

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Further Reading

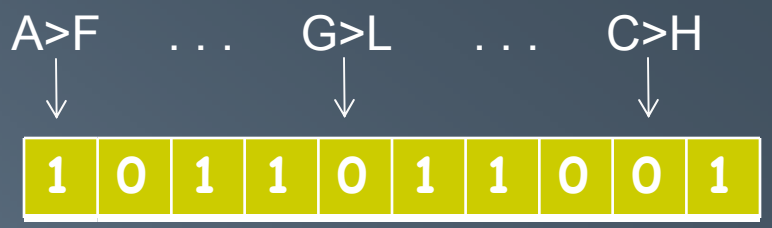
Price, N.D., et al, "*Systems Biology and the Emergence of Systems Medicine*," Genomic and Personalized Medicine: From Principles to Practice (Ginsburg, G. and Willard, H, editors), In Press – feel free to email me if you'd like an advance copy.

Challenges for genome-scale biochemical network simulations

- Constraint-based approaches only ones currently used at the genome-scale
  - Optimization methods (e.g. flux balance analysis) computationally inexpensive
  - Optimization-based re-engineering of networks is feasible for small numbers of permutations, but not large - so are areas of large-scale optimization of re-engineering problems that could benefit from 'exascale' resources
- Genome-scale dynamic models not yet feasible
- Genome-scale stochastic, single-cell models even further away

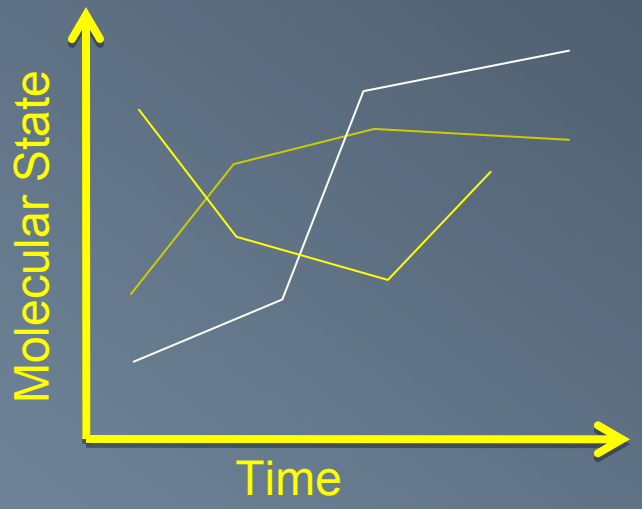
Moving into the Blood

- Differentiating multiple diseases
  - Organ specific molecular signatures
  - Combining multiple signatures
  - Broader studies for differentiation



Readout: Cancer 1, 2, 3 …
Stage 1, 2, 3, …

- Stratification vs. Progression
  - Different diseases
  - Different stages



Acknowledgments

University of Illinois

Price Lab

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Seth Hanson
Azeem Husain

Institute for Systems Biology

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M.D. Anderson Cancer Center

Wei Zhang, Ph.D.
Jonathan Trent, M.D.
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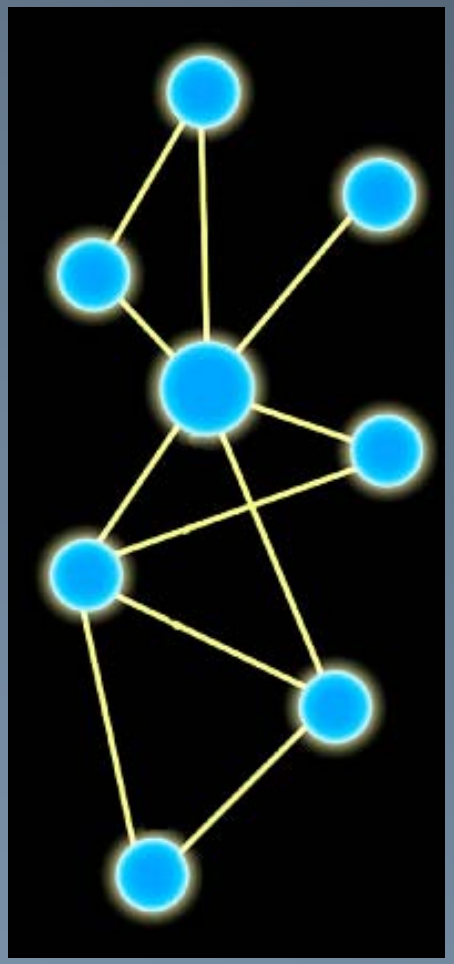
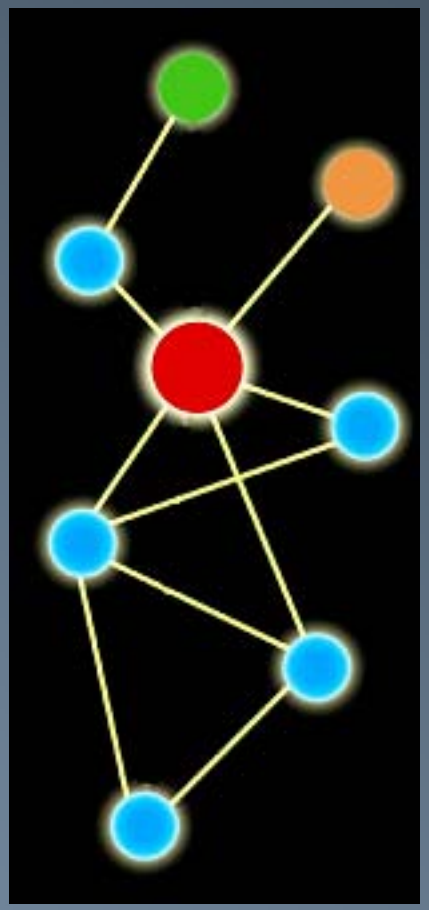
Lab Website

www.igb.uiuc.edu/labs/price/home.html

Disease Arises from Disease Perturbed Networks



Non-Diseased



Diseased

dynamics of pathophysiology

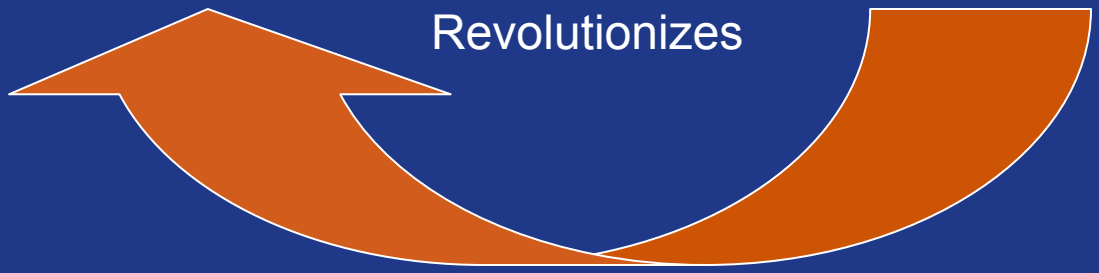
diagnosis

therapy

prevention

Biology/Medicine

Technology
Computation

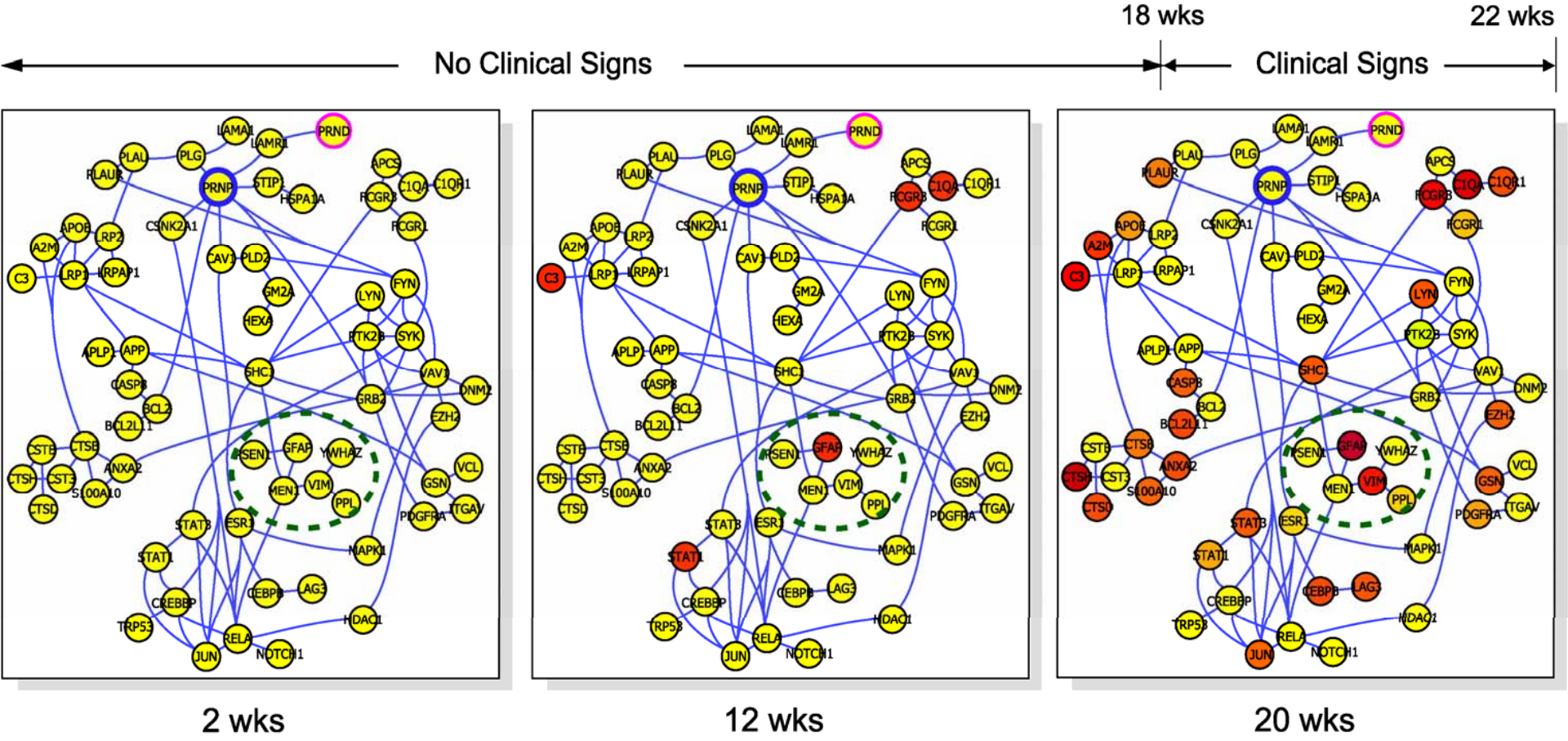


Biology dictates what new technology should be developed; technology opens new frontiers in biology for exploration.

Computational Challenges: moving to the exascale

- Systems Biology
- Personalized Medicine
  - Individualized genome sequences for most people in U.S. and other developed nations (moving into rest of world eventually as well)
  - So, billions of sequences
    - How to read the signals
  - Blood diagnostic

Dynamics of a Prion Perturbed Network



Innovations for the Next 20 Years in Biology and Medicine:

- Systems approaches to biology and medicine will dominate biological sciences in the 21st century--global science networks and strategic partnerships.
- Systems approaches will pioneer new opportunities in agriculture, bio-energy, biology, bio-remediation, health, nutrition, an understanding of human development, neurobiology and better educational strategies.
- Systems approaches will move medicine from its current reactive mode to predictive, preventive, personalized and participatory (P4 medicine) modes--with a focus on wellness.
- The digitalization of biology and medicine will constitute a far greater revolution than the digitalization of information technologies.
- P4 medicine and the digitalization of medicine will enable health care to become cheap and easily executed. Therefore exportable throughout the globe including to the developing world.
- Strategic partnerships and international networks in science will allow us to attack big scientific problems.

Enormous economic opportunities in biology

Outline

- Molecular signature classifiers
- Relative expression reversals
- Diagnosis similar cancers requiring very different treatments
  - Gastrointestinal stromal tumor
  - Leiomyosarcoma
- Survival prognosis marker

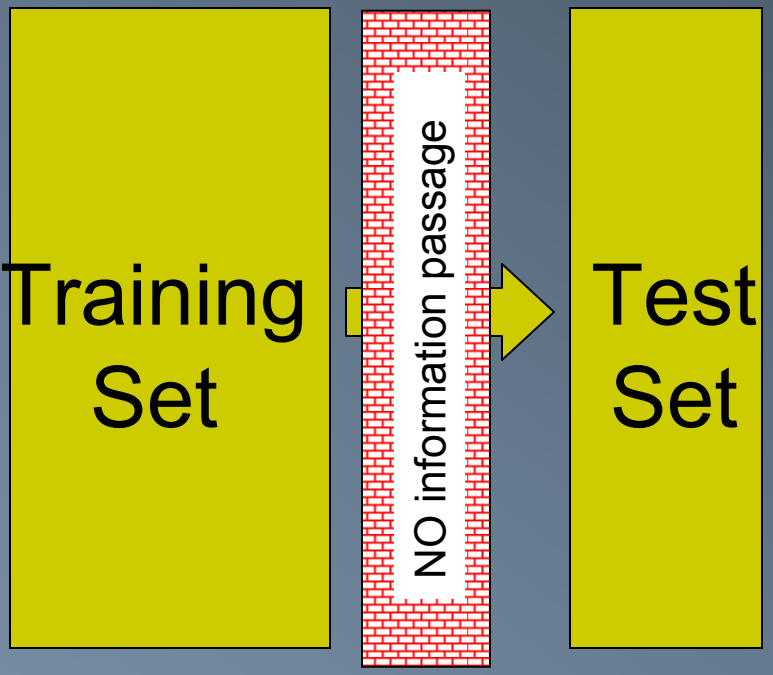
Molecular signature classifiers

- The goals of molecular classification of tumors:
  - Identify subpopulations of cancer
  - Inform choice of therapy
- Generally, a set of microarray experiments is used with
  - ~100 patient samples
  - ~ 10^4 transcripts (genes)
- This very small number of samples relative to the number of transcripts is a key issue
  - Feature selection & model selection
- Also, the platform of microarray used can have a significant effect on results

Estimating Error on Future Cases

- Methodology
- Best case: have an independent test set
- Resampling techniques
  - Use cross validation to estimate accuracy on future cases
  - Feature selection and model selection must be within loop to avoid overly optimistic estimates

Resampling: Shuffled repeatedly into training and test sets.



Average performance on test set provides estimate for behavior on future cases

Can be MUCH different than behavior on training set

Relative Expression Reversal Classifiers: The Top Scoring Pair Approach

- Find a classification rule as follows:
  - **IF** *gene A* > *gene B* **THEN** class1, **ELSE** class2
- The classifier is chosen finding the most accurate and robust rule of this type from *all possible pairs* in the dataset
- If needed a set of classifiers of the above form can be used, with final classification resulting from a majority vote (*k*-TSP)

Geman, D., et al. Stat. Appl. Geneti. Mol. Biol., 3, Article 19, 2004
Tan et al., *Bioinformatics*, 21:3896-904, 2005

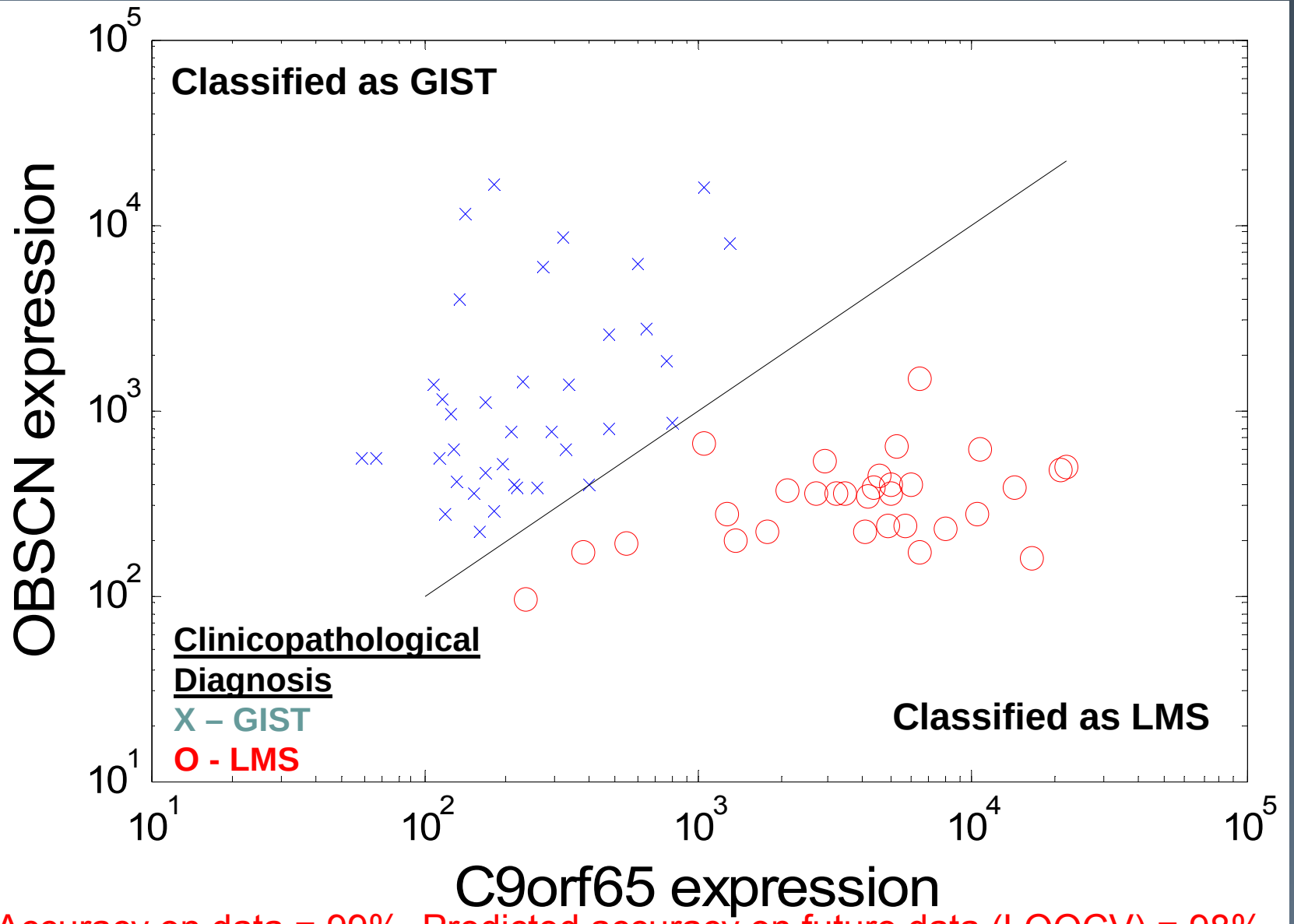
Rationale for k-TSP

- Based on concept of **relative expression reversals**
- Advantages
  - Does not require data normalization
  - Does not require population-wide cutoffs or weighting functions
  - Has reported accuracies in literature comparable to SVMs, PAM, other state-of-the art classification methods
  - Results in classifiers that are easy to implement
  - Designed to avoid overfitting
    - n= number of genes, m = number of samples
    - For the example I will show, this equation yields:
    - 1 0^9 << 10^20

$$\binom{n}{2} << 2^m$$

Diagnosing Types of Sarcoma
GIST and LMS

- Gastrointestinal Stromal Tumor (GIST) and Leiomyosarcoma (LMS)
  - Morphologically very similar and thus hard to correctly distinguish using current methods
  - Have different treatments, so correct diagnoses is critical
    - Can be a life or death decision
- Key differences
  - Gleevec efficacy
    - GIST: 50-80% effectiveness in completely eradicating the cancer
    - LMS: negligible effects
  - Expression of c-kit protein
    - Almost never expressed in LMS
    - Mixed for GIST – but majority have c-kit expression
    - Heterogeneous within the tumor



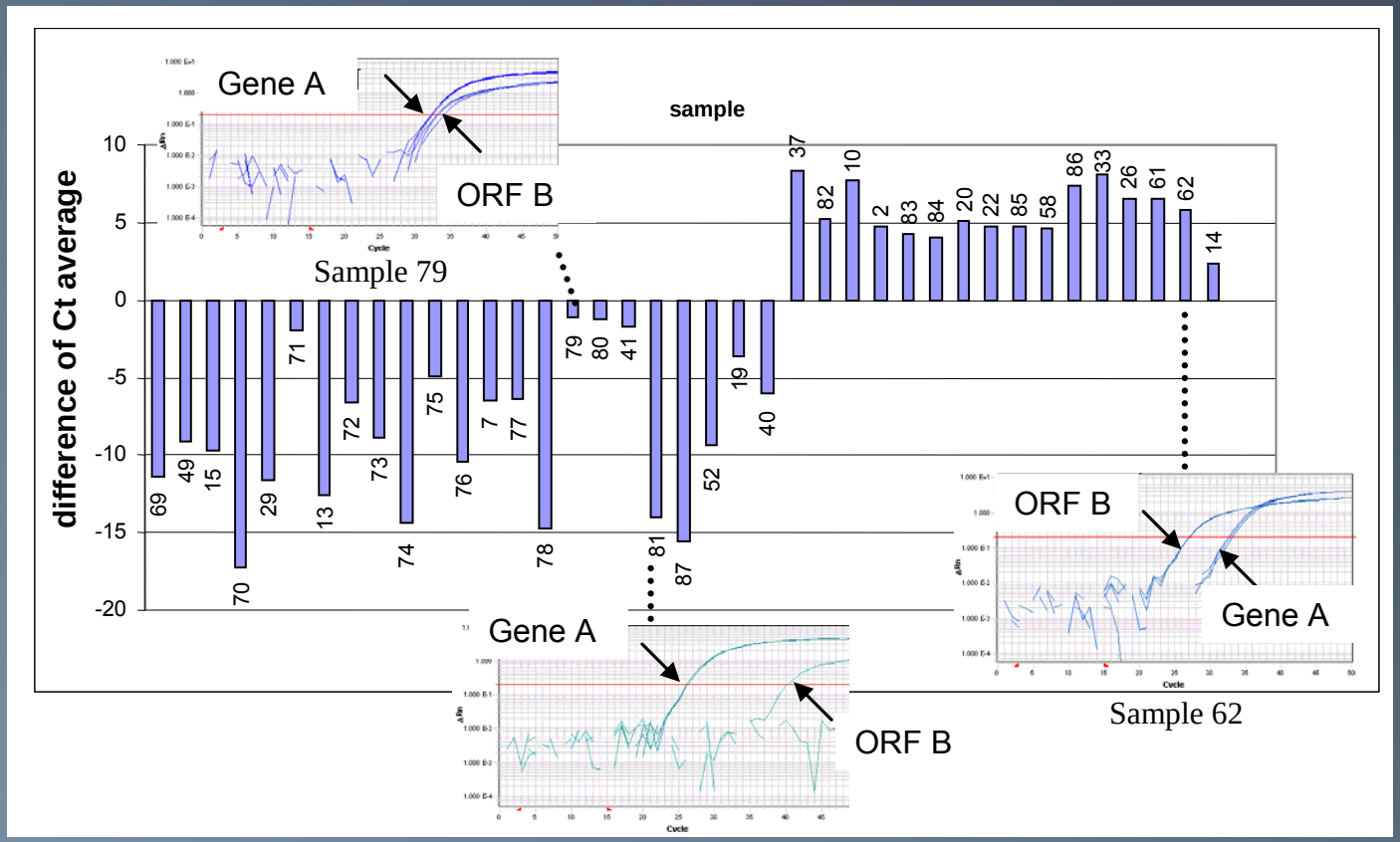
Accuracy on data = 99% Predicted accuracy on future data (LOOCV) = 98%

Price, N.D. et al, *PNAS* (2007)

RT-PCR Classification Results

LMS

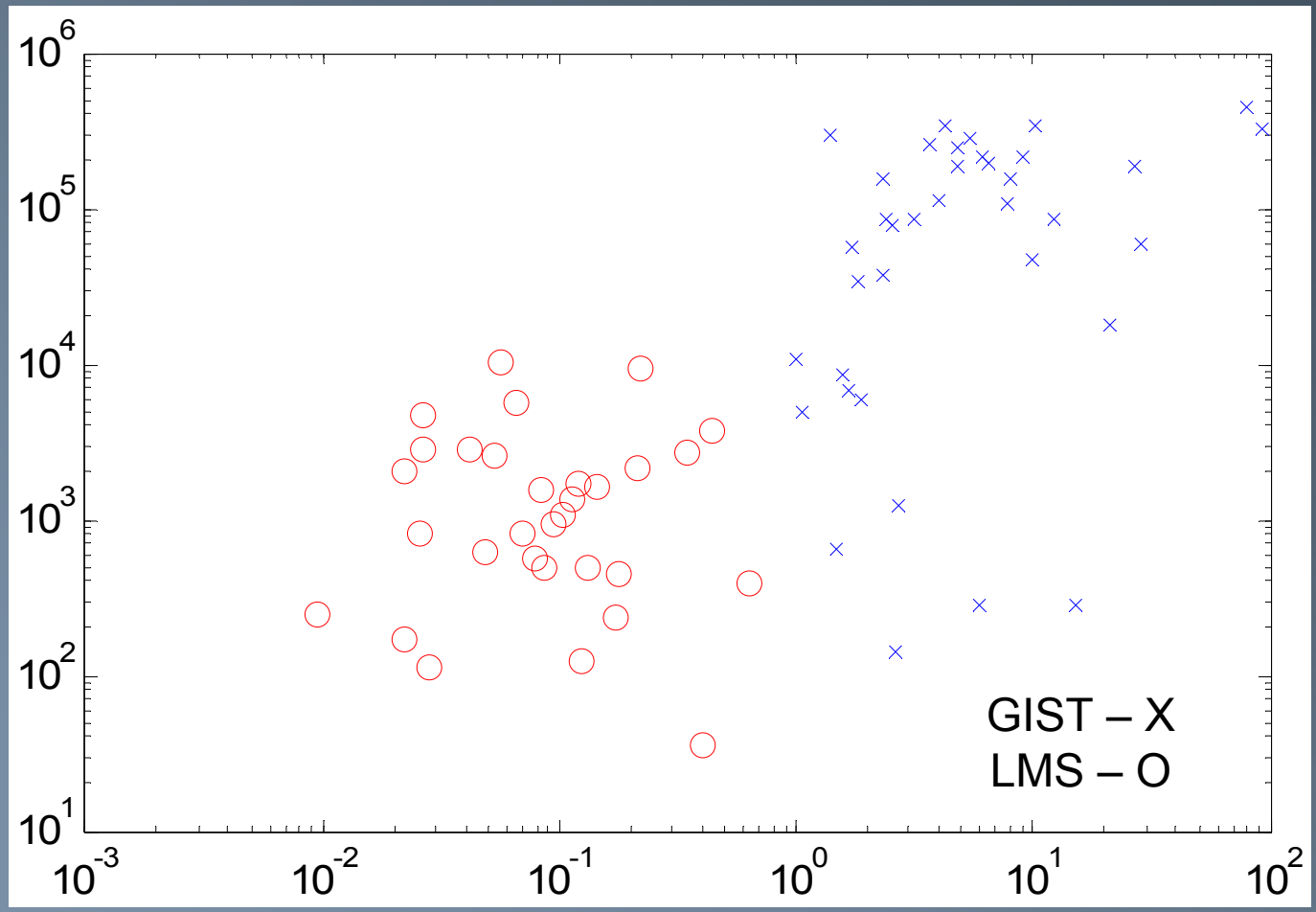
GIST



- **100% Accuracy**
  - 19 Independent Samples
  - 20 samples from microarray study
    - including previously indeterminate case

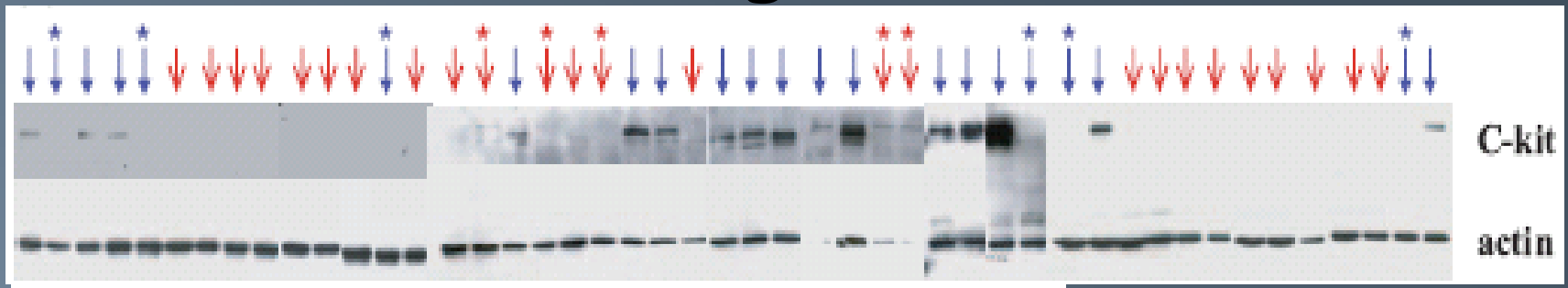
Price, N.D. et al, *PNAS* (2007)

Comparative accuracies of c-kit expression and the 2-gene classifier



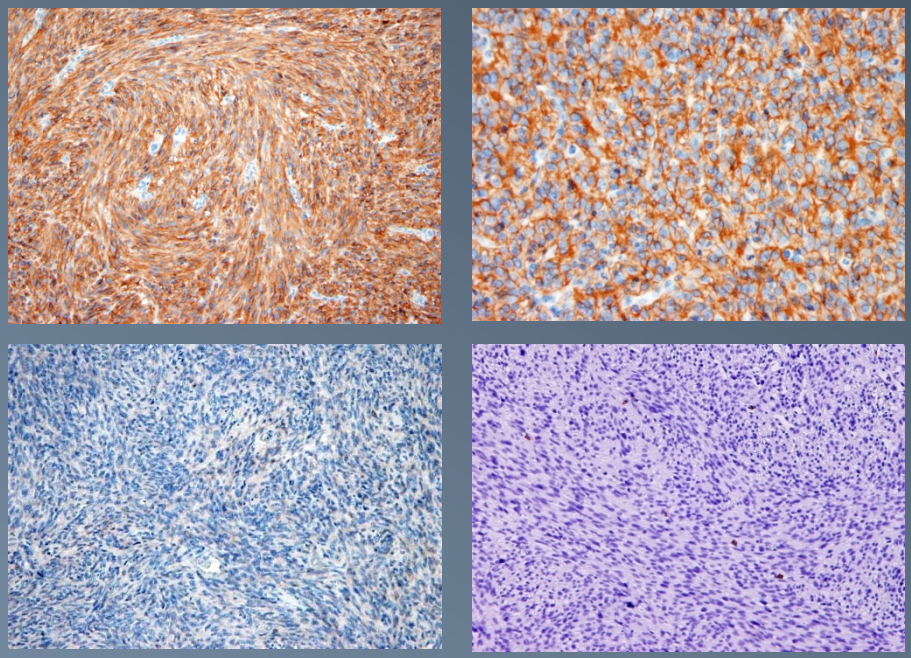
Price, N.D. et al, *PNAS* (2007)

Kit Protein Staining of GIST-LMS



Blue arrows - GIST Red arrows - LMS

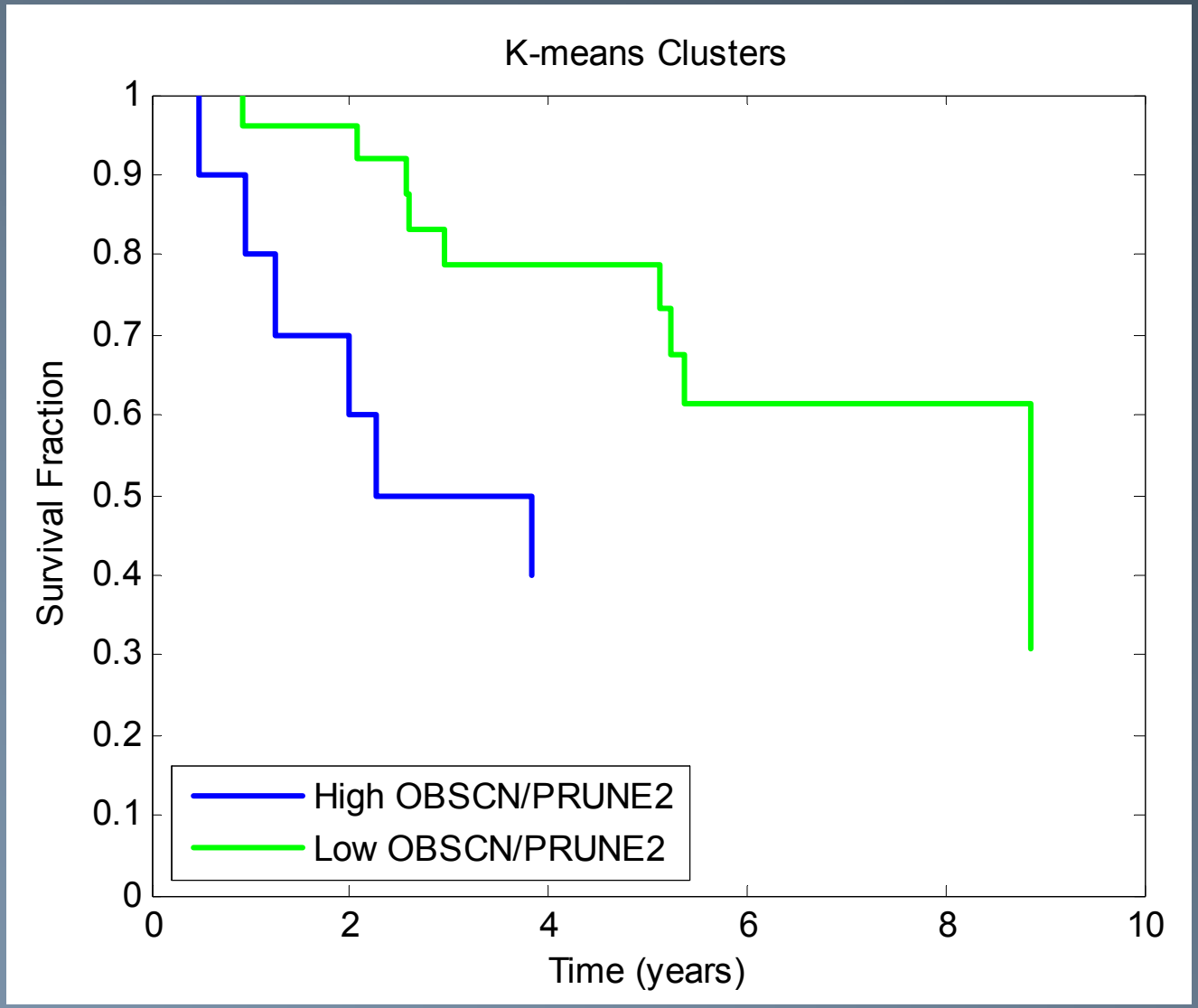
- Top Row – GIST Positive Staining
- Bottom Row – GIST negative staining



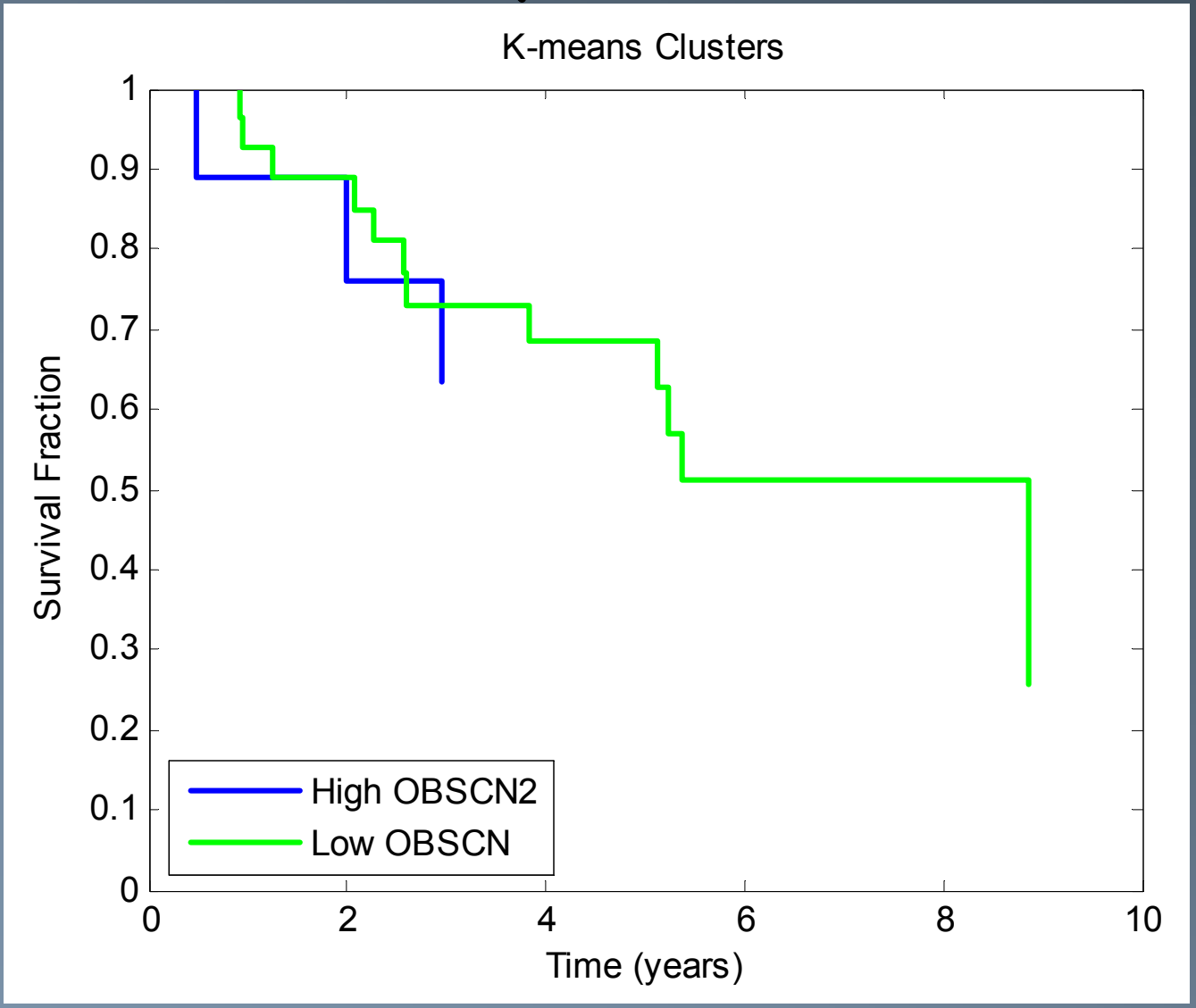
Accuracy as a classifier ~ 87%.

Price, N.D. et al, *PNAS* (2007)

TSP and survival of GIST patients



OBSCN Expression & Survival



No real predictive capacity

TSP methods perform comparably to best machine learning techniques on multiple cancers

Table 3. LOOCV accuracy of classifiers for binary class expression datasets

Method	Leukemia	CNS	DLBCL	Colon	Prostate1	Prostate2	Prostate3	Lung	GCM	Average
TSP	93.80	77.90	**98.10**	**91.10**	**95.10**	67.60	97.00	98.30	75.40	88.26
k-TSP	95.83	**97.10**	97.40	90.30	91.18	75.00	97.00	98.90	85.40	**92.01**
DT	73.61	67.65	80.52	80.65	87.25	64.77	84.85	96.13	77.86	79.25
NB	**100.00**	82.35	80.52	58.06	62.75	73.86	90.91	97.79	84.29	81.17
k-NN	84.72	76.47	84.42	74.19	76.47	69.32	87.88	98.34	82.86	81.63
SVM	98.61	82.35	97.40	82.26	91.18	76.14	**100.00**	**99.45**	**93.21**	91.18
PAM	97.22	82.35	85.71	85.48	91.18	**79.55**	**100.00**	**99.45**	79.29	88.91

The best prediction rate for each particular data set is highlighted in boldface.

Tan, A.C. et al, *Bioinformatics* (2005)

A few general lessons

- Choosing markers based on relative expression reversals of gene pairs has proven to be very robust with high predictive accuracy in sets we have tested so far
  - Simple and independent of normalization
- Easy to implement clinical test ultimately
  - All that's needed is RT-PCR on two genes
- M.D. Anderson Cancer Center is now further evaluating this test as part of its clinical biomarkers program – so hopefully this will benefit patients in the near term

Future Directions

- Evaluate and extend methods based on relative expression reversals to:
  - Differentiate many diseases simultaneously
  - Evaluate more complex phenotypes
    - Survival
    - Distant and local recurrence
    - Metastasis
  - Integrate with network information to inform types of comparisons to make