Scalable Computational Methods for the Analysis of High-Throughput Biological Data

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Outline of Talk

Biological Foundations

Correlation Coefficients

Graph Algorithms

High Performance Computations

Radiological Data Analysis

Ongoing Work

Foundations

Systems Biology

- **How do biological entities function in unison and at all levels of scale?**
  - **genes**
  - **proteins**
  - **cells**
  - **tissues**
  - **organisms**
- **Linkage, communication and networks (*graphs!*)**

Foundations

Omics:

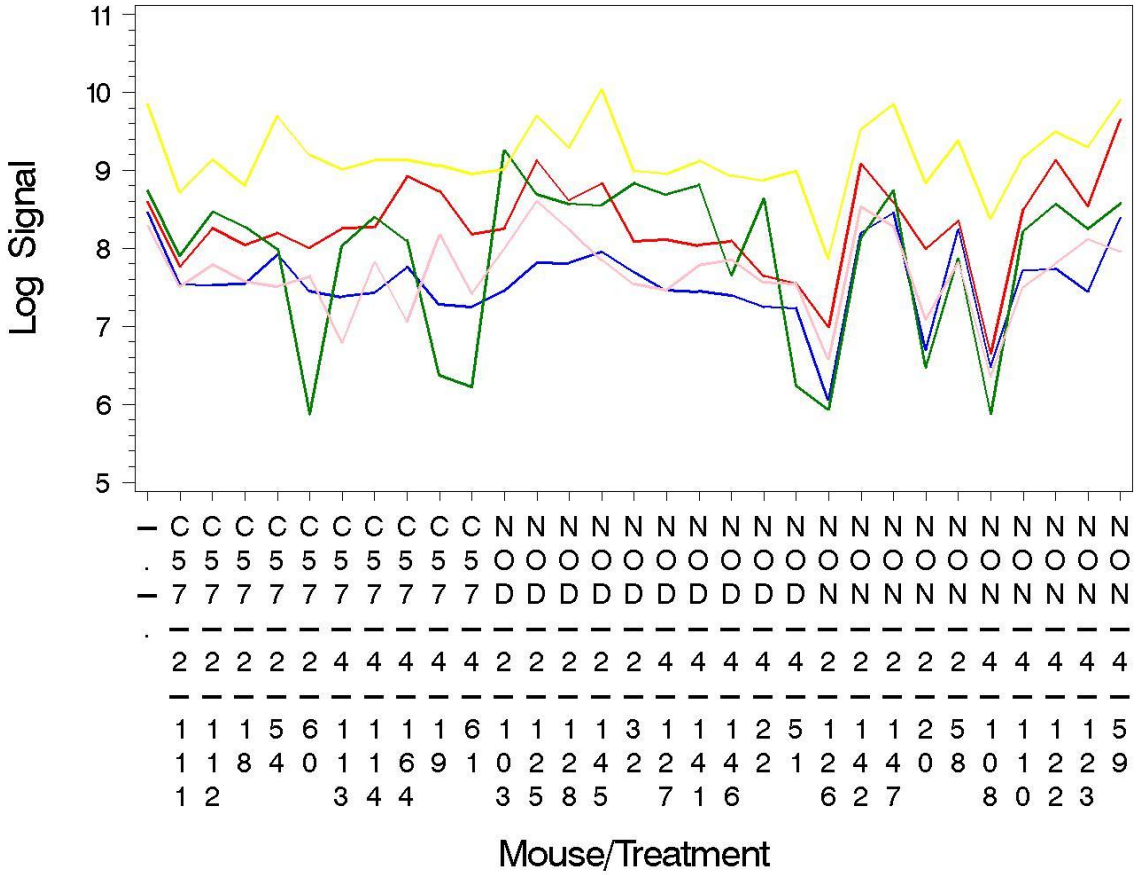
- **Key to deciphering complex systems**
- **Humans: 10^{13}+ cells, 200+ cell types**
- **Genome (blueprint, 20K+ genes, 10M+ polymorphisms)**
- **Proteome (functional units, unknown # of proteins)**
- **Transcriptome**
  - **Translation (tRNA) via transcription (mRNA)**
  - **Function and Signaling (siRNA, miRNA, etc)**
- **Other: metabalome, lipidome, interactome, ...**

Correlation

Correlation Coefficients

Here are five mouse Genes with Pearson correlations of at least 0.65. What of

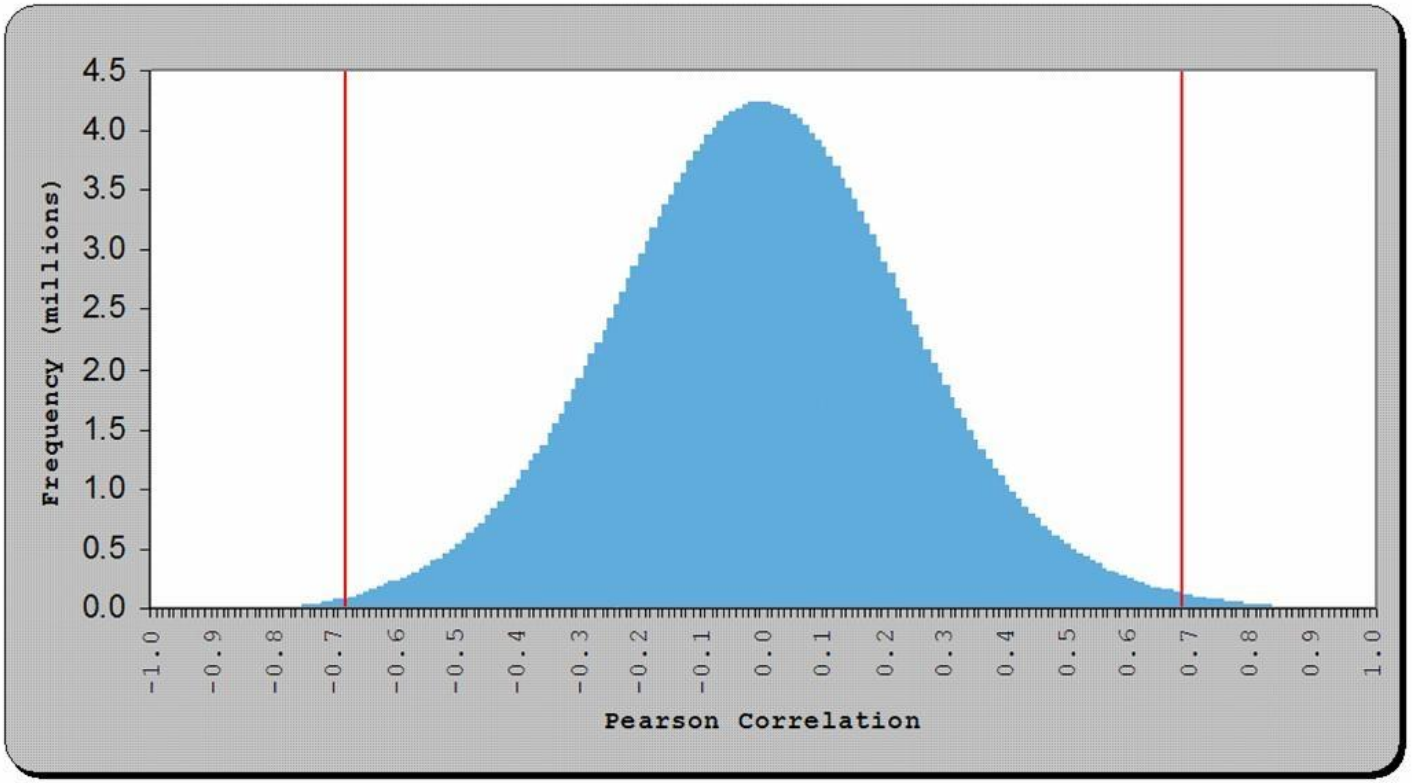
- **noise?**
- **experimental design?**
- **circadian rhythms?**
- **sex, tameness, etc?**
- **other confounds?**
- **other metrics?**



Correlation

Coefficient Profiles, High-Pass Filtering and Graphs

- Pearson, Spearman, Mutual Information, ...
- p-values, q-values, Bonferroni corrections, false discovery rates, ...

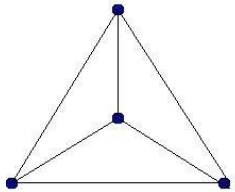


Dense Subgraph Extraction

Computational Tools

Maximum Clique

K_4



- must run often
- time is a limiting factor
- exploit fixed-parameter tractability (FPT)
  - *NP*-complete problem on n and k
  - solve in time $f(k)n^c$ not $n^{f(k)}$
  - Vertex Cover (dual) in time $O(1.2759^k k^{1.5}+kn)$

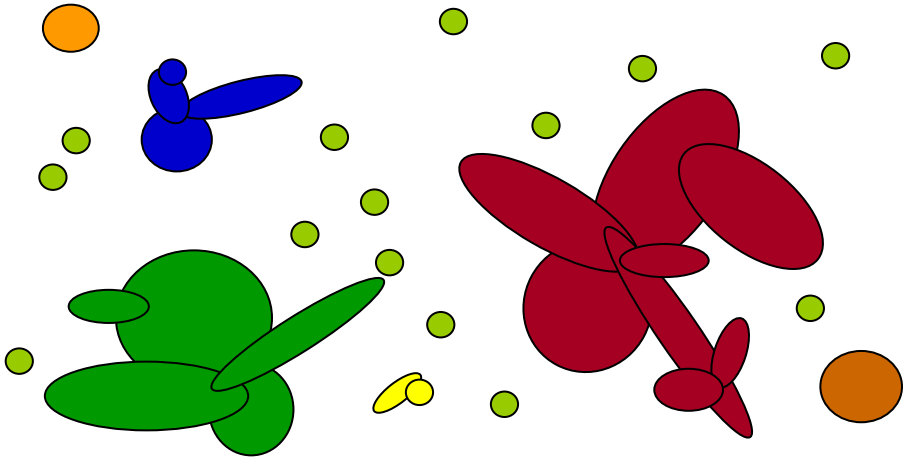
Dense Subgraph Extraction

Computational Tools

Maximum Clique

Maximal Clique

- huge outputs
- various orderings
- memory is often the limiting factor



Dense Subgraph Extraction

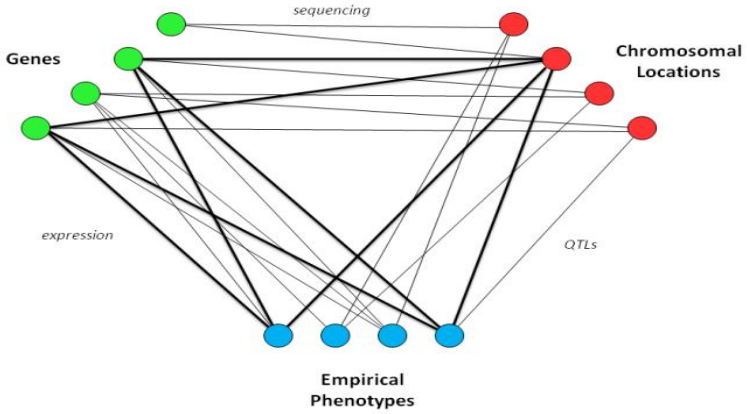
Computational Tools

Maximum Clique

Maximal Clique

Other Clique Variants

- *k*-clique
  - new algorithms
  - *k*-partite graphs
- Paraclique
  - form of soft thresholding for noisy data



A 2-2-1 three-clique

Supercomputer Implementations

Codes ported to platforms such as the SGI Altix (NERSC)

- **256 dual-CPU processors, each clocked at 1.5 GHz**
- **two terabytes of shared memory**

Supercomputer Implementations

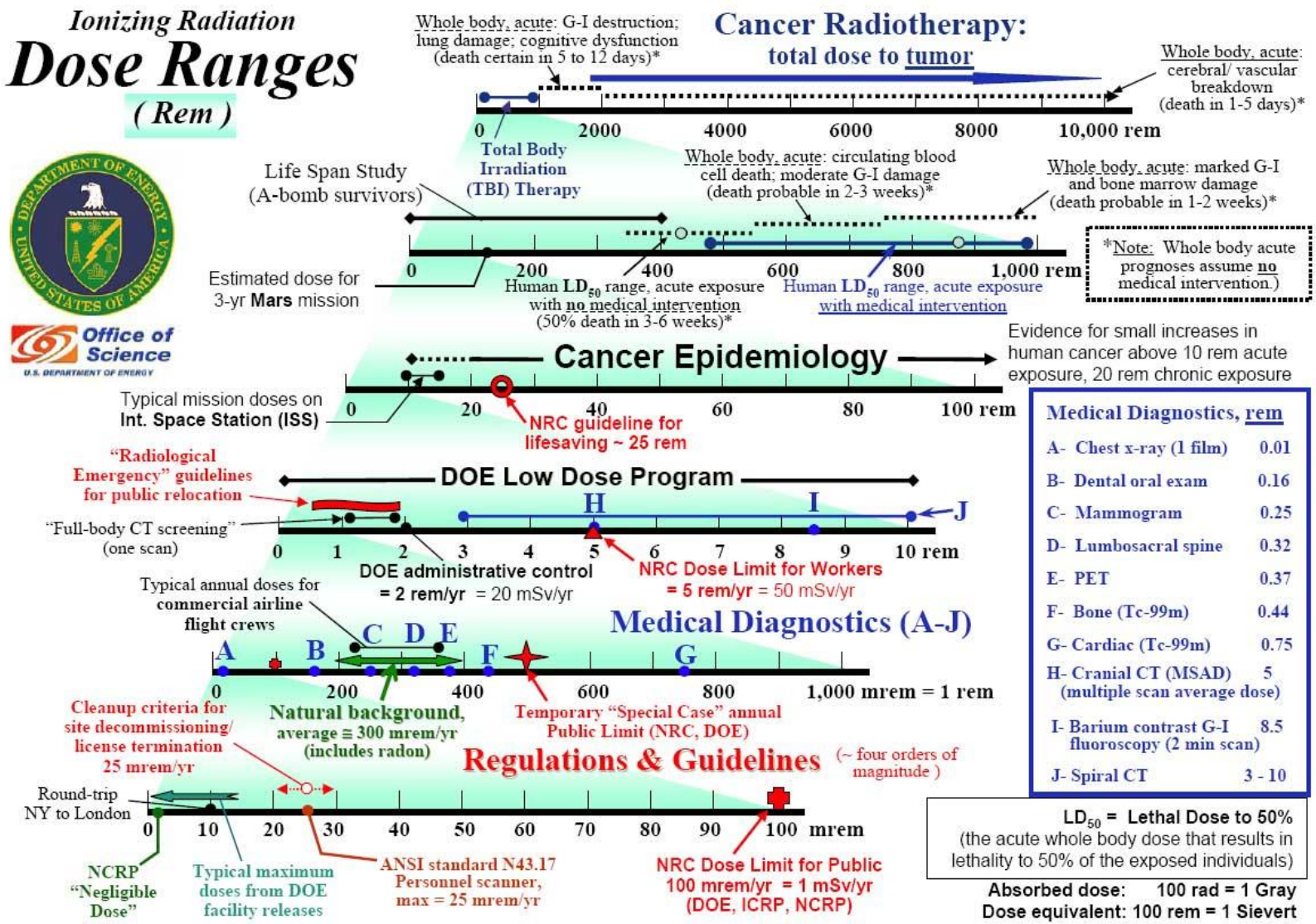
And Kraken, the new Cray XT5 system at ORNL

- currently the world's largest academic (non defense) computer
- 10^5 processor cores, nearly 10^{12} calculations/second (a petaflop)

Sample Application

Low dose ionizing radiation and its impact on human health

- Sources of low dose radiation exposures
  - medical diagnostics
  - hazardous waste abatement
  - handling materials for nuclear weapons and power systems
  - even terrorist acts such as dirty bombs
- In all these the major type of exposures will be low dose IR (primarily X- and gamma-radiation) from fission products
- Are low doses safe, perhaps even therapeutic?
- Identify biological pathways that are activated or repressed by IR
- Understand the risks so that we may protect the workforce



http://lowdose.tricity.wsu.edu

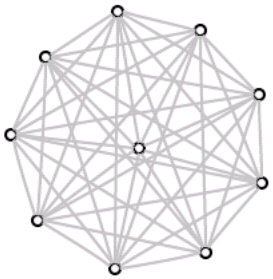
Sample Application

Case-control mouse data obtained at ORNL

- six strains, two durations
- acute dose of ten centigrays (rads)
- harvest skin, spleen, thymus, testis
- measure 21,547 transcripts

Sample Results

Example 1: a striking clique of size ten in dose



- populated with genes whose function is either associated with oxidative stress response or is unknown
- such an overexpressed ontology has an astronomically low p-value (unlikely to have occurred by mere chance)
- yet the same ten genes in control are only tenuously connected
- share a common transcription factor associated with IR?

Sample Results

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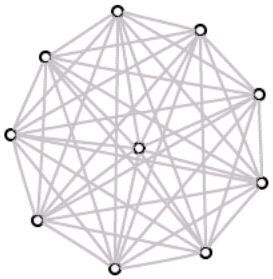

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Example 2: gene for Carboxylesterase 2 (*Ces2*)

- catalyzes hydrolysis of xenobiotics
- differentially expressed with IR
- differentially correlated with many immune function genes
- present in 31% of dose cliques, but only 0.7% of control cliques
- plays some central role in low dose IR response?

Sample Results

Example 3: gene for Tubby-like Protein 4 (*Tulp4*)

- a nucleus of six genes are putatively coregulated in dose
- in fact they appear together in 5765 dose cliques
- yet no more than two occur together in any control clique
- this nucleus includes genes known to be involved in
    - immune function
    - stress mediation
    - and so these are consistent with IR response

Sample Results

Example 3: gene for Tubby-like Protein 4 (*Tulp4*)

- a nucleus of six genes are putatively coregulated in dose
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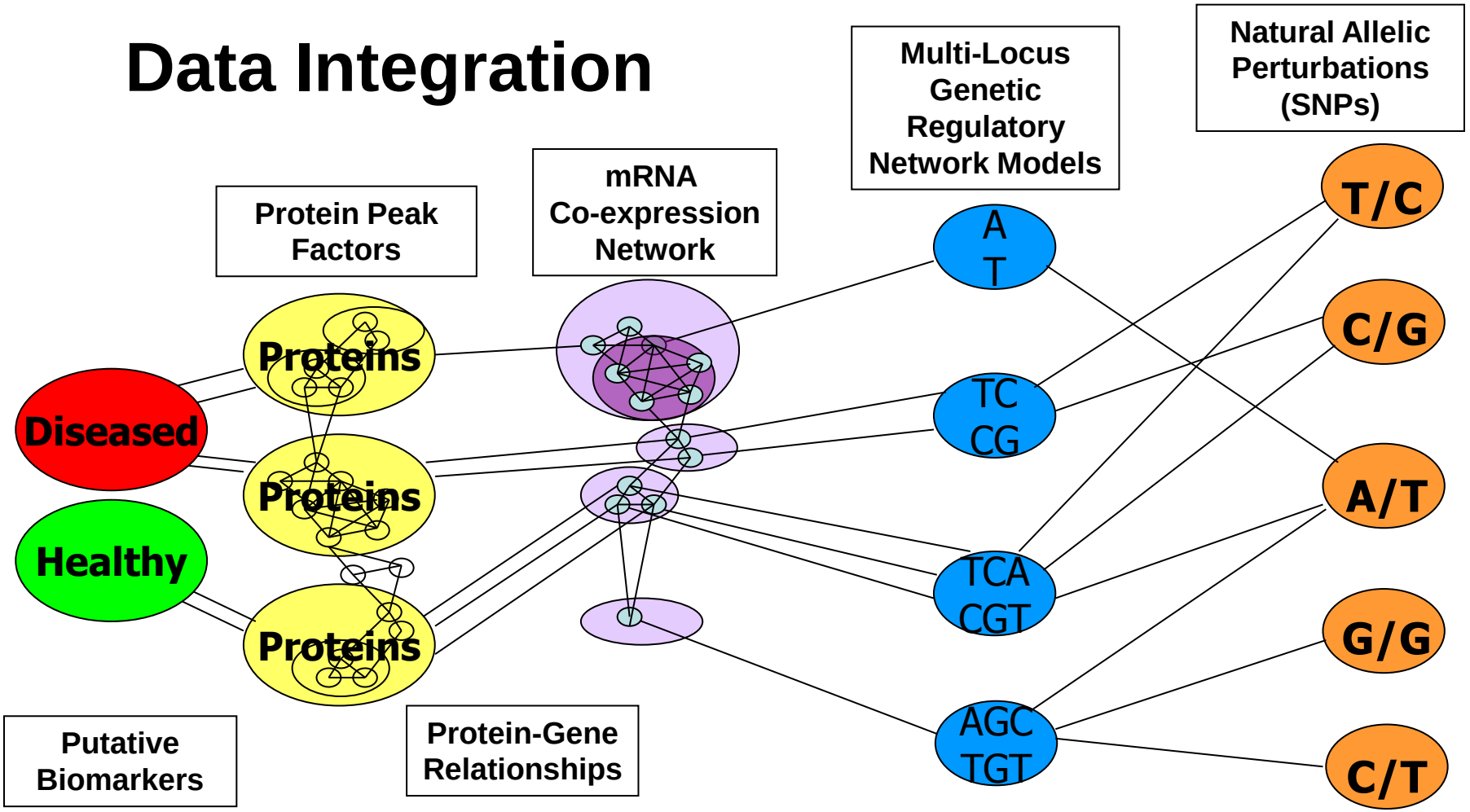
- this nucleus includes genes known to be involved in
    - immune function
    - stress mediation
    - and so these are consistent with IR response
- but one of these is Tulp4...why is a tubby-like protein here?
- original classification
    - based on sequence similarity to Tub, an obesity protein
    - responsive to oxidative stress
- it's in 4.7% of the dose cliques and only 0.01% of control
- novel role for Tulp4 as a transcriptional regulator of immune response to IR?

Sample Ongoing Work

Data Integration



Collaborators

Research Scientists (Incomplete!):

- Elissa Chesler (ORNL)
- Arnold Saxton (UT)
- Brynn Voy (ORNL)

Current Students:

- Patricia Carey
- John Eblen
- Boloye Gomero
- Jeremy Jay
- Sudhir Naswa
- Clinton Nolan
- Charles Phillips
- Gary Rogers
- Dinesh Weerapurage

Recent PhD Graduates:

- Faisal Abu-Khzam
- Xinxia Peng
- Andy Perkins
- Yun Zhang

Recent MS Graduates:

- Nicole Baldwin
- Bhavesh Borate
- Jordan Lefebvre
- Zuopan Li
- Jon Scharff

Come Join Us!

The University of Tennessee and Oak Ridge National Laboratory

- Applications
  - Alcoholism, Allergy, Cancer, Diabetes, Neuroscience, Radiology...
- Combinatorial Analysis of Algorithms
- Complex Cross (2^{10} RI Mouse Lines)
- Database and Website Development
- High Performance Computing
- Metabolomics, Proteomics, Transcriptomics, ...
- RNAi and µRNA Interference
- Work Alongside Both Computer and Domain Scientists!

Collaboratory Science at the Langston Lab

Computer Science, Mathematics, Molecular Biology, Statistics