Drug Discovery in the Era of Big Data

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Novartis Institutes for Biomedical Research
Developmental and Molecular Pathways

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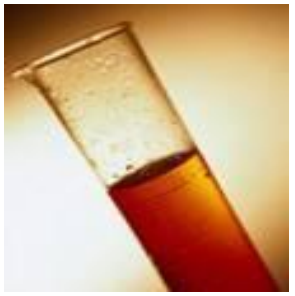
Novartis Institutes for BioMedical Research (NIBR)

Who we are

- Unique research strategy driven by patient needs
- World-class research organization with about 5 000 scientists globally
- Intensifying focus on molecular pathways shared by various diseases
- Integration of clinical insights with mechanistic understanding of disease
- Research-to-Development transition redefined through fast and rigorous “proof-of-concept” trials
- Strategic alliances with academia and biotech strengthen preclinical pipeline



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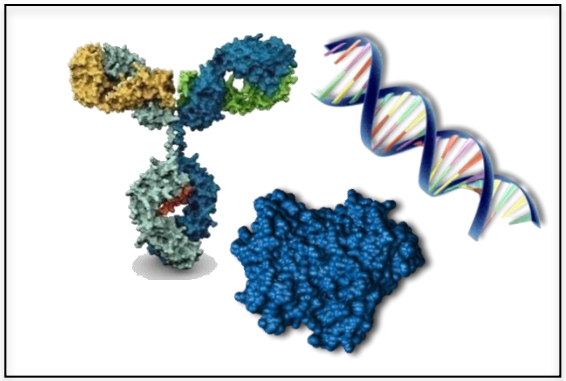
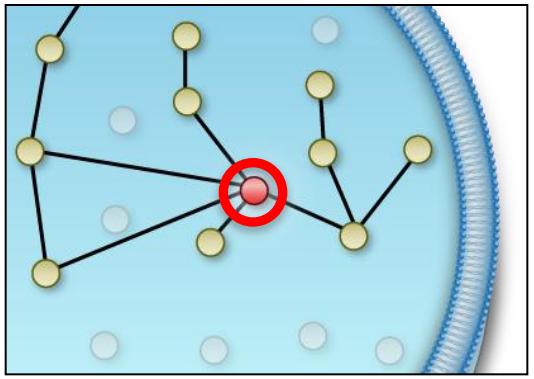
What we do

Antibody, siRNA and protein therapeutics

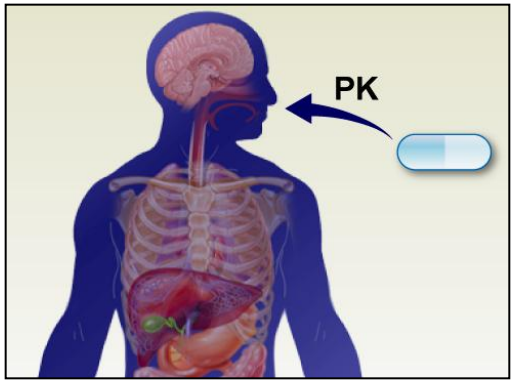


Medicinal Chemistry

Target Discovery - Pathways

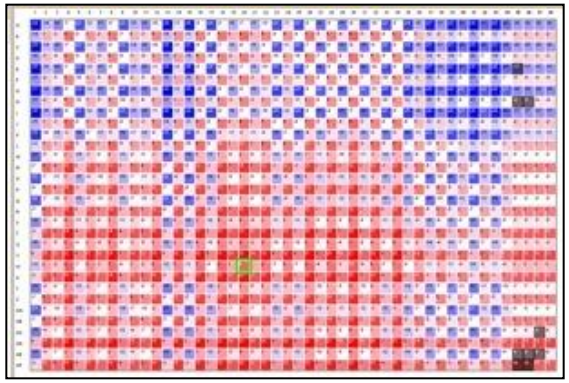


Translational Medicine



Preclinical Safety

Assay Development



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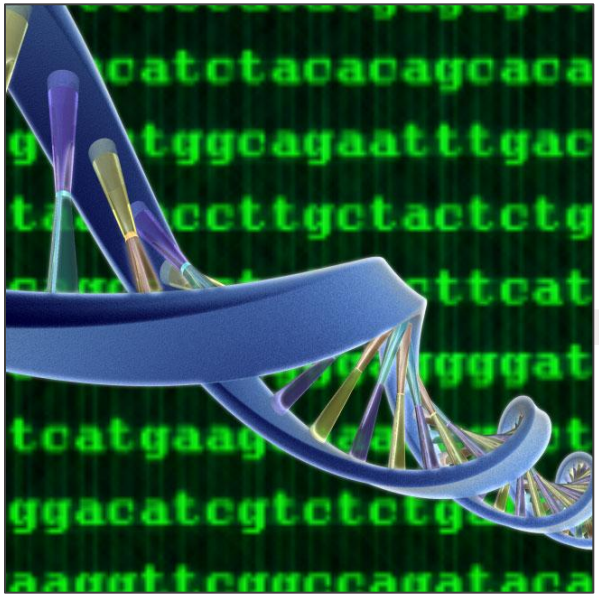
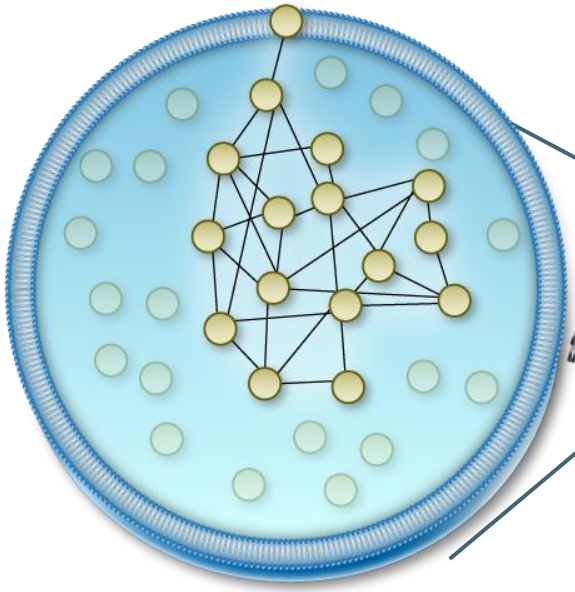
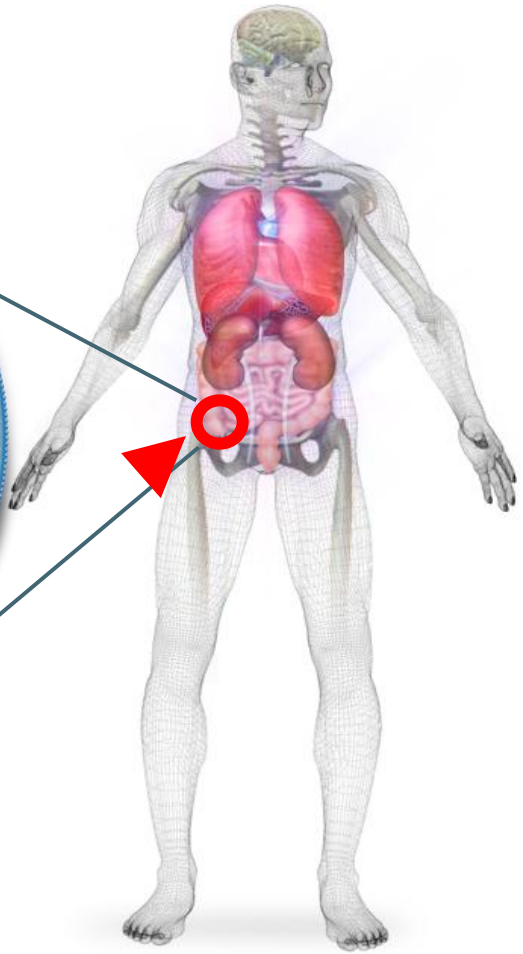
How we do it



Genome





Human Disease

Protein Networks, Molecular Pathways, are the Functional Units of the Cell

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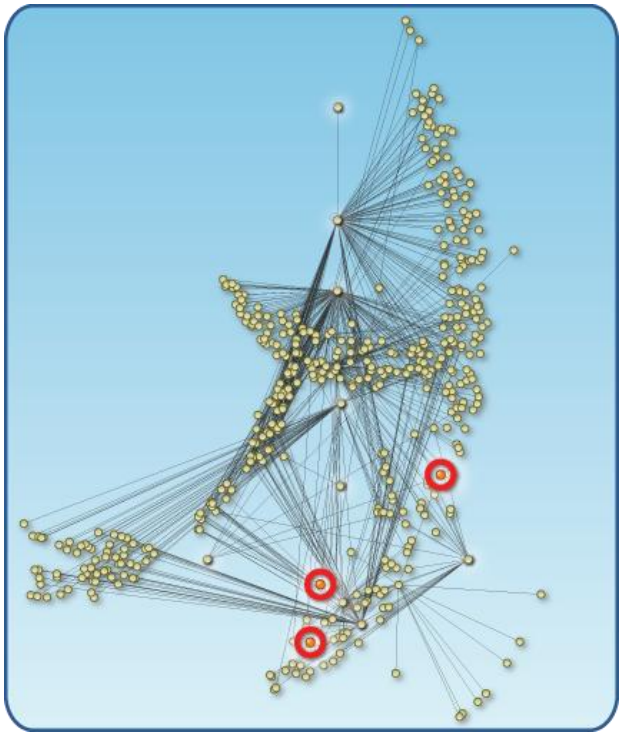
Developmental and Molecular Pathways

- Pathway Analysis for Target Identification/Validation:
  - Genomics
  - Proteomics
  - Model Organisms
  - High-throughput Screening
  - Computational Biology
  - RNAi Technology



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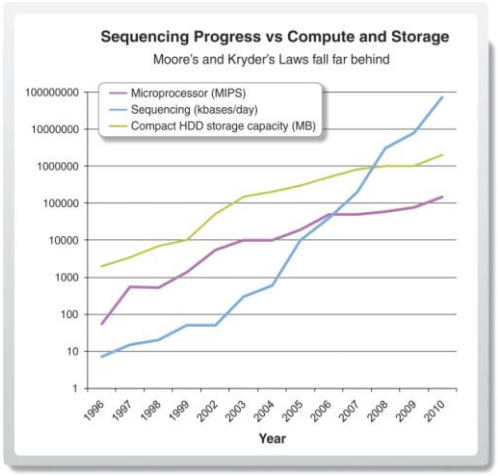
Current and Future Hurdles

Increasing Data Size



A doubling of sequencing output every 9 months has outpaced and overtaken performance improvements within the disk storage and high-performance computation fields.

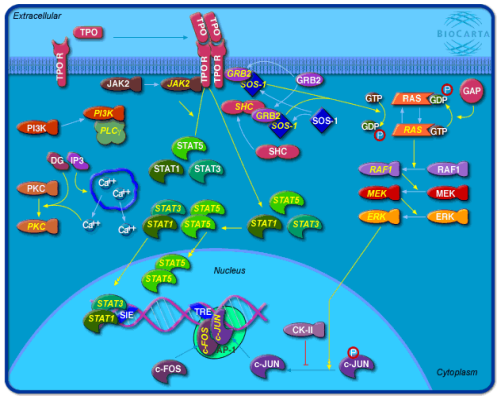
S D Kahn Science 2011;331:728-729

Increasing Dimensionality of Data

Public and NIBR Data

Biochemistry HTS	Proteomics	siRNA
Transcriptomics	Cell based screening	
Signature	High Content	Copy number
Exon array	NGS sequencing	Mutation
Compound Sensitivity	Metabonomics	

Increasing complexity



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Analytics at NIBR

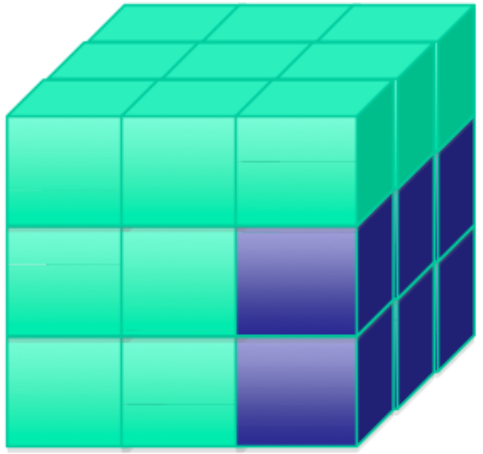
Where we are…what we need

- Standard solutions
  - R, Matlab, S (your programming language of choice)
  - SGE linux cluster
  - Custom code (MPI)
  - Analytics within a database is limited
  - Hadoop/Mahout
- Data sizes are growing rapidly and endpoints are unclear.
- Our problem lies in complex analytics on ever increasing data sizes.
- Where we need to be
  - Systems that mimic R but work on TB size data sets.
  - Need a large-scale analytics system that just works
    - Multiple users: scientists, analysts, developers with broad range of skill sets

SciDB

Data Management System for Large Scale Analytics

- DMAS – Data Management and Analytics System
  - Open source
- Data Model:
  - Nested multi-dimensional arrays
  - Array cells can be tuples of values or other arrays
  - Arrays can be sparse
- Data Storage:
  - Arrays are “chunked” in multiple dimensions in storage
  - Chunks are partitioned across multiple nodes
  - Each node is shared nothing
  - Chunks have adjustable overlap
- Architecture:
  - Share nothing cluster (10’s-1000’s of nodes)
  - Queries refer to arrays as primary data type
  - Query planner optimizes for specific function



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Feature Highlight – Multi-dimensional Arrays

Promoter Signature Profiling

What pathways are being perturbed by a modulator?

LMF

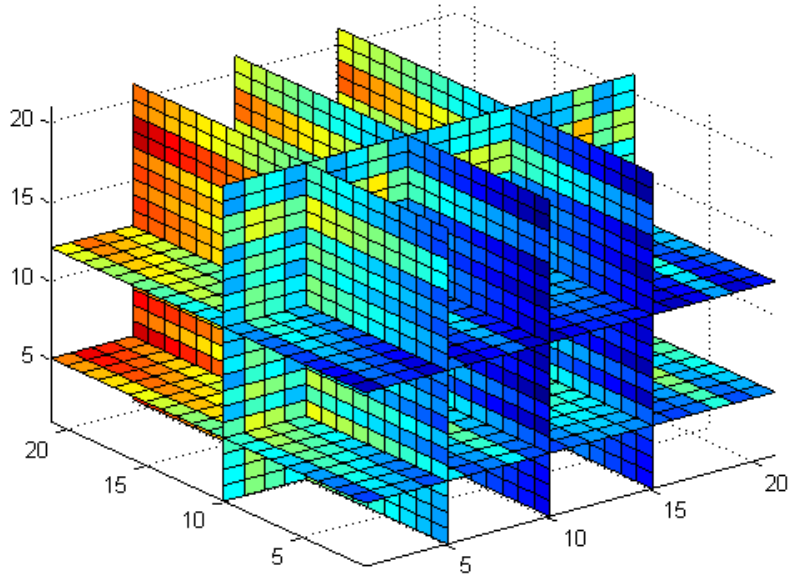
What compounds have similar transcriptional profiles?

HIP-HOP

What is the target of the modulator in yeast?

Chemical Proteomics

What proteins bind to my compounds?



Natural extensions:

- Subsetting by different dimensions
- Correlation by each dimension – where do they intersect
- Multi-dimensional statistics?

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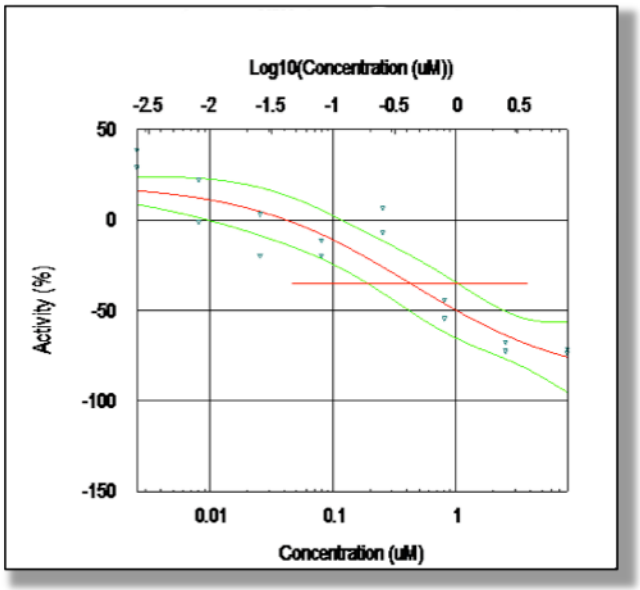
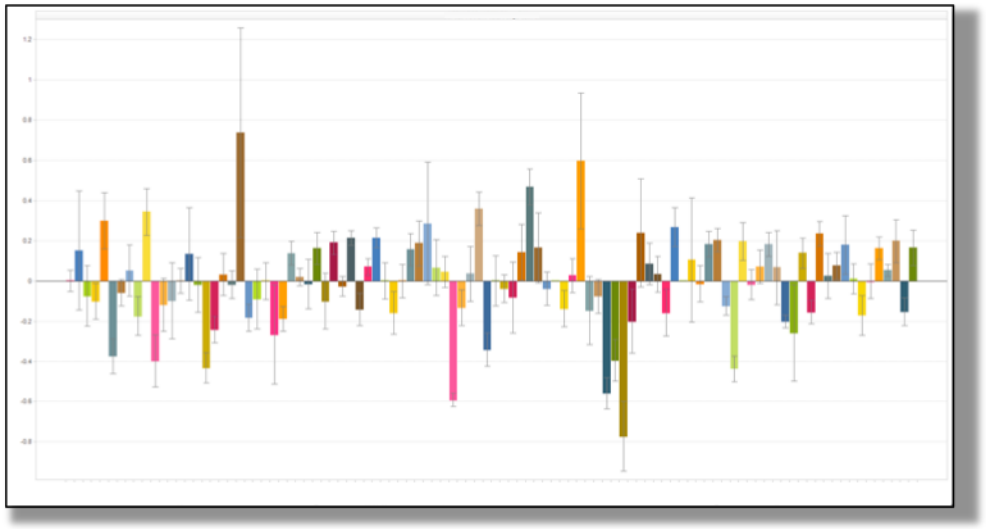
Feature Highlight – Uncertainty





- Experimental measurements have an inherent error which is often discarded upon propagation through various analytics
- SciDB aims to incorporate a simple model of uncertainty – normal distributions for elements (i.e. standard deviations)

SciDB

Feature Highlight – Data Persistence / Provenance

- Arrays are immutable unless specifically defined otherwise

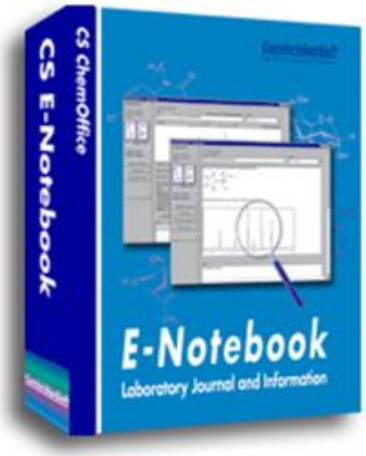
```
CREATE UPDATABLE ARRAY U1 <a: double > [x=0:5,3,0, y=0:5,3,0]

INPUT (U1,'/tmp/load.txt');
```

- Even when declared as updatable, original cell values are never overwritten…a new version is created.

```
SCAN(U1@DATETIME('02/20/2002'))
```

- Log files guarantee repeatability of data derivation

- ELN for computational biologists!



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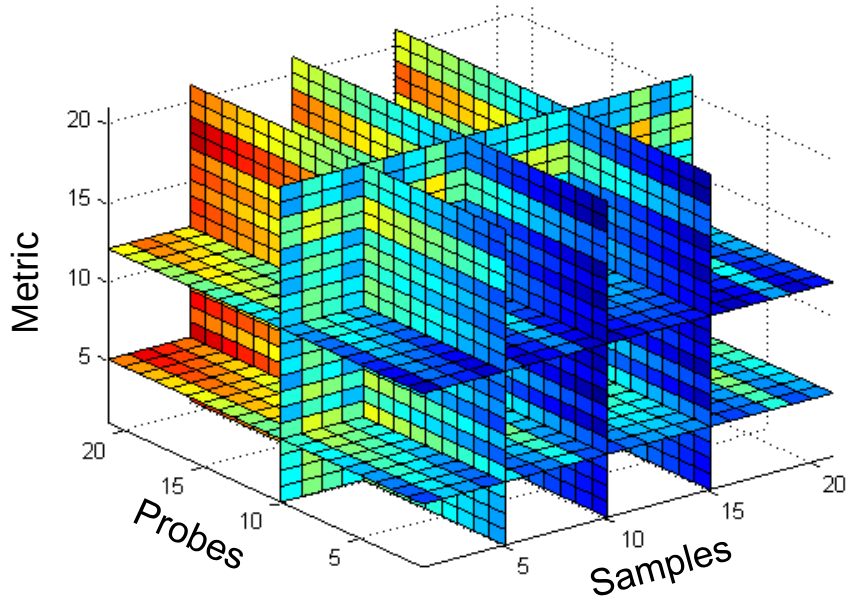
Example Use Case – Transcriptional Profiling

- Microarray – platform for simultaneously measuring the expression levels of thousands of genes
- 60,000+ arrays
- 60,000 probes (multiple probes per gene)
- >100 indications
- 6B+ data points
- Use cases:
  - Target finding
  - Patient stratification
  - Biomarker identification



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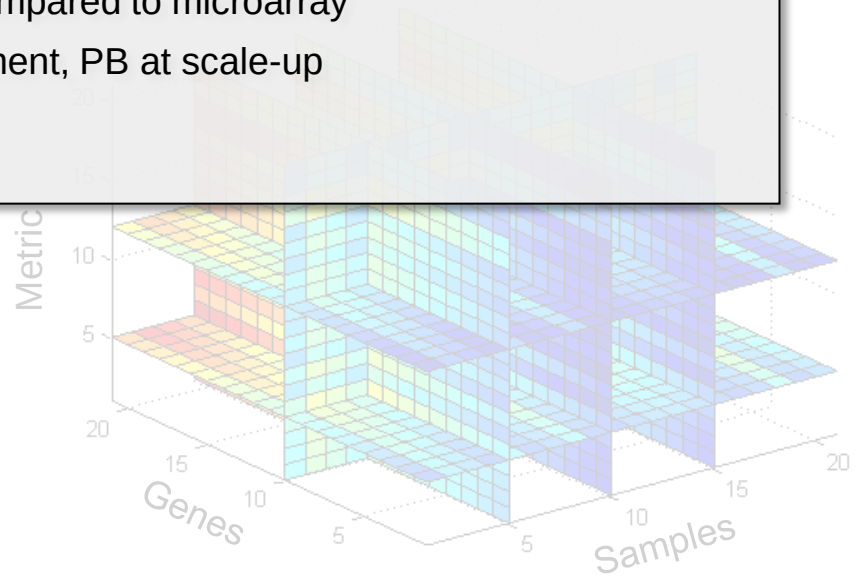
- Quickly being replaced by Next-Generation Sequencing
  - Digital readout
  - Highly reproducible, highly sensitive
  - Detects ~25% more genes than microarray
  - ~2000x more data points compared to microarray
  - GB per lane, TB per experiment, PB at scale-up



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Example Use Case – Transcriptional Profiling

- Quickly being replaced by Next-Generation Sequencing

Microarray	NGS
	
Store and mine the names of all people in Eurasia	Store and mine the names of all people ever born in the history of the world, 90x

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Example Use Case – Transcriptional Profiling

- Array query language (AQL)
  - Similar in syntax to SQL

    CREATE ARRAY B <y: double, err2: double> [i=0:99,10,0, j=0:99,10,0]

    SELECT * FROM A, B

    SELECT count(part) FROM B GROUP BY i AS part

- Array Functional Language (AFL)

```
CREATE EMPTY ARRAY Expo < Resp : double > [ Probe(int64)=2000,40,0, ID(string)=200,40,0 ]
load(Expo,'/tmp/expo.txt')

min ( Expo, Resp, ID )
max ( Expo, Resp, ID )

store (
    join (
        pearson ( Expo AS E1, Expo AS E2 ),
        repart (
            cross_join (
                transpose ( "Expo@1:ID"),
                "Expo@1:ID"
            ),
        Expo_Covar)
    ),
Expo_Pearson)
```

- Extensibility through UDF (PostgreSQL); operate on array

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Example Use Case – Transcriptional Profiling

- Create the array
  - create array md_bounded
    <response:double NOT NULL,empty_indicator:indicator NOT NULL>
    [algo(string)=24,1,0, sample(string)=49820,1000,0, probe(string)=65000,1000,0]
- Count the number of elements in one “slice” of an array
  - count (slice (md_bounded, algo, 'MAS5_150'));
  - Query execution time: 9.39 s
- Find the min/max of array across one dimension
  - aggregate (md_bounded, min(response), max(response), algo)
  - Query execution time: 41 minutes, 29 s
- For the MAS5_150 algorithm, what is the average response for each sample?
  - aggregate (slice (md_bounded, algo, 'MAS5_150'), avg(response), sample)
  - Query execution time: 1 minute, 3 s
- For the MAS5_150 algorithm, what is the average response for each probe?
  - aggregate (slice (md_bounded, algo, 'MAS5_150'), avg(response), probe)
  - Query execution time: 1 minute, 15 s

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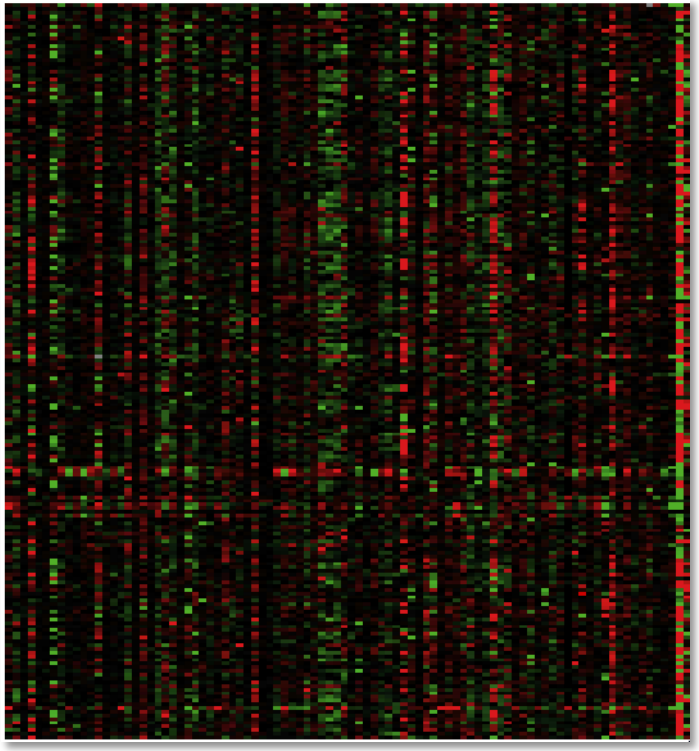
Example Use Case – Transcriptional Profiling

- What questions do we want to ask?
  - What genes have similar expression profiles?
  - What diseases “look like” each other?
- There is an abundance of literature answering these questions on the small scale…we want to be able to answer it across the entire data set.
- Simple first test for SciDB
  - Pearson correlation as a database query:
    - Data matrix: 60,000+ samples x 60,000+ probes
    - Infrastructure:
      - 4 nodes, 16 cores, 2.4GHz, 1TB drives
    - 270 minutes, 19 s (* Oct 2011)



store (pearson (slice (md_bounded, algo, 'MAS5_150'), slice (md_bounded, algo, 'MAS5_150')), md_bounded_MAS5150_pearson)

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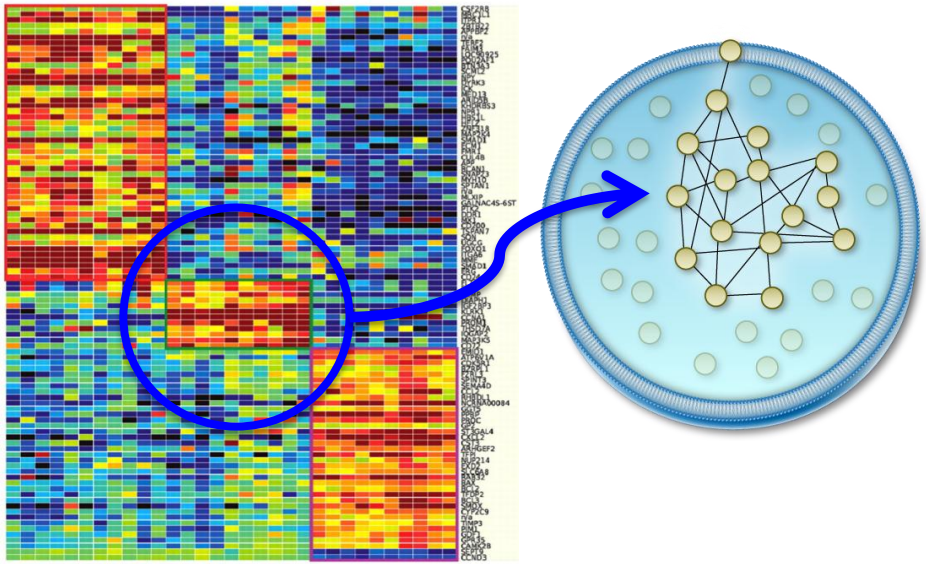
Example Use Case – Transcriptional Profiling

- Biclustering
  - Are there combinations of genes/samples that correlate strongly with each other? Are certain pathways over-represented?
  - Singular value decomposition
    - Kopp-Schneider A et al, Bioinformatics 2011 vol. 27 (15) pp. 2089-2097

- Hybrid R/SciDB algorithm implemented
- 2160 x 60,000 matrix
- Amazon EC2
  - 4 nodes (2 XEON cores, 2.66 Ghz)
  - 8 GB memory
- 3 iterations -> ~31 hours
- * SciDB Oct 2011 build



Li G et al. Nucl. Acids Res. 2009;37:e101-e101

SciDB

Where does it fit at NIBR?

- Significant momentum in the field of “big data” analytics
- Blend new technologies with legacy systems
- “Right tool for the job”