Using MicroArray Explorer with the NCI/CIT/ATC mAdb Web Server, Academic and Commercial Chips

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MAExplorer: http://www.lecb.ncifcrf.gov/MAExplorer

BCTT-07-19-2001 (Rev: 7-30-2001)

#### Abstract

- The Microarray Explorer (**MAExplorer**) is a versatile Java-based data mining bioinformatic tool for analyzing quantitative cDNA expression profiles across multiple microarray platforms and other DNA labeling systems.
- These include common NIH chips such as NCI/ATC, Incyte and Affymetrix. Data is downloaded as required from the ATC server or other source and reside on the user's computer. Incyte and Affymetrix data is converted using the Cvt2Mae conversion program. With MAExplorer, it is possible to: 1) analyze the expression of individual genes; 2) analyze the expression of gene families and clusters; 3) compare expression patterns; 4) directly access other genomic databases for genes of interest.
- Analyses are performed in real-time and may be viewed and directly manipulated in array pseudo-images, scatter plots, reports, histograms, expression profile plots, and cluster analyses plots. Raw data may be normalized under a variety of methods.

- A key feature is the gene data filter for constraining a working set of genes to those passing the intersection of a variety of user-specified logical and statistical tests. Resulting sets of genes may be saved as named sets and subsequent set operations may be performed resulting in derived gene sets. These in turn may be used in redefining the data filter or exported. Similar sets of hybridized samples may be saved as named sets and used for reconfiguring experiment subsets. Reports may be generated with hypertext Web access to UniGene, GenBank, and other Internet databases for sets of genes found to be of interest. Users may save their exploration states on the local computer, and later recall or share them with other scientists. The emphasis on direct manipulation of genes and sets of genes in graphics and tables provides a high level of interaction with the data, making it easier for investigators to test ideas when looking for patterns.
- MAExplorer, a sample set of 38 MGAP hybridizations, a reference manual, tutorials and documentation may be freely downloaded from http://www.lecb.ncifcrf.gov/MAExplorer.

#### **MAExplorer is Compatible with mAdb Data**

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Axon's <u>Web Site</u>			instructions								
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MAExplorer			A Java data mining application for gene					<u>Manual</u> (Online)			
Developed by and Available from			expression data using a	Peter	Revision	Current	Link to				
LECB/FCRF/NCI.	MAE	MAExplorer	clustering,	<u>Lemkin</u>	History	version	Download				
MAExplorer <u>Web Site</u>			direct-manipulation graphical, spreadsheet and					mAdb data			
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#### **MAExplorer Home Page** http://www.lecb.ncifcrf.gov/MAExplorer

#### 🔆 MicroArray Explorer - MAExplorer - Netscape File Edit View Go Communicator Help Back Reload Home Search Netscape Security Shop Sookmarks 🎝 Location: http://www-lecb.nciforf.gov/MAExplorer/ MAExplorer **MAExplorer - MicroArray Explorer** (Stable release: 0.90.08. Beta release: Introduction Overview le monstrations **MicroArray Explorer for Data Mining Gene Expression Patterns Bocumentation** The Microarray Explorer (MAExplorer) is a Java-based data-mining facility for cDNA microarray databases. It may be Manual (on right) Manual (new window) freely downloaded and run as a stand-alone application on your computer, or run as an applet in your Web browser. The Manual (7Mb Zip) exploratory data analysis environment provides tools for the data-mining of quantitative cDNA expression profiles across Manual (entire) Newsletters multiple microarrays. + Short Tutorial Advanced tutorial With this program it is possible to: 1) analyze the expression of individual genes; 2) analyze the expression of gene families Menu summary and clusters; 3) compare expression patterns and outliers; 4) directly access other genomic databases for clones of interest. • Quick Start Glossarv In the applet version, data is downloaded as required from the server to the user's Web browser where real-time analyses Index are performed. The stand-alone version uses previously quantified array data copied to the local computer where it may save • Help Desk data from data mining sessions. Add Documents (PDF) Microarray data may be viewed and directly manipulated in array pseudoimages, scatter plots, histograms, expression profile plots, cluster analyses (similar clones, K-means, hierarchical clusters, etc.), and reports. A key feature is the clone data filters **Bata format conversion** User's array data for constraining a working set of clones to those passing a variety of user-specified tests. Reports may be generated with hypertext Web access to genomic databases such as UniGene, GenBank, dbEST, I.M.A.G.E., NCI/CIT mAdb Clone DB C2M Cvt2Mae converter and other Internet databases for sets of clones found to be of interest. Downloading MAExplorer A major focus of this tool is interactive data mining with access to other supporting Web genomic databases. The emphasis Stand-alone version NEW Revision notes on direct manipulation of clones and sets of clones in graphics and tables provides a high level of interaction with the data making it easier for investigators to test ideas when looking for patterns. MAE Install MAExplorer It was developed by the NCI Laboratory of Experimental and Computational Biology (LECB) in collaboration with the download NIDDK Laboratory of Genetics and Physiology (LGP). MAExplorer was created to help analyze microarray data for the LGP's Mammary Genome Anatomy Program (MGAP) designed to identify and understand genetic pathways operative during normal mammary gland development and tumorigenesis. Note that 38 hybridizations from the MGAP database are Disolaimer included as a demonstration database when you download the stand-alone version of MAExplorer MGAP-MAExplorer home MAExplorer may be used as an applet to access the Mammary Genome Anatomy Project (MGAP) microarray Web data Contact [ Lemkin ] through http://mammary.nih.gov/mgap or directly at http://www.lecb.ncifcrf.gov/mae. mkin Qncifed.gov

The Reference Manual describes the details of MAExplorer as well as showing a number of screens illustrating various operations. Several tutorials are available as well 38 hybridizations from the MGAP database

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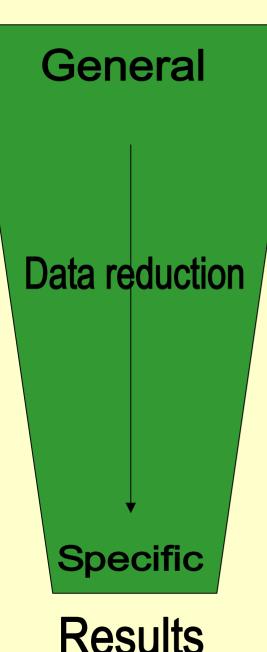
MAExplorer was Developed for the Ongoing Mammary Genome Anatomy Program (MGAP)

- MGAP models, histology, expression http://mammary.nih.gov/
- Mouse models of
  - 1. normal mammary development C57B6
  - 2. Knock-outs: Stat5a (-,-) & (+,-), CEBP null, TGF $\alpha$  etc.
  - 3. Tumor models: WAP taq, p53 mutant, etc.
  - 4. Transgenics: WAP Int3, BRCA1, etc.
- Initially, MAExplorer was a <u>Java applet</u> for analyzing MGAP arrays **http://www.lecb.ncifcrf.gov/mae**
- MAExplorer identified genes in preferentially expressed during lactation, *Nucleic Acids Res.* (2000) **28**:4452

## I. The Problem and Goals of Array Analysis

- Assume we have microarray data in a spreadsheet of quantified spots and the genes they represent What do we do with all those spots?
- Could look for **patterns of changes** of experimental conditions with quantitative gene expression for well formed questions
- **Correlation of gene expression changes** with biological state implies a relationship but does not imply cause and effect
- Having found correlations, review findings with annotated bioinformatic data sources (PubMed) and validate with additional lab experiments
- Handles Cy3/Cy5 ratio (ATC, Incyte, etc), <sup>33</sup>P intensity (Affymetric, etc.), and academic chips using **Cvt2Mae** converter program

#### **Data Mining - Finding Putative Relevant Patterns**



Quantified array spot data for multiple samples

Organize by sample, gene expr, gene sets

Change views: normalization, data filters

Visualize and query: plots, cluster, reports

Explore external genomic databases

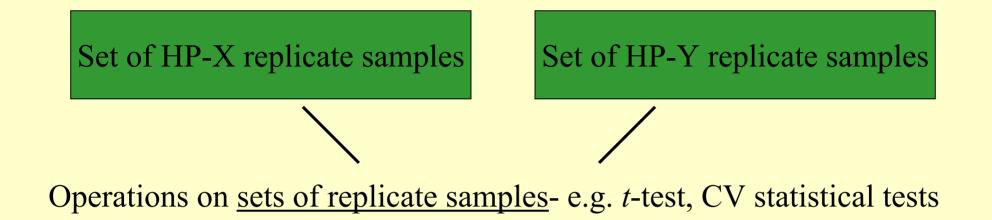
## I.1 What is the MicroArray Explorer?

- MAExplorer is a flexible Java stand-alone (off-line) or applet (Web-based) microarray data-mining tool
- Handles multiple arrays with replicates and expression profiles
- Handles intensity or ratio (Cy3/Cy5) quantified microarray data
- Data-filters gene sets by statistics, clustering, gene set operations
- Allows direct manipulation of data in graphics, spreadsheets
- Accesses genomic Web servers from plots and reports
- Freely downloadable from MAExplorer Web site
- Stand-alone <u>installers</u> are provided for Windows, MacOS, Solaris, Linux, Unix, etc.

# **I.2 Types of Experiments**

- What **types of expression** could we analyze?
- Discover **patterns of differential expression** using visual, statistical, and clustering methods:
  - 1) of individual genes,
  - 2) of gene families and clusters of genes,
  - 3) as a function of conditions: development, time (eg. cell cycle), cell lines, disease progression, pathways models, etc.
- Finding genes with **similar gene expression** may help in understanding a gene's functional behavior or pathways
- These are **statistical entities**. The more data samples and replicates are available, the better these estimates will be

## I.3 Operations on 2- & N-conditions of Samples<sup>(1)</sup>



Order list of HP-E samples

Operations on order lists of samples: e.g. clustering, Expr. Profile plots

<sup>(1)</sup> "HP" is hybridization probe i.e. the sample hybridized to the chip

# I.4a Choosing HP-X, HP-Y Sets and HP-E Lists

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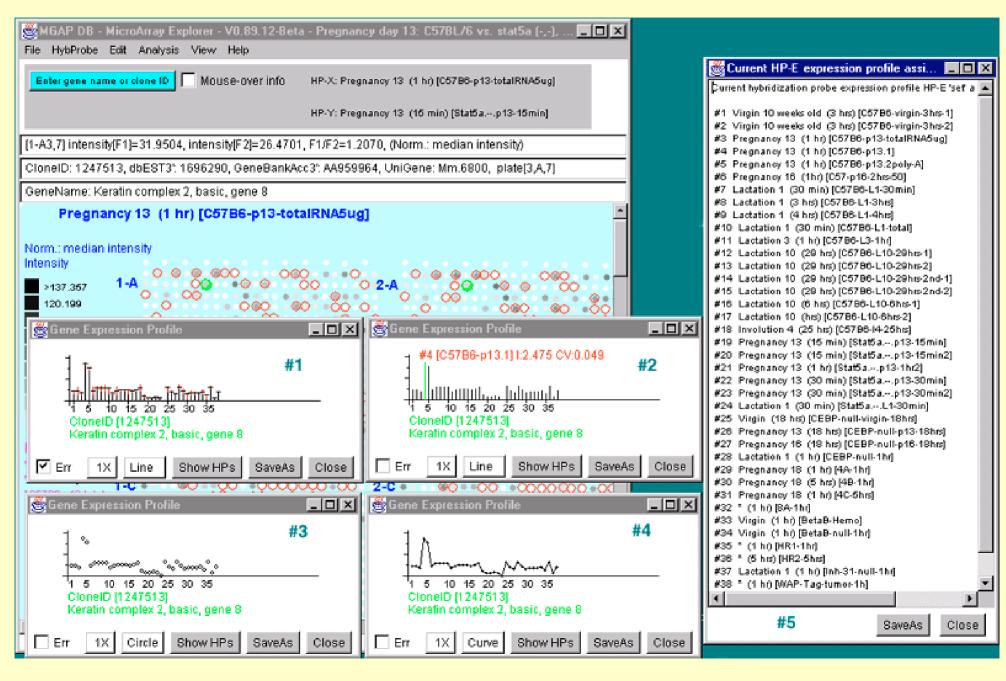
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## **I.5 Definition: Gene Expression Profile**

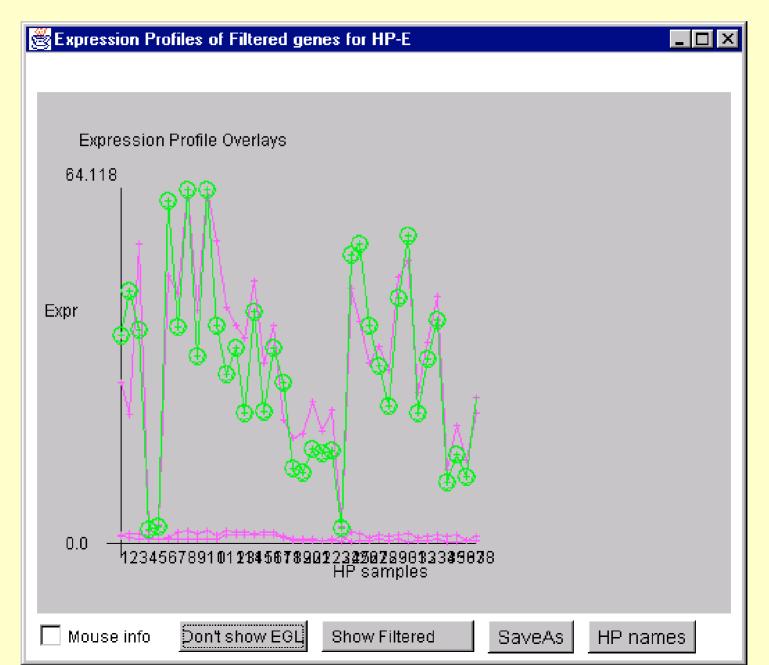
- An expression profile e<sub>j</sub> of an ordered list of N normalized spot values samples v<sub>jk</sub> (k=1 to N) for a particular gene j
- The expression profile  $\mathbf{e}_{j}$  for a particular gene  $\mathbf{j}$  is:  $\mathbf{e}_{j} = (\mathbf{v}_{j1}, \mathbf{v}_{j2}, \mathbf{v}_{j3}, \dots, \mathbf{v}_{jN})$
- A difference between two genes p and q may be estimated as a N-dimensional metric "distance" between e<sub>p</sub> and e<sub>q</sub>
- Euclidean distance:  $d_{pq} = 1/N \left( \sum_{j=1:N} (v_{pj} v_{qj})^2 \right)^{1/2}$
- Other distance measures: correlation coefficient, city-block, etc.
- If distance is scaled to [0:1], then **Similarity** measure:  $s_{pq} = 1 d_{pq}$

## **I.6a Expression Profile Plots - Examples**



# **I.6b Expression Profile Overlay Plots**

• Overlay EP plots for onco and proto-oncogenes in EGL for MGAP database



#### I.7 Why Do We Need to Cluster the Data?

- Clustering methods are one way to perform **gene discovery** by finding similar expression in a set of genes over a set of experiment samples
- A gene cluster is a set of genes that represent **similar gene expression** across that set of experiment samples
- Some clusters may contain genes be related by pathway or biological function
- Many ways to cluster the data (such as):
   C.1 Find genes with similar expression to known gene
   C.2 K-means clusters where the number of clusters K is fixed
   C.3 Hierarchical clustering where a binary hierarchy is created

### **I.8 Find Similar Genes to Seed Gene**

- Find a sorted list of all genes  $\{g_j\}$  similar to gene  $g_s$
- Determine if  $\mathbf{g}_{j}$  is similar to <u>seed gene</u>  $\mathbf{g}_{s}$  if distance  $\mathbf{d}_{js}$  < threshold T

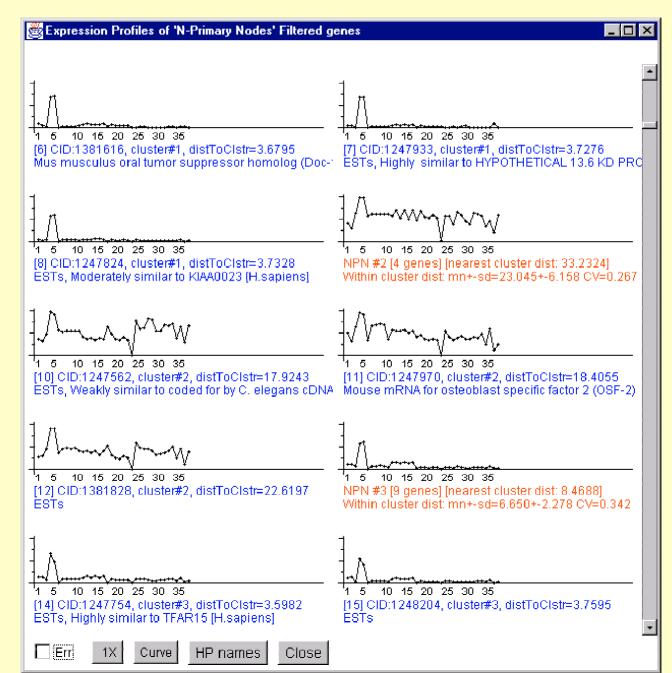
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#### **I.9 K-means Clusters K Sets of Similar Genes**

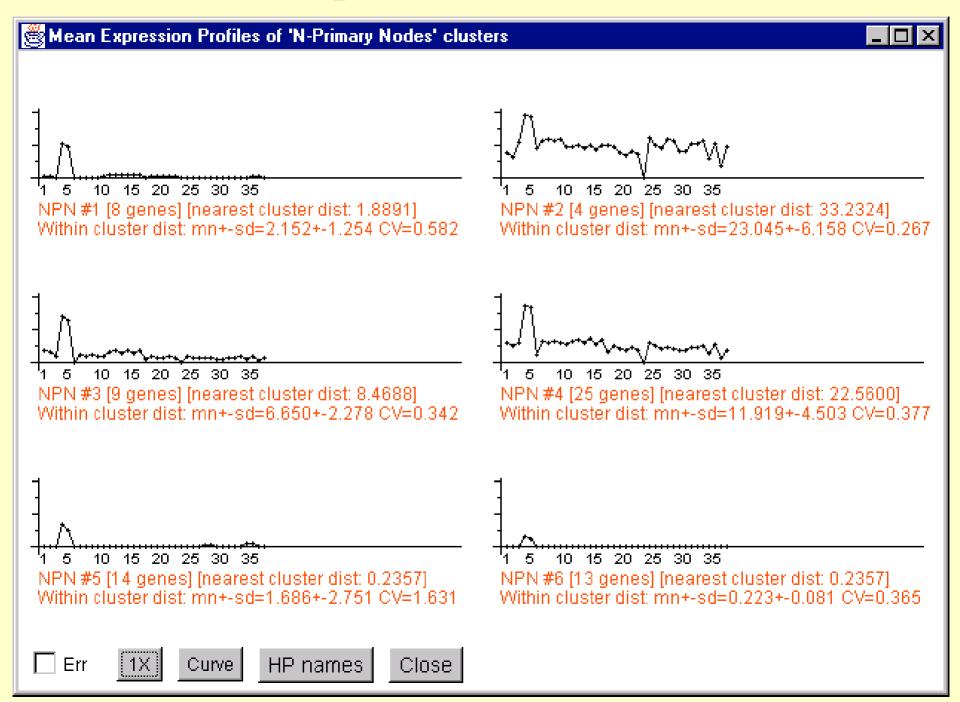
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HP-Y: Pregnancy 13 (15 min) [Stat5ap13-15min]			0.409 ESTs			
Norm.: median intensity	1001000		0.440 ESTs			
rSq=0.956, n=73, X(mn+-sd)=(22.965+-26.977), Y(m	1249225	****************** 5		ulus heat shock transcripti 	on factor 1 (Hsf1) gene, p	partial ods
	1382094	and a second sec		ility group protein 1 i viral proto-oncogene		
	1248055		0.578 ESTs	e e com la conserva de la 2000 de		
Mouse-over info Show all genes SaveAs Close		5	1.173 Surfeit ger	ne 4		
* *Siana.~.pia~a	1248054		1.173 ESTs, Hig	hly similar to HYPOTHE	FICAL 34.7 KD PROTEIN	I IN SPT10-0CD14 IN 📰
LOCIDE July Dr	1382500	5	1.191 ESTs			
*C5786-virgin-3h ************************************	1248068	***** 5 F	5.842 ESTs			
*C57-p18-2hrs50 ** ** + *** * +*** *	1248279		10.278 ESTs NEN M3 genesi i	n cluster (distNext: 0.235)	wiCdistrant-sda0.222+	0.081 CV=0.365 ES1
*C57B6-L1-30min	1381603	-		kly similar to ubiquitin co		Contraction of the second
*C5796-L1-3hs	1247579			ly similar to SEROTRAN		
*C5796-L1-4hrs	🗖 i a i 👘			· ·		
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1						
	Reco	ompute	EP plot	Mean EP plot	Cluster-Report	Mn-Cluster-Report
	Clust	terGram	SaveAs	Close		

## **I.10a List of Expression Profiles Plots of Clusters**

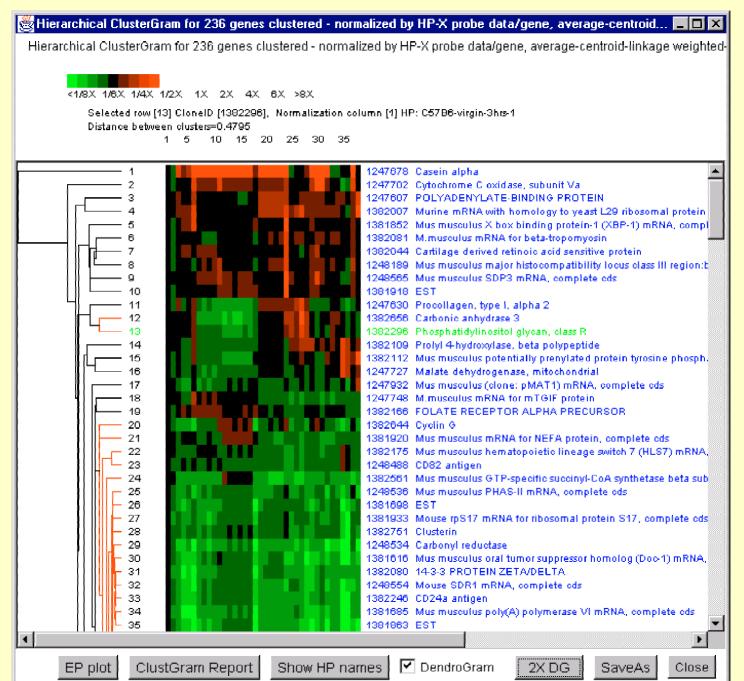
• Scrollable list of EP plots showing genes from clusters #1, #2, #3



#### **I.10b Mean Expr. Profiles of K-means Clusters**



## **I.11 Hierarchical Clusters of Similar Expression**



#### **I.12 The Data Mining Paradigm: "Drill Down" to Discover Patterns**

```
Start
              77
            Have initial model of what may be related
    ----> Organize samples into sets of conditions
           Set data pre-filters (normalization, stat. Filters, etc)
           Examine Plots (scatter, expression, histograms, etc)
           Cluster current gene subset and view cluster plots
Refine views
  +<---- Evaluate results for interesting data relationships
  Χ
  +<---- Save interesting gene sets
           Found interesting results, make reports, export results
              77
            Done
```

## Summary

- MAExplorer is a flexible microarray data-mining tool running on the user's computer
- Uses direct-manipulation, data filtering, built-in graphics, statistics, clustering, gene and sample set operations
- Manages multiple samples, replicates, sets, expression profile lists where the state may be saved on the disk for later use
- Cvt2Mae data conversion tools allows use with common chips
- Plug-ins will allow extension with new analytic methods by users
- MAExplorer identified genes in preferentially expressed during lactation, *Nucleic Acids Res.* (2000) **28**:4452
- Freely available for download with documentation on Web site