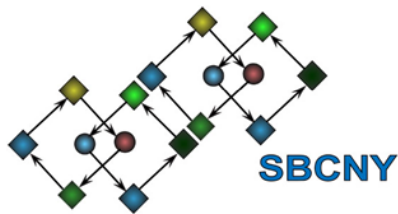


Direct Methods for Utilizing Prior Knowledge to Infer Regulation from Changes in Expression Data



Avi Ma'ayan, Ph.D.

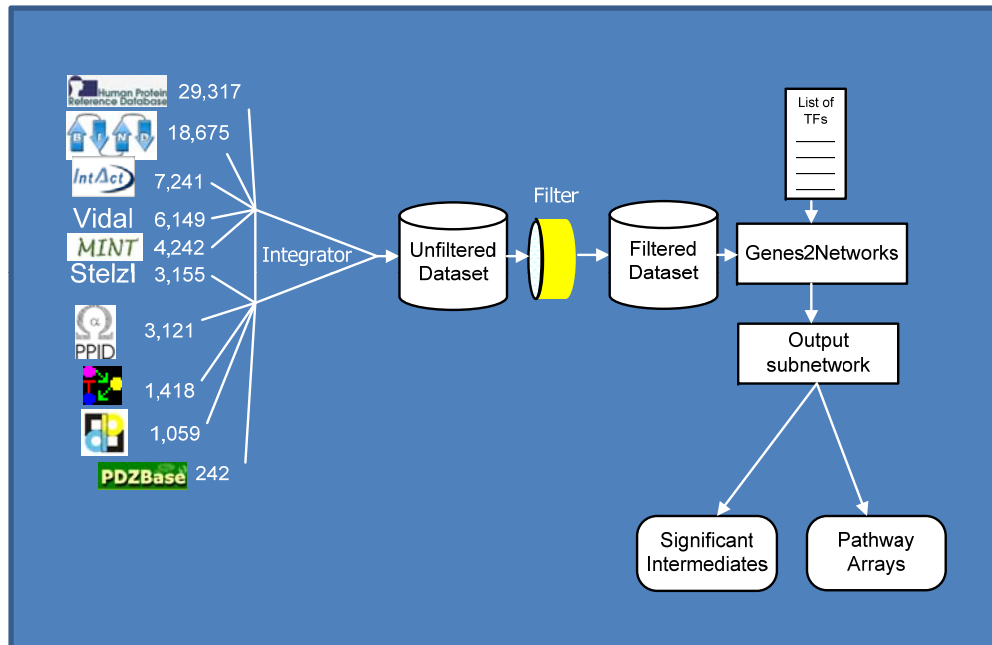
Assistant Professor

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Genes2Networks- protein-protein interactions database and subnetwork reconstruction tool



Seth I Berger, Jeremy M Posner, Avi Ma'ayan
 BMC Bioinformatics 2007, 8:372

Genes2Networks

Welcome to Genes2Networks.
 Status: Displaying Results

Specify Seed Genes and Settings

Seed Gene List:

Entrez Gene Name	delete-all
CREB1	IXI
MAPK1	IXI
RAF1	IXI
RPS6KB1	IXI

Settings:
 Max Path Length: 2
 Significance Cutoff: 2.5

Colors:
 Seed: Red
 Significant: Yellow
 Other: LightGrey

Background Datasets:
 Select All / Select None

Upload Sig Database

Dataset Filtering:
 Max Ints per Ref: 4
 Min Refs per Int: No Filter

Details: MAPK1
 MAPK1->RPS6KA5 [1] 9687510
 MAPK1->PRKCE [0] 15225643
 MAPK1->FOS [1] 11359735
 MAPK1->MAP2K1 [0] 16123044
 MAPK1->MAP2K1 [0] 11741894
 MAPK1->MAP2K1 [0] 11832456
 MAPK1->MAP2K1 [0] 11352317
 MAPK1->CREB1 [1] 8941362
 MAPK1->MAPK1 [0] 10963973

Download Network in sig format.
 Download Seed Gene List.

Clustering and significant intermediates analysis:
 Number of genes from your seed list: 4
 Number of intermediate components: 8
 Number of interactions in subnetwork created from seed list: 18
 Total components in the background network: 2130
 Total interactions in the background network: 11184

Significance of Intermediates sorted by z-score:

Gene name	Links	Links in background	Links to seed	Links in subnetwork	z-score
RPS6KA5	4	11184	2	18	24.86634
MAP2K1	23	11184	2	18	10.21092
PRKCE	29	11184	2	18	9.04873
FOS	51	11184	2	18	6.69973

<http://actin.pharm.mssm.edu/genes2networks>

KEA- kinase-substrate interaction database and web-based system for kinase enrichment analysis

KEA Kinase Enrichment Analysis
 | Web Application | Command Line Version |

Paste Entrez Gene Symbols here:
 AATF, ABL1, ABLIM1, ACIN1, ADD1, ADH7, AKAP2, ALMS1, ANKRD26, ANXA2P2, AP1M1

Find Targets of:
 Kinase-Class
 Kinase-Family
 Kinase

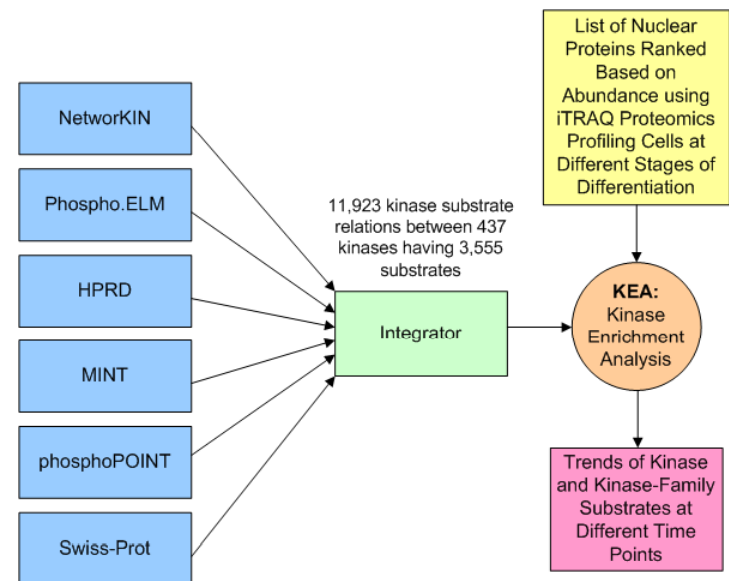
Computation Complete
 Identified Substrates:
 147 out of 298 (49%)

Create Subnetworks
 Connect Substrates

Sort by Clicking Header

Kinase-Family	Substrates/Input-List	Substrates/Database	Fraction/Input-Substrates	Fraction/Database	Difference	p-Value
MAPK	64	ATF2, BDP1				0
CDK	59	CTNNB1				0
GSK	45	DVL3, HDAC1				0
RSK	38	HNRPC				0
PKC	35	HSF1, IFI16				0.01625
CK1	27	JUN, NCL				0
CK2	25	PACS1, PIN1				0.00047
PIKK	24	SRPK1				0.00009
SRC	20	TOP2A, VAMP4				0.41219
EGFR	15	ADD1, KIF21A				0.24279
PKA	14	MAPK14				0.13721
INSR	12	MAPK3				0.16758
STE20	12	MFAP1				0.12172
ABL	10	MRE11A, OSBP				0.02256
STE11	10	SLC12A2, TFIP11				0.33109
CAMKL	10	UBE1				0.05246

Network Graph: A central node 'JUN' is connected to various other nodes including MAPK3, MAPK14, PKC, CK1, CK2, PIKK, SRC, EGFR, PKA, INSR, STE20, ABL, STE11, CAMKL, and others.



BIOINFORMATICS APPLICATION

Systems biology

KEA: kinase enrichment analysis

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<http://amp.pharm.mssm.edu/lib/kea.jsp>
 Lachmann and Ma'ayan. *Bioinformatics* **11**, 87 (2010)

ChEA- chip-chip and chip-seq database of protein-DNA interactions and enrichment analysis tool

- 115 unique transcription factors
- 104 publications
- 35,194 genes
- >150 ChIP-X assays (ChIP-chip, ChIP-seq, ChIP-PET)
- Average targets per transcription factor \approx 1,300
- Total interactions 251,697

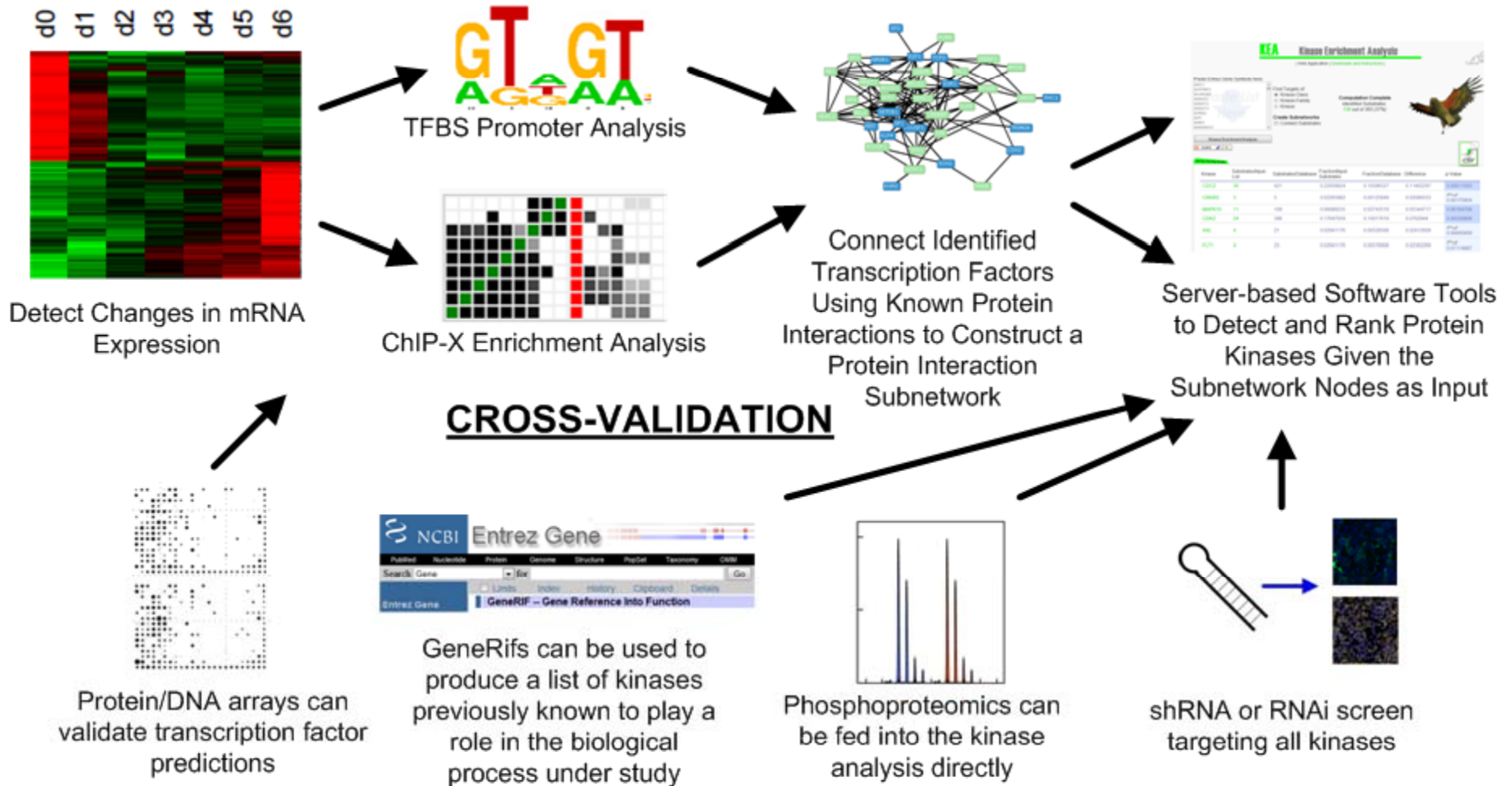
ChEA works well for determining TFs regulating gene expression changes: Myc was inferred as an effector of Estrogen in MCF7 cells

Transcription Factor	Target/Input List	Target/Database	Fraction/Input Targets	Fraction/Database	%fold Difference	p-Value
MYC-18358816	114	3413	0.39583	0.11939	3.31547	0
MYC-19079543	52	1458	0.18056	0.051	3.54015	0
MYCN-18555785	74	2261	0.25694	0.07909	3.24868	0
E2F1-18555785	118	4172	0.40972	0.14594	2.80746	0
MYC-19030024	135	3868	0.46875	0.13531	3.46436	0
MYC-18555785	42	1200	0.14583	0.04198	3.47411	0.000000000005
KLF4-18555785	61	2444	0.21181	0.08549	2.47745	0.000000000049
ZFX-18555785	72	3249	0.25	0.11365	2.19968	0.000000000119
KLF4-19030024	43	1502	0.14931	0.05254	2.84168	0.000000001143

Lachmann A, Xu H, Krishnan J, Berger SI, Mazloom AR, Ma'ayan A. ChEA: Transcription Factor Regulation Inferred from Integrating Genome-Wide ChIP-X Experiments. Bioinformatics. 2010 Aug 13. [Epub ahead of print] |

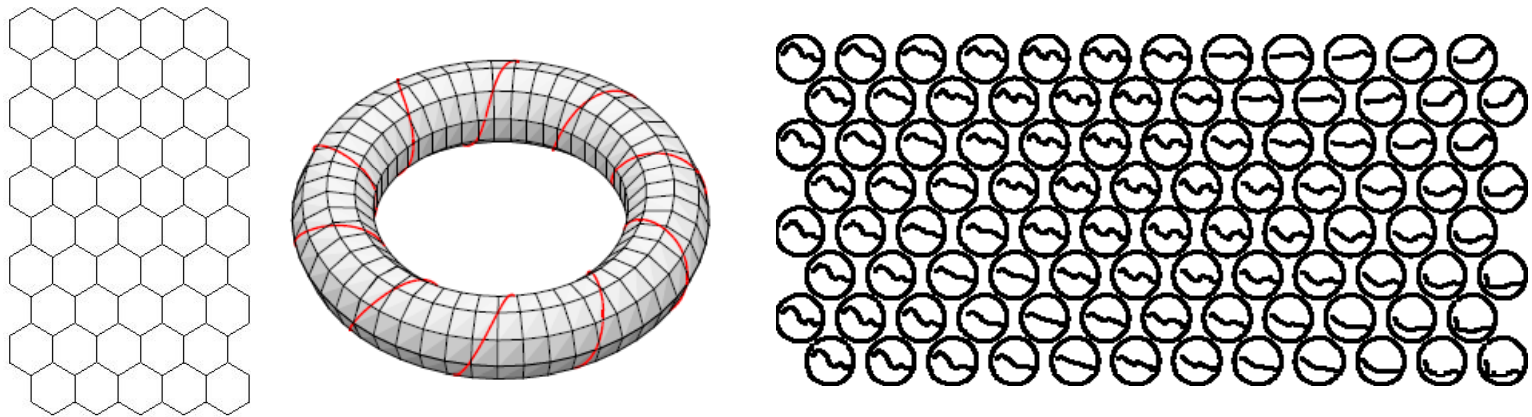
<http://amp.pharm.mssm.edu/lib/chea.jsp>

Most likely protein kinases can be inferred from changes in gene expression by “meshing” ChEA, Genes2Networks, KEA and other tools and methods



High-dimensional time-series data can be visualized as a hexagonal grid movie

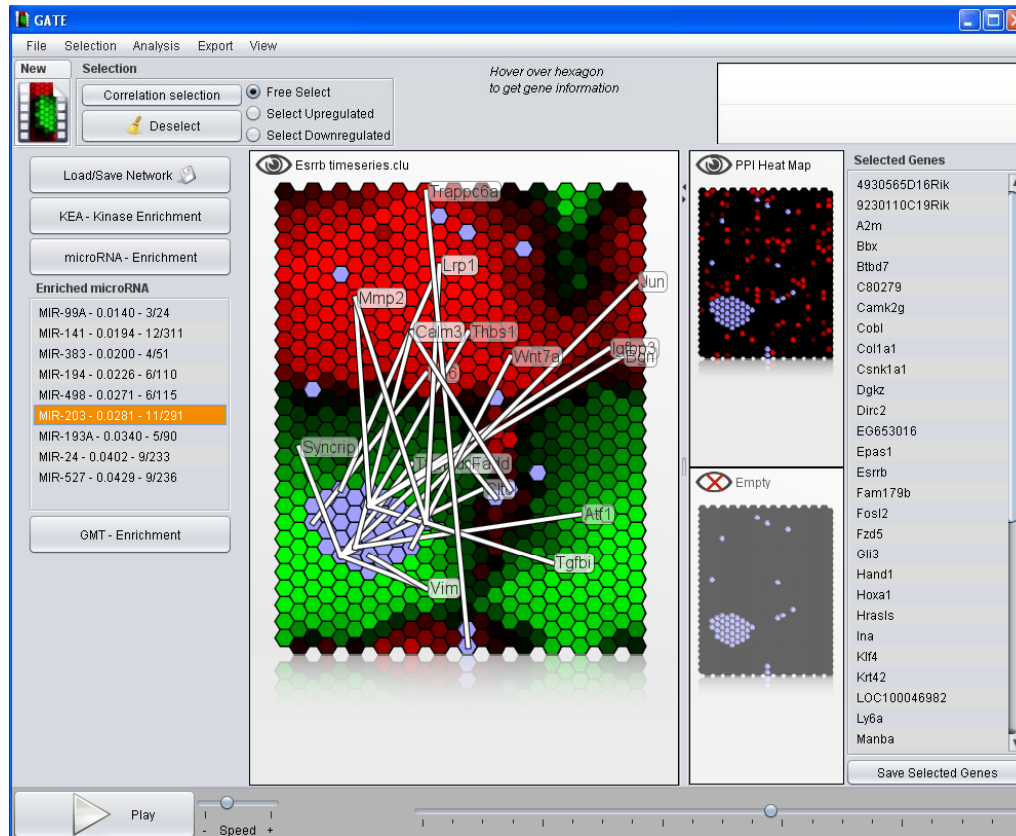
Arrange genes on a lattice such that nearby genes on the lattice have similar temporal expression patterns. Color cells by changing expression to make a movie.



Macarthur BD, Lachmann A, Lemischka IR, Ma'ayan A. GATE: Software for the Analysis and Visualization of High-Dimensional Time-series Expression Data. *Bioinformatics*. 26, 143-144 (2010)

<http://amp.pharm.mssm.edu/maayan-lab/gate.htm>

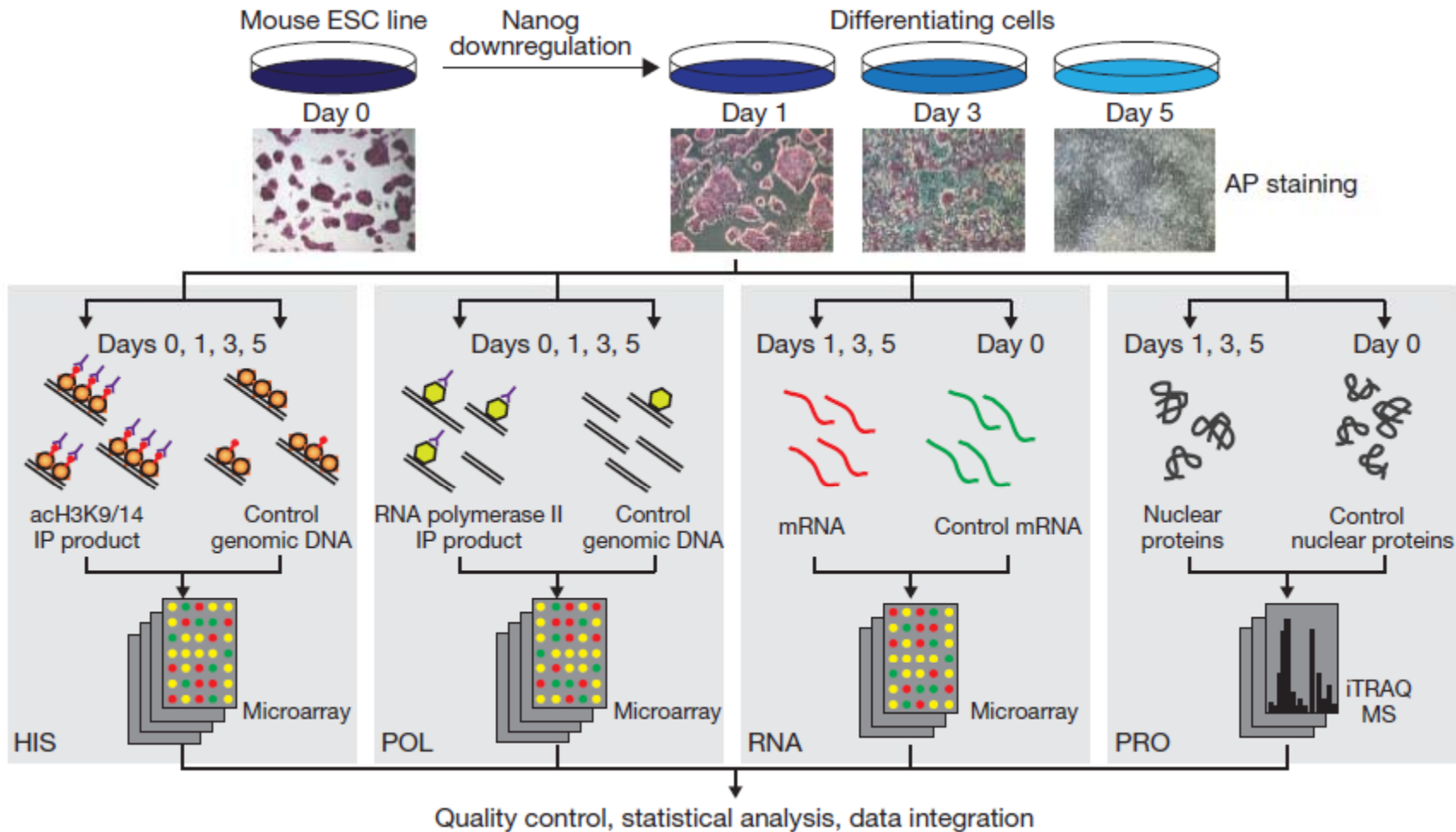
GATE (Grid Analysis of Time-Series Expression): Software for Analysis and Visualization of High-Dimensional Time-series Expression Data



Macarthur BD, Lachmann A, Lemischka IR, Ma'ayan A. GATE: Software for the Analysis and Visualization of High-Dimensional Time-series Expression Data. *Bioinformatics*. 26, 143-144 (2010)

<http://amp.pharm.mssm.edu/maayan-lab/gate.htm>

Analysis of multi-layered regulatory data collected as a time-series using GATE



Lu R, Markowetz F, Unwin RD, Leek JT, Airoidi EM, MacArthur BD, Lachmann A, Rozov R, Ma'ayan A, Boyer LA, Troyanskaya OG, Whetton AD, Lemischka IR. Systems-level dynamic analyses of fate change in murine embryonic stem cells. *Nature* 462:358 (2009)