



Building a digital systems microscope

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Research questions

Why is person A severely affected by dengue virus infection, and person B not?

Can we *predict* whether a drug will work for A? For B?

How about drug *combinations*?

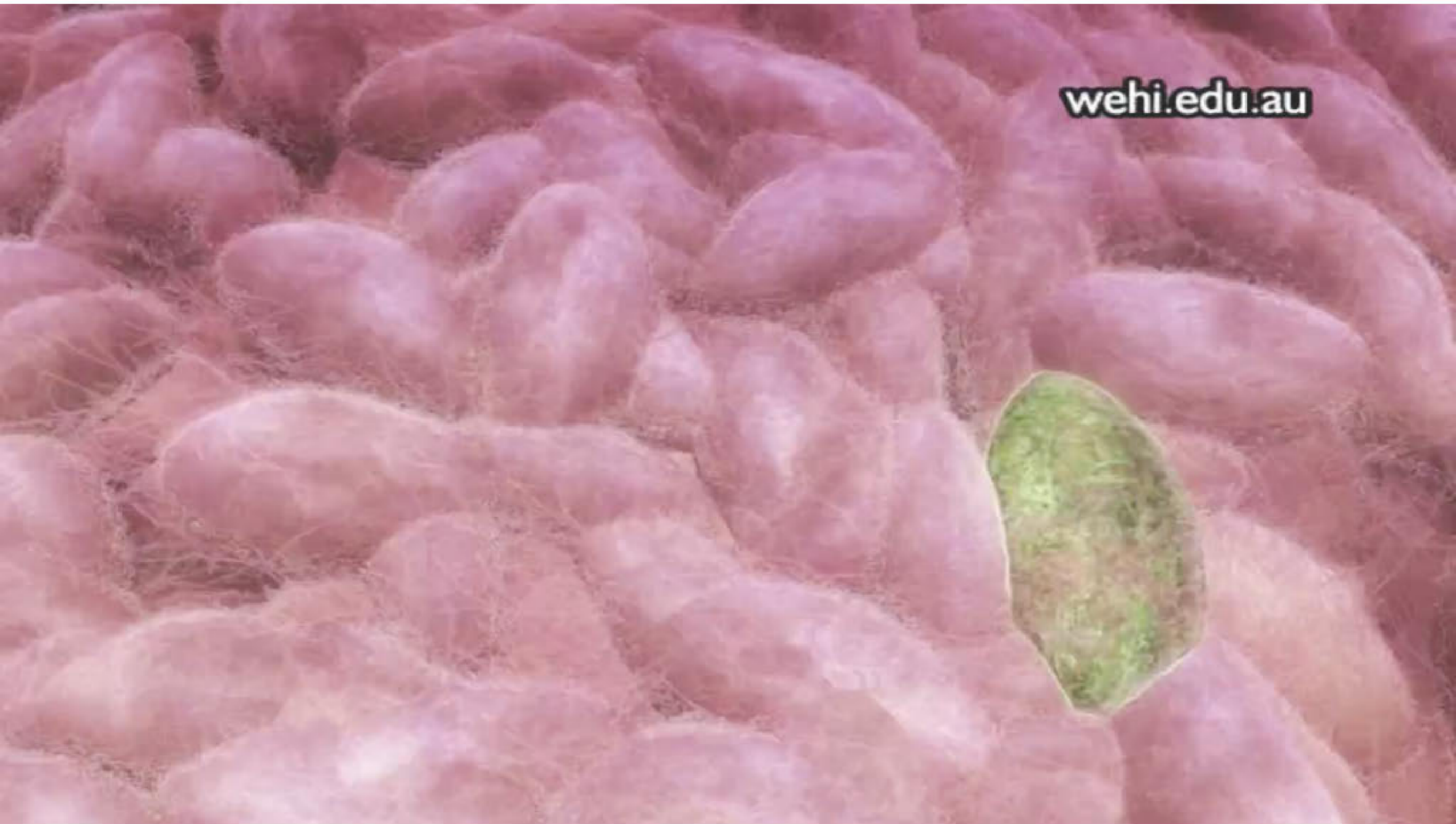
Why do more and more people become allergic to their environment?

How to diagnose breast cancer *before* it starts?

Can we find the better drug targets against malaria/HIV/tuberculosis/Alzheimer's/colon cancer/...



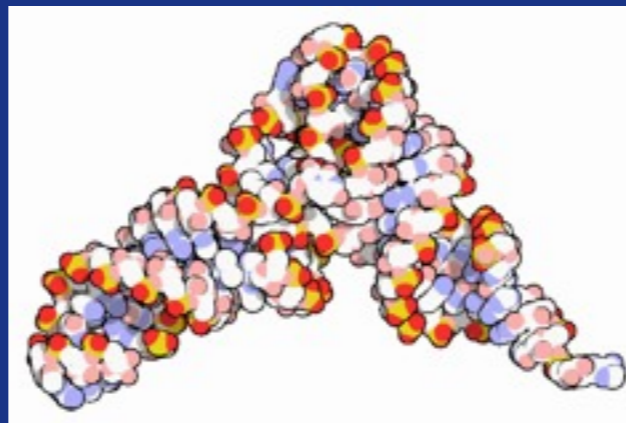
wehi.edu.au



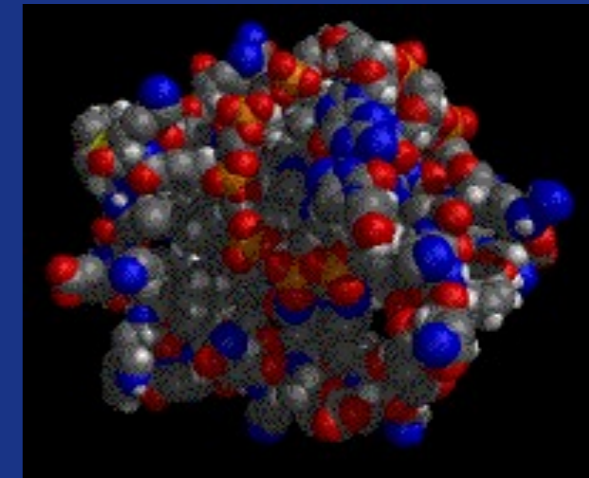
Systems Biology: From molecules to systems



DNA / genes

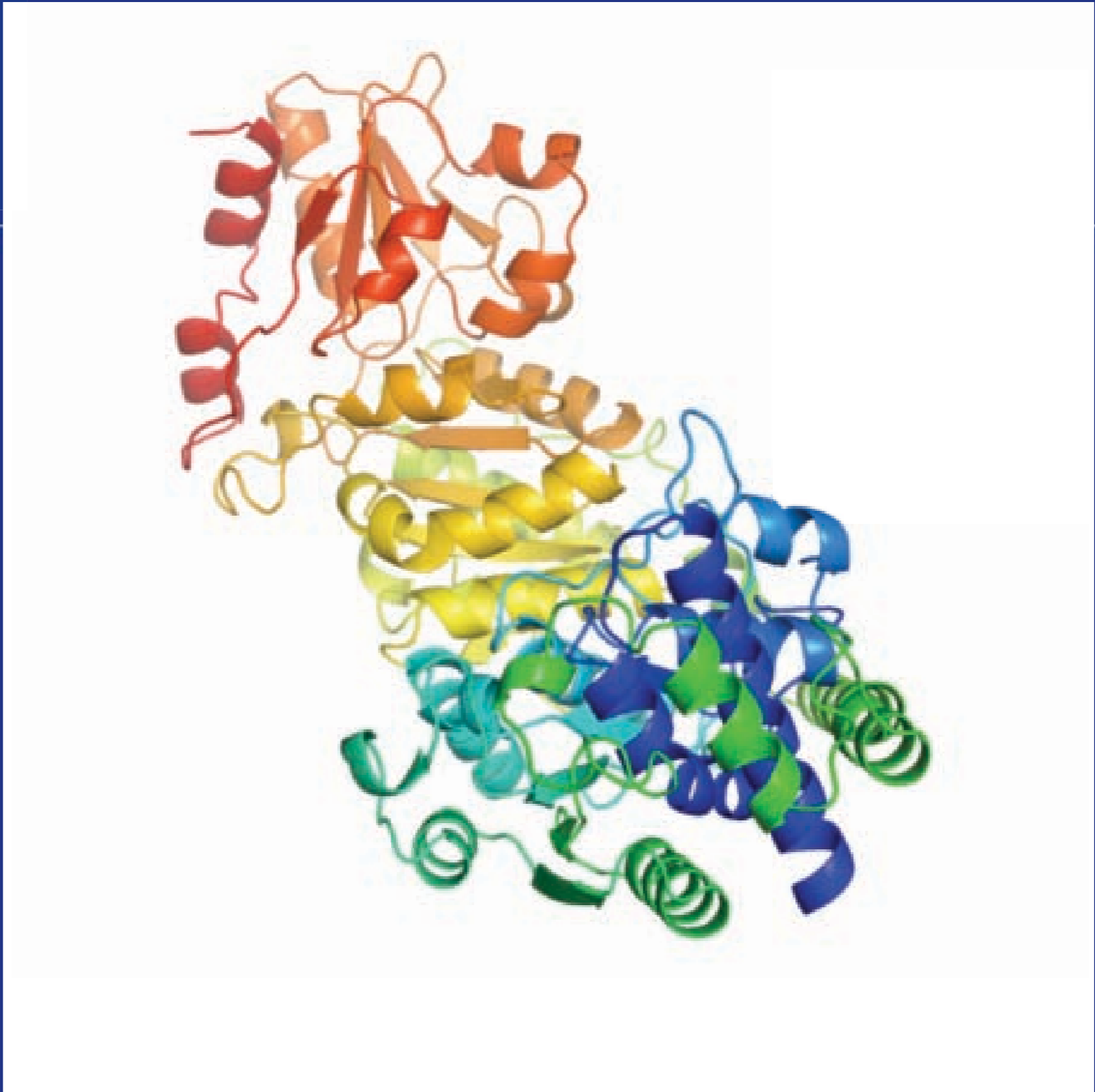


RNA

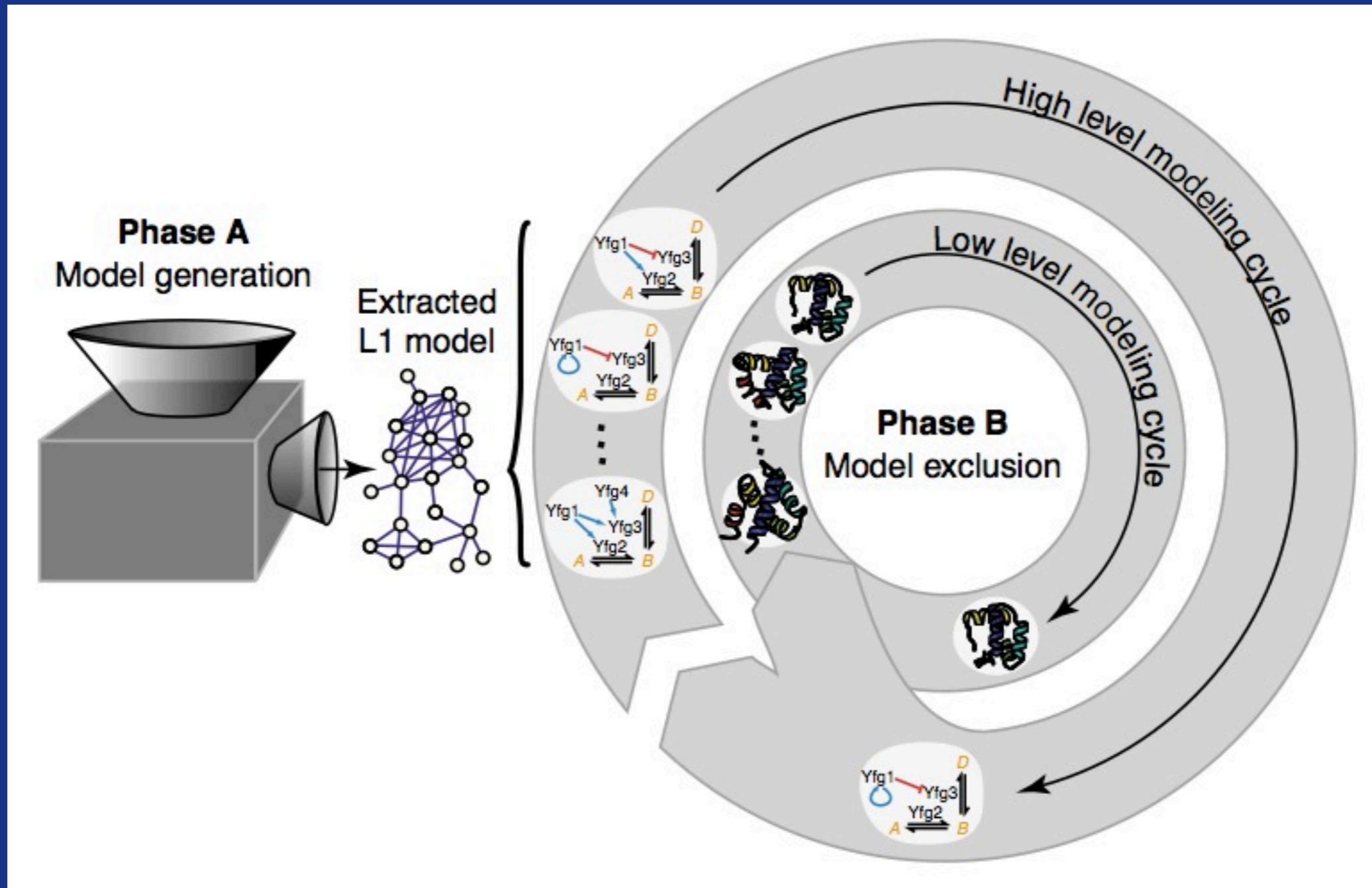


Protein

- Experimental technologies & data
- Computational models

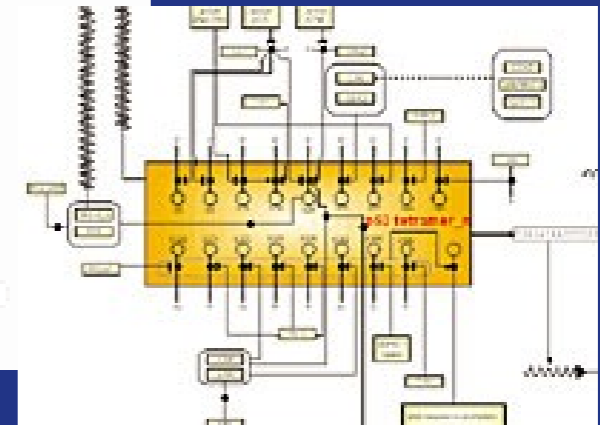
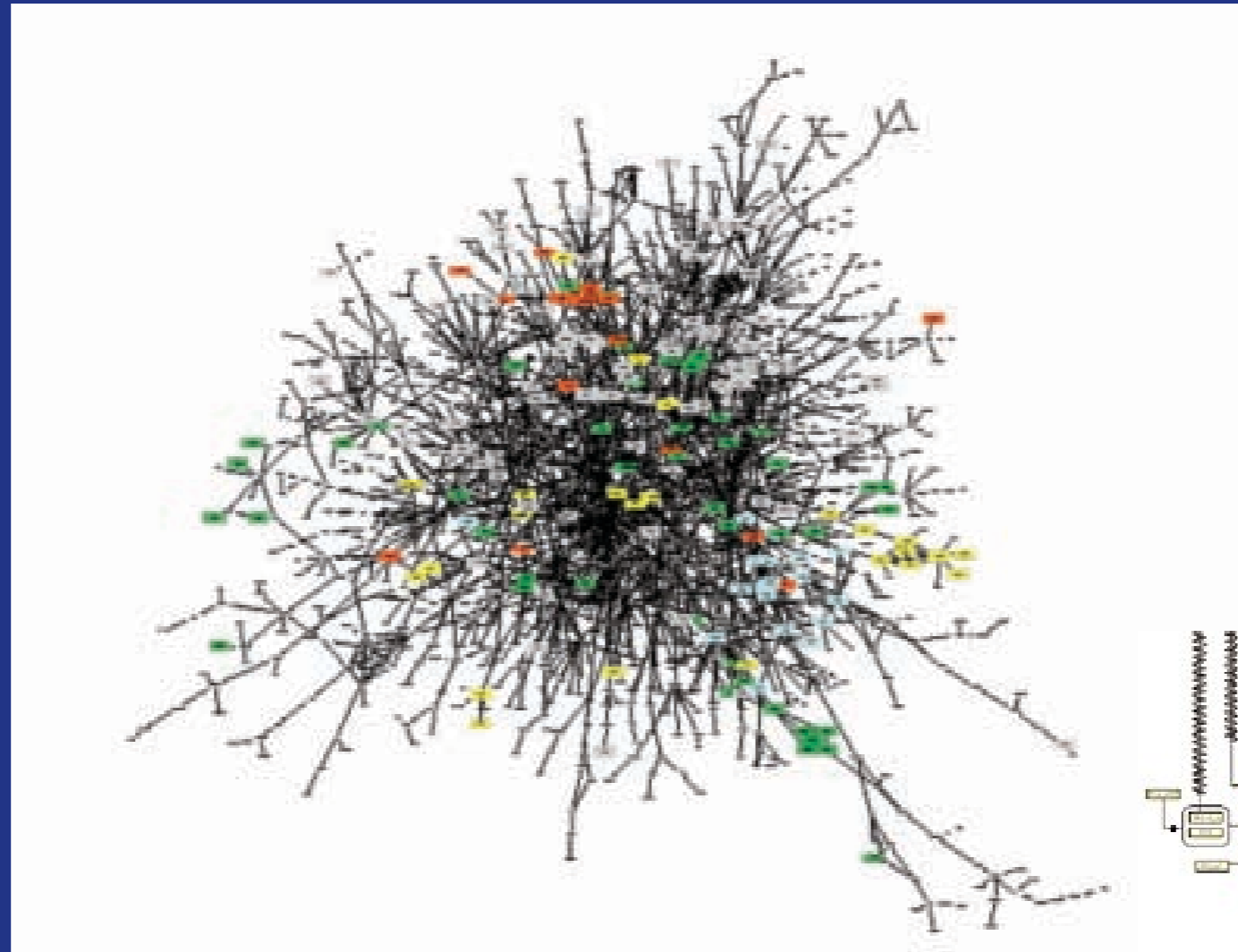


High-level and low-level modeling



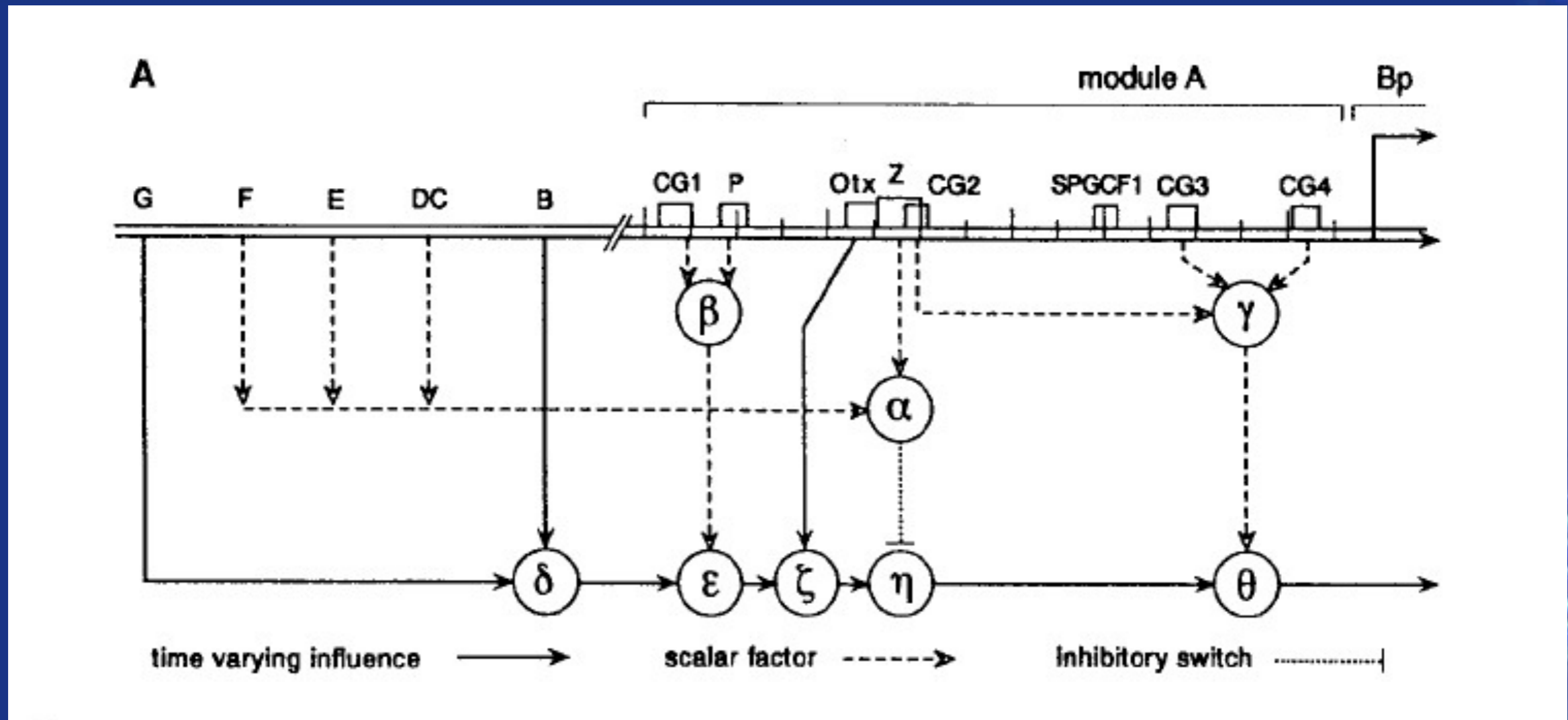
Ideker and Lauffenburger (2003), TiBS

What is complex about biological systems?



I. Biological parts interact in large networks.

What is complex about biological systems?



Yuh, Bolouri, Davidson (1998), Science

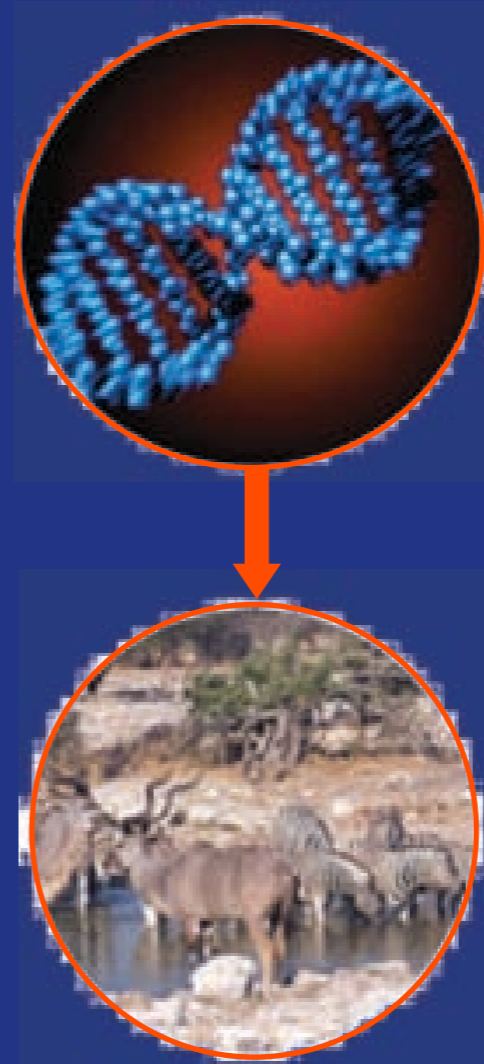
What is complex about biological systems?

B	
if (F = 1 or E = 1 or CD = 1) and (Z = 1)	Repression functions of modules F, E, and DC mediated by Z site
$\alpha = 1$	
else $\alpha = 0$	
if (P = 1 and CG₁ = 1)	Both P and CG ₁ needed for synergistic link with module B
$\beta = 2$	
else $\beta = 0$	
if (CG₂ = 1 and CG₃ = 1 and CG₄ = 1)	Final step up of system output
$\gamma = 2$	
else $\gamma = 1$	
$\delta(t) = B(t) + G(t)$	Positive input from modules B and G
$\varepsilon(t) = \beta * \delta(t)$	Synergistic amplification of module B output by CG ₁ -P subsystem
if ($\varepsilon(t) = 0$)	Switch determining whether Otx site in module A, or upstream modules (i.e., mainly module B), will control level of activity
$\xi(t) = Otx(t)$	
else $\xi(t) = \varepsilon(t)$	
if ($\alpha = 1$)	Repression function inoperative in endoderm but blocks activity elsewhere
$\eta(t) = 0$	
else $\eta(t) = \xi(t)$	
$\Theta(t) = \gamma * \eta(t)$	Final output communicated to BTA



What is complex about biological systems?

DNA
mRNA
Proteins
Pathways/Modules
Cells
Tissues
Organs
Individuals
Populations
Ecosystems

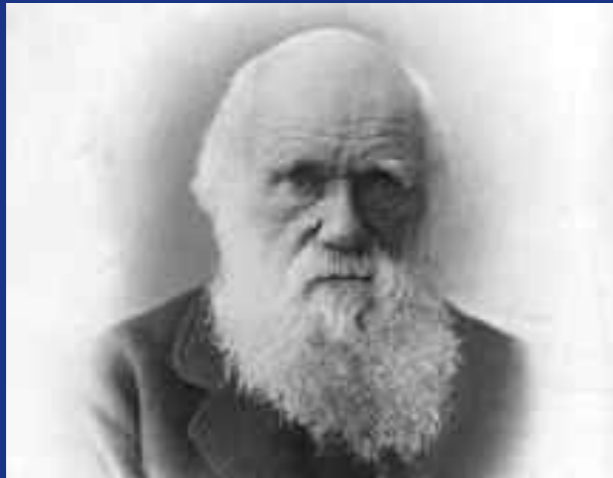


2. Different levels interact.

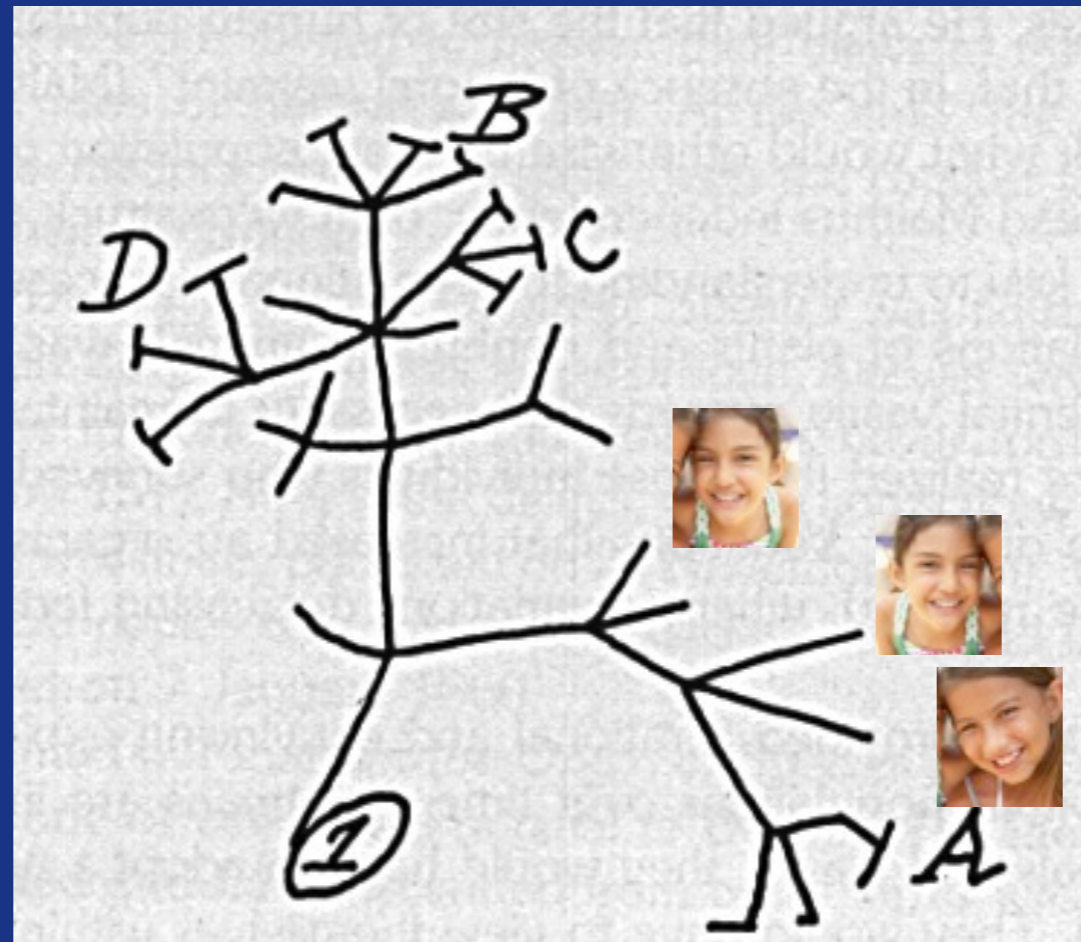
What is complex about biological systems?



What is complex about biological systems?



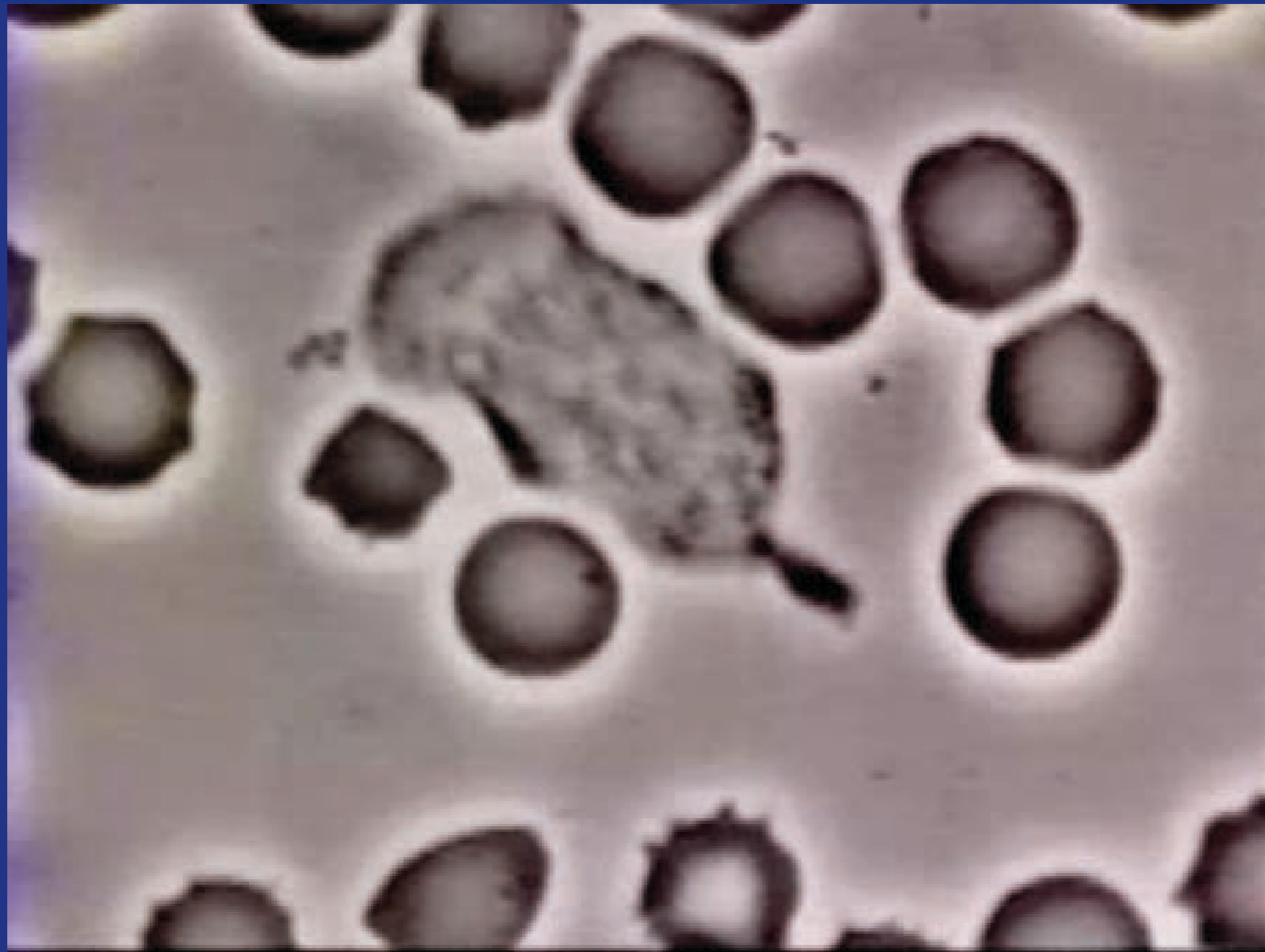
Charles Darwin



1837

3. Different parts are related by evolution.

What is complex about biological systems?

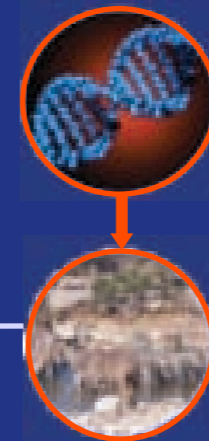
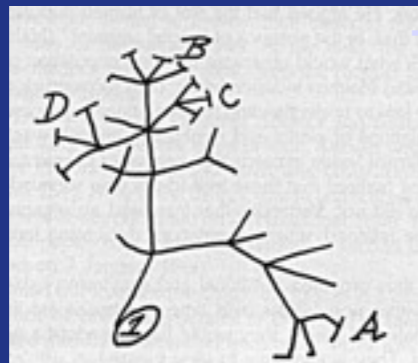


4. Interacting timescales.

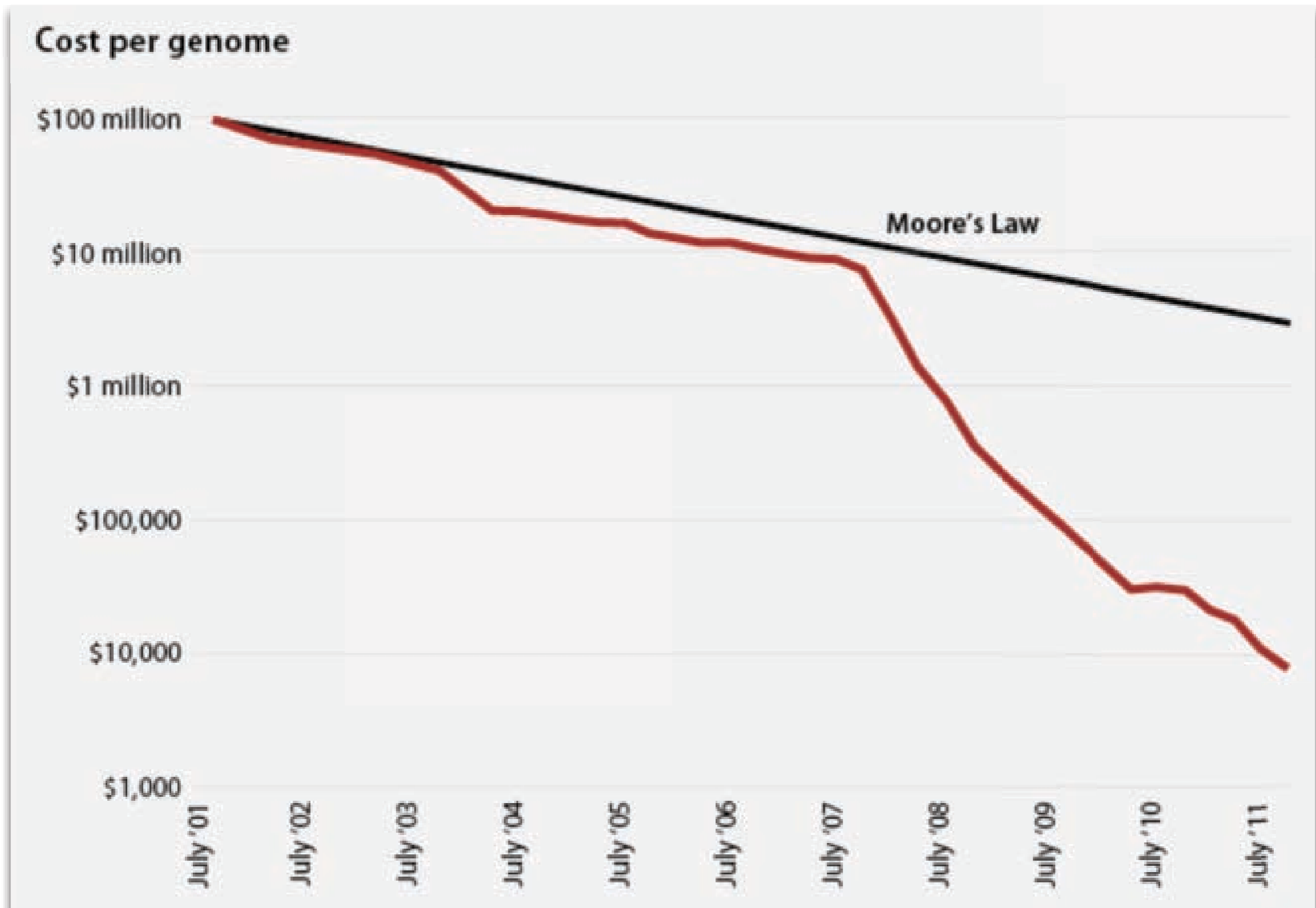


What is complex about biological systems?

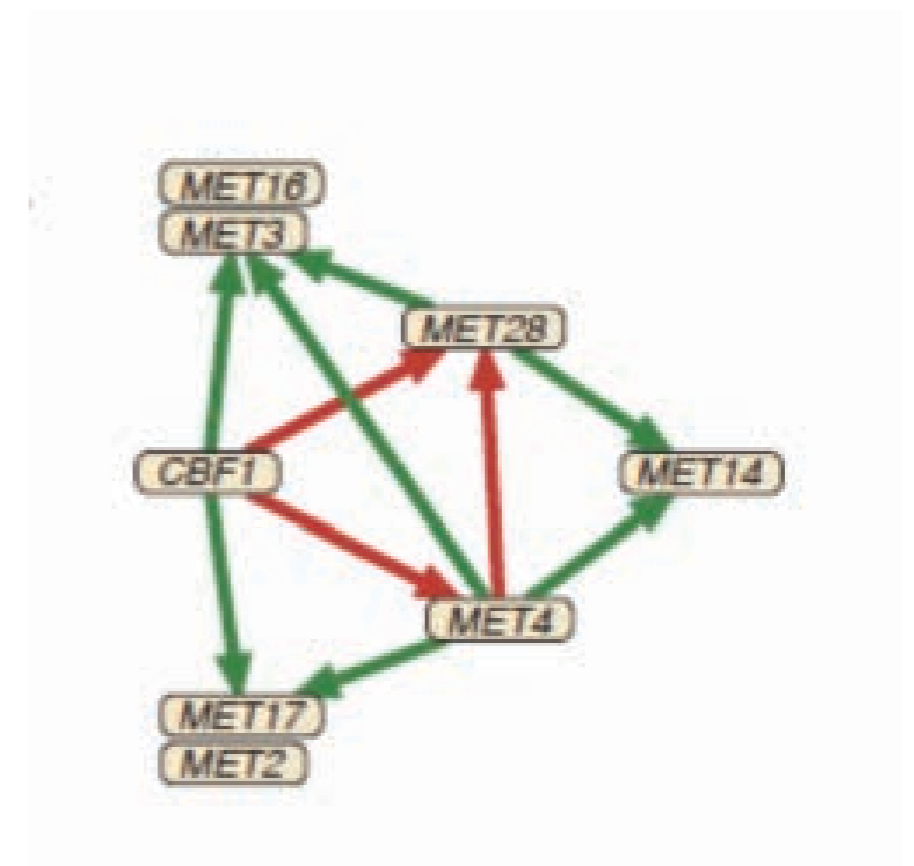
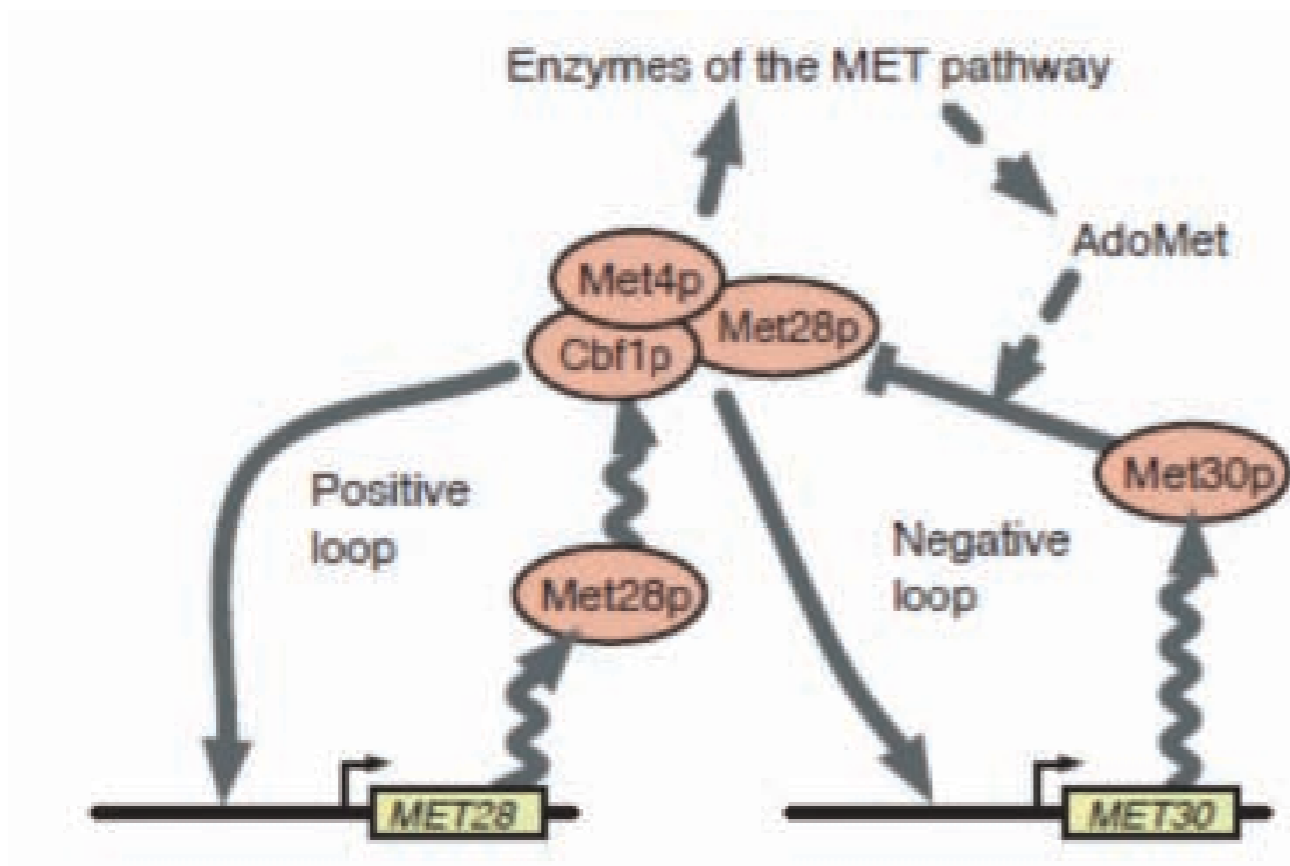
Four nonlinear contexts.



DNA/RNA sequencing technology



Textbook dream and large-scale reality



Visualization of interaction networks

The first large-scale PPI dataset

A comprehensive analysis of protein–protein interactions in *Saccharomyces cerevisiae*

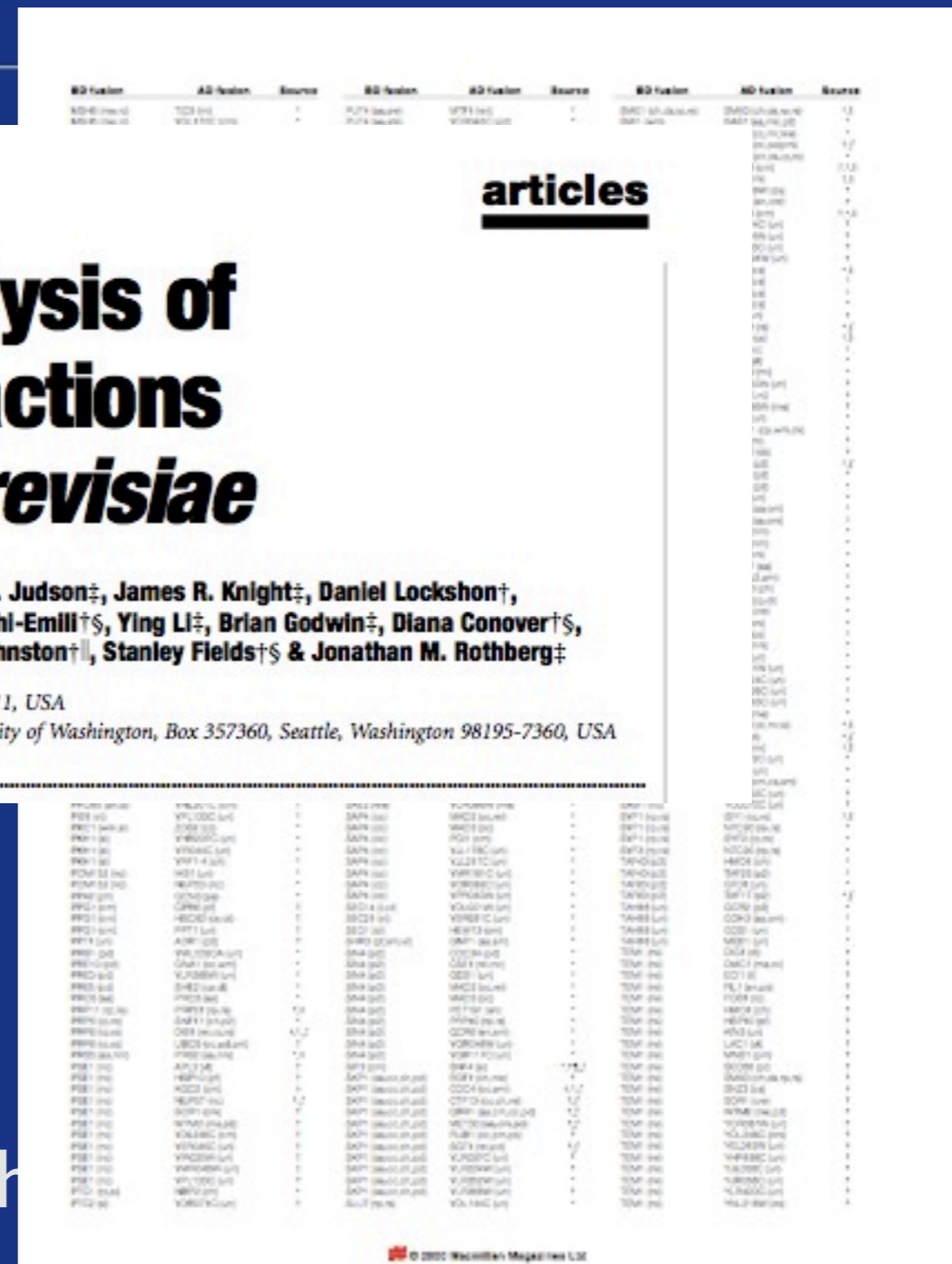
Peter Uetz^{*†}, Loïc Giot^{*‡}, Gerard Cagney[†], Traci A. Mansfield[‡], Richard S. Judson[‡], James R. Knight[‡], Daniel Lockshon[†], Vaibhav Narayan[‡], Malthreyan Srinivasan[‡], Pascale Pochart[‡], Alia Qureshi-Emili^{†§}, Ying Li[‡], Brian Godwin[‡], Diana Conover^{†§}, Theodore Kalbfleisch[‡], Govindan Vijayadamodar[‡], Meljia Yang[‡], Mark Johnston^{†||}, Stanley Fields^{†§} & Jonathan M. Rothberg[‡]

[‡] CuraGen Corporation, 555 Long Wharf Drive, 11th Floor, New Haven, Connecticut 06511, USA

[†] Departments of Genetics and Medicine and [§] Howard Hughes Medical Institute, University of Washington, Box 357360, Seattle, Washington 98195-7360, USA

* These authors contributed equally to this work

- ~50% false positives/false negatives
- Is this data good for anything?

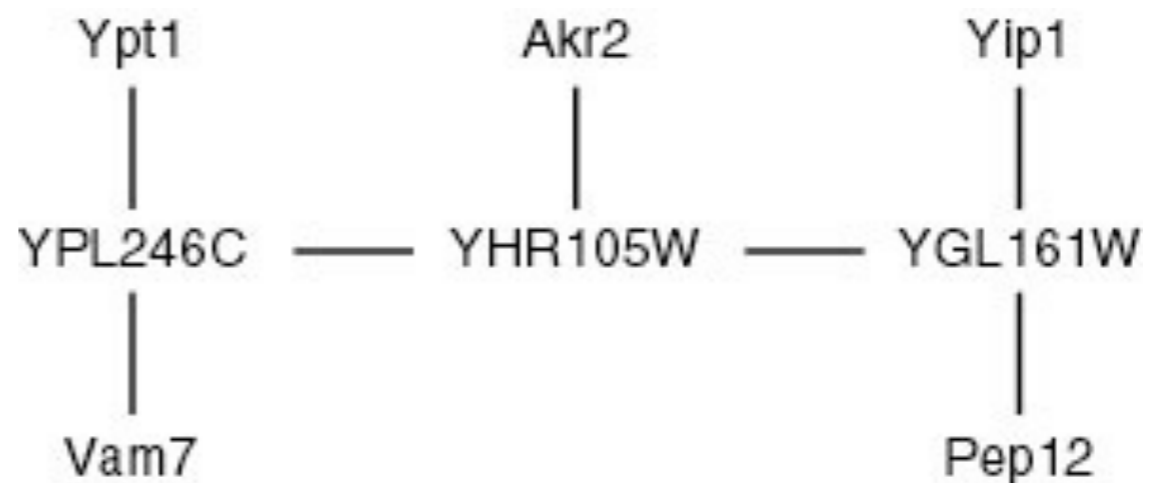


Advantages of graphical representation

Linear

Ypt1 — YPL246C
Akr2 — YHR105W
Yip1 — YGL161W
YPL246C — Vam7
YGL161W — Pep12
YPL246C — YHR105W
YHR105W — YGL161W

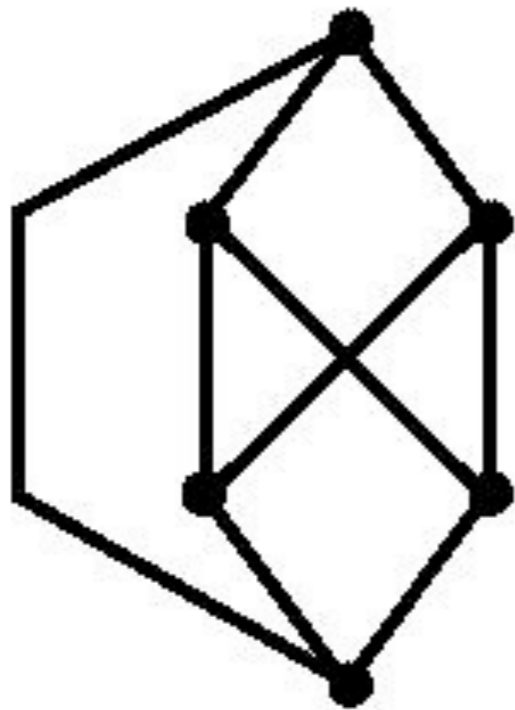
Graphical



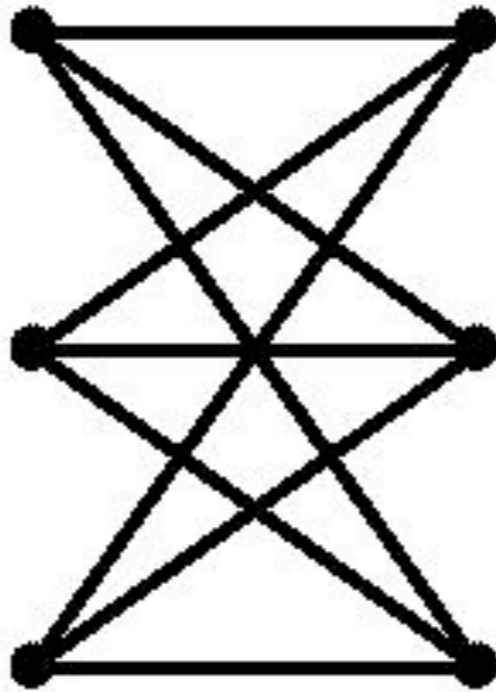
Questions to assess usefulness

- How many interactions involve YHR105W?
- Are YHR105W and Pep12 closely related?

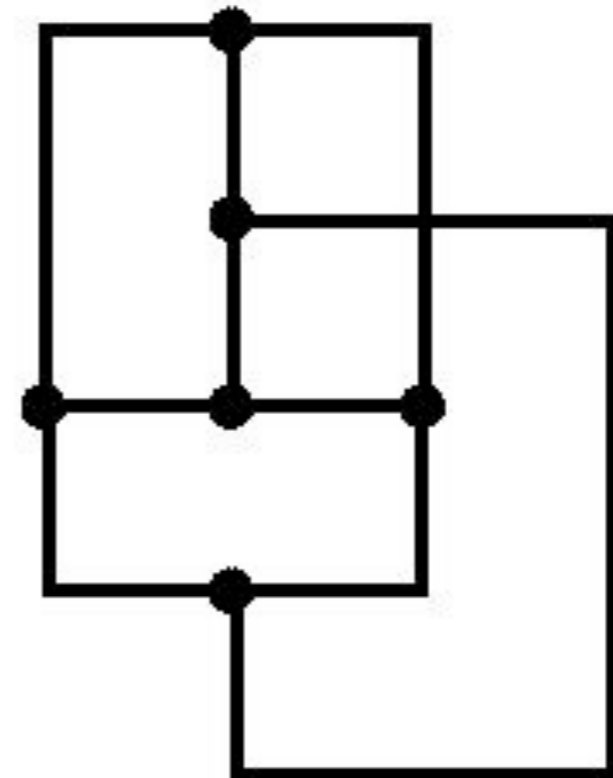
One graph, many visualizations



(a)

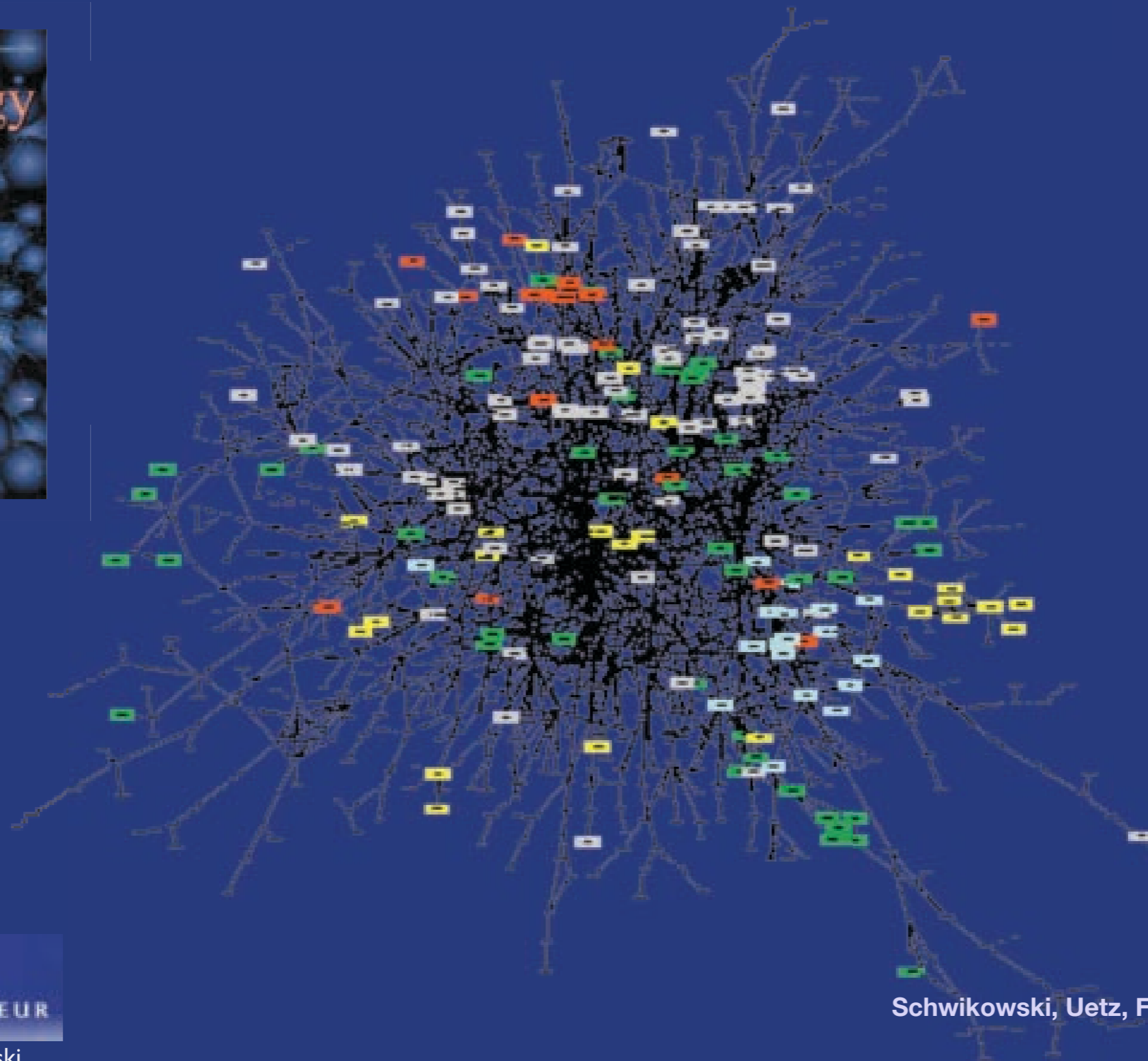
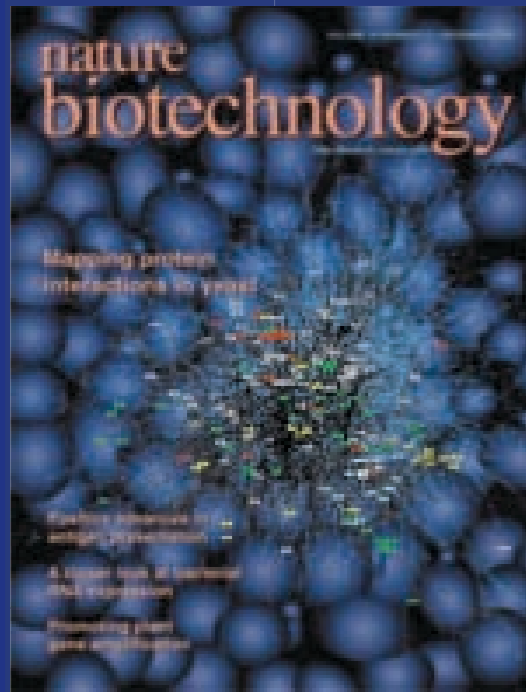


(b)

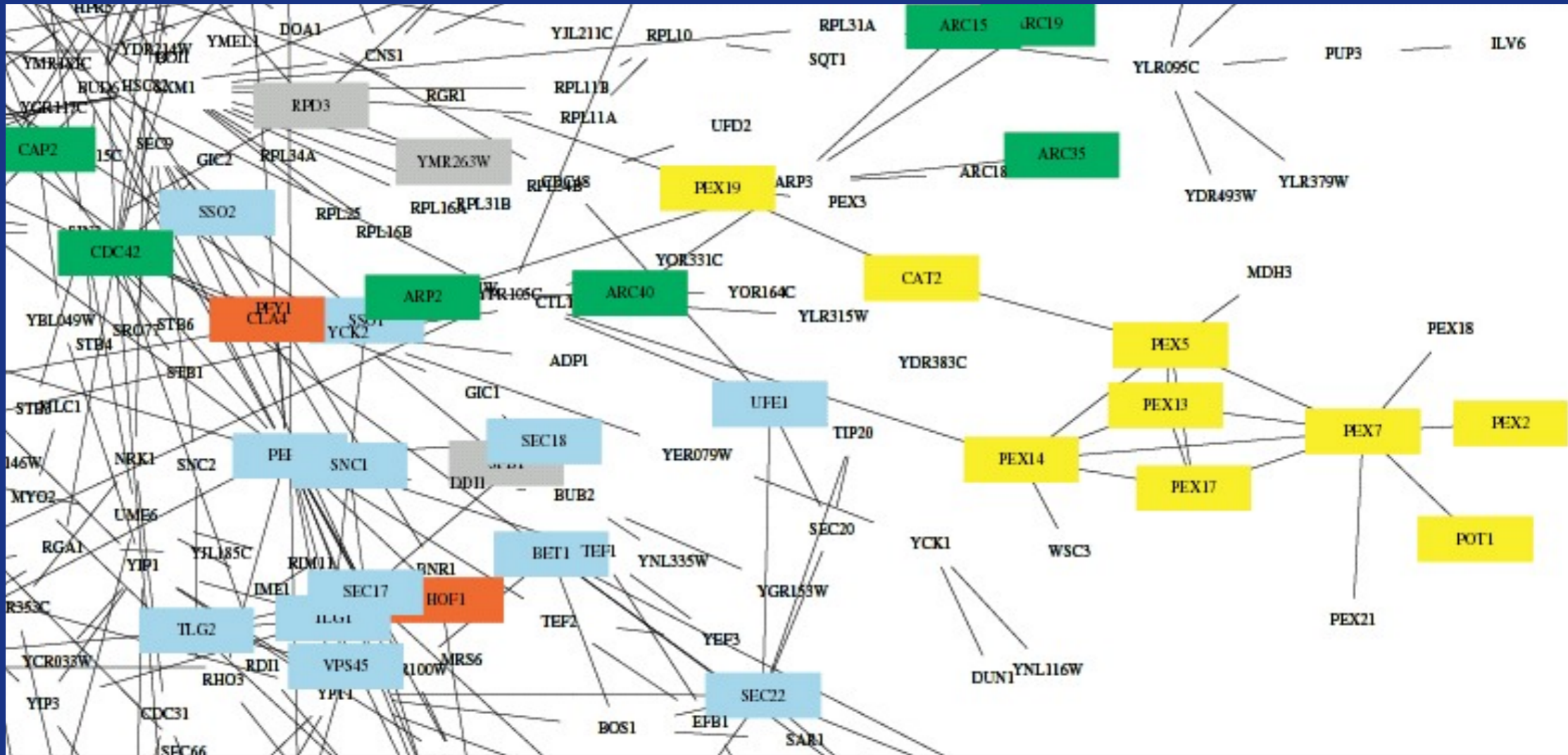


(c)

Visualization

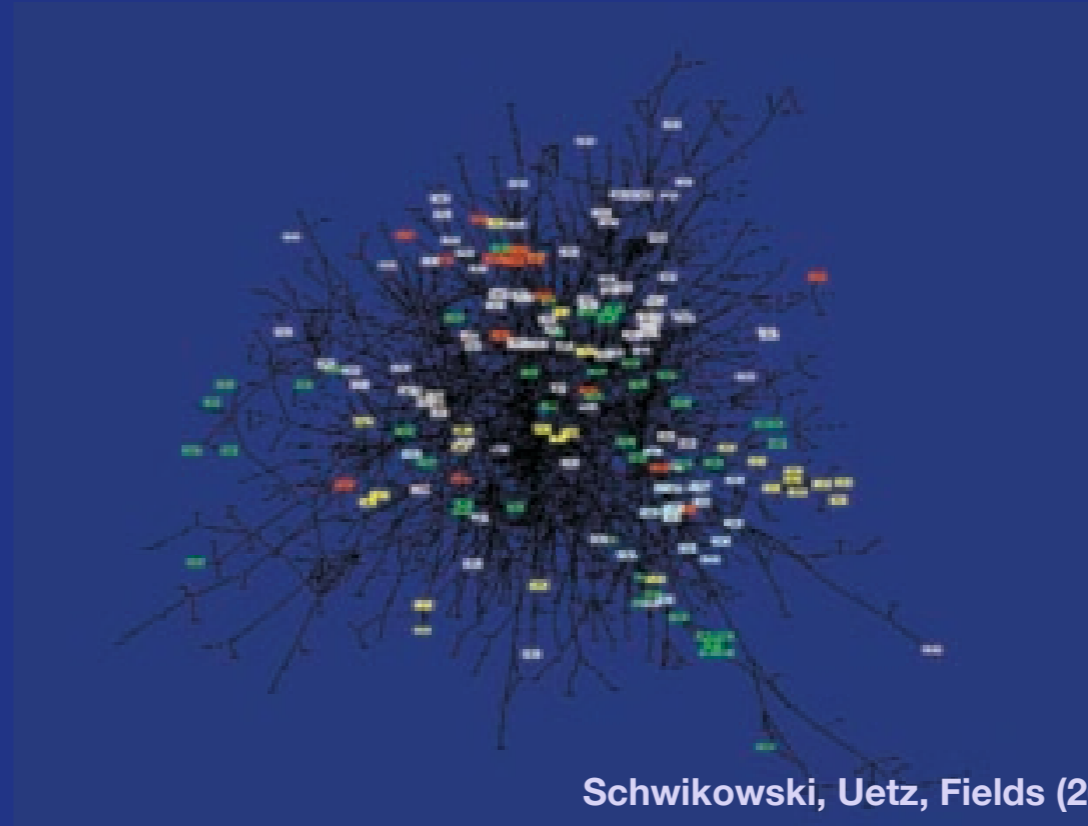


Visualization



Statistical analysis

- Correlation interacting proteins/function?
- Is that correlation statistically *significant*?
- Exploitable for function prediction?



Protein interactions contain information about cellular roles

Simple prediction algorithm for the cellular role of a protein

- 1) Rank known cellular roles among the interactors from most frequent to least frequent.
- 2) Take the first three (or less) roles as predictions.

Accuracy on 1,393 out of 2,039 proteins: 72% (6 out of 8)
...on 100 scrambled networks: 12% (1 out of 8).

Protein networks – built by association

Melanie L. Mayer and Philip Hieter

The total genome sequence era has provided complete catalogs of the genes of several organisms and offered the challenge of understanding the functions of large numbers of previously uncharacterized proteins. Historically, the functions of genes (i.e., their encoded proteins) have been determined by analysis of mutant phenotypes, genetic interactions, biochemical activities, homology to other proteins of known function, and physical interactions with other proteins. Schwikowski et al.¹ have compiled comprehensive protein–protein interaction data sets from the yeast community and find that these interactions form one large network of 2,358 interactions among 1,548 proteins and several smaller networks. Analysis of these networks allows assignment of potential function to uncharacterized proteins and the discovery of potential interactions within and across cellular processes and compartments. These connections represent a gold mine for formulating and experimentally testing specific hypotheses about gene function.

The total genome sequence era has also made possible the ongoing development (and validation) of methodologies that address

gene function on a genome-wide scale (functional genomics)². Several new approaches are aimed at determining the function of large sets of proteins and defining how these macromolecules interact within complex networks. These include computational biology driven approaches, such as correlated phylogenetic profiles (which predict that proteins that function in a common pathway or complex will evolve in a similar fashion and be either preserved or eliminated in a given genome)³, structure-based functional genomics (which aims to assign functions to uncharacterized proteins based on structure prediction), and the analysis of domain fusion events (which is based on the premise that two domains that are fused in one organism are likely to interact in another organism in which both domains are in separate proteins)^{4,5}. Functional assignments for newly discovered proteins have also been made by partnering them with proteins of “known” function by analyzing large

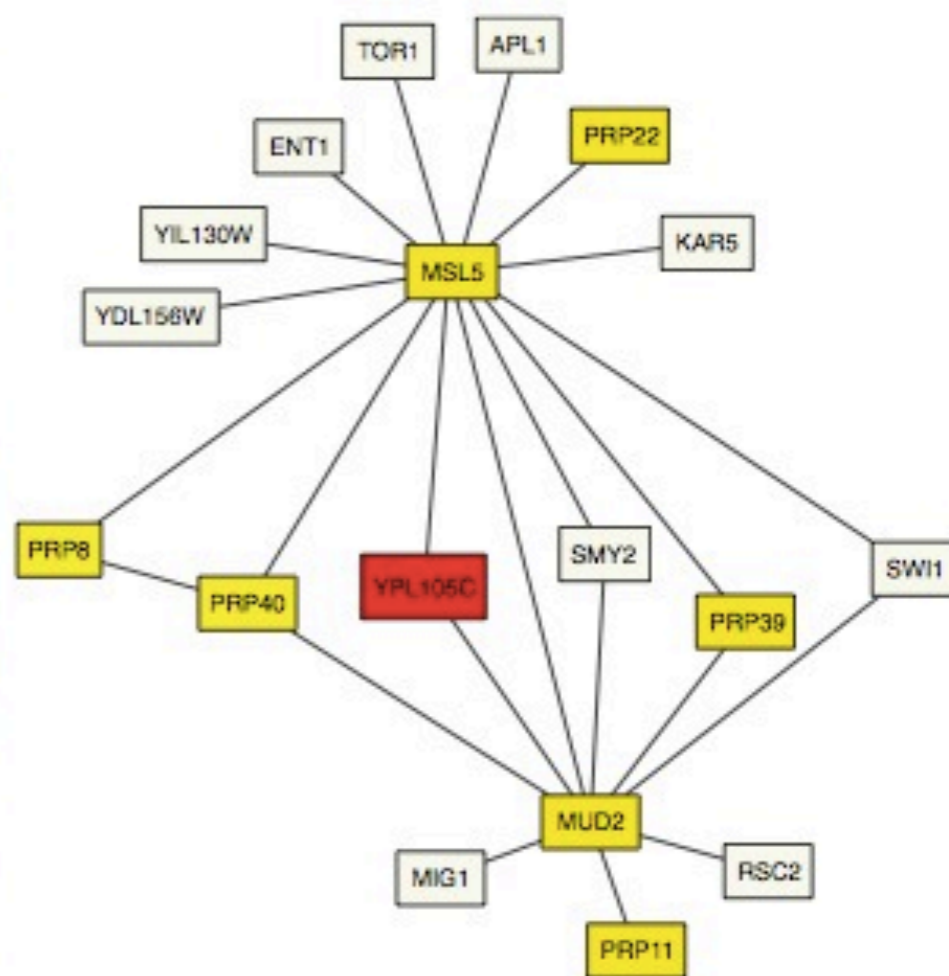


Figure 1. Enhanced protein function prediction via an annotated protein interaction web. A network of protein interactions is diagrammed up to a distance of two steps around YPL105c (marked red), an ORF that encodes a protein of unknown function. Proteins known to play a role in RNA splicing are marked yellow. This local web is connected at multiple points around the periphery to a larger network of 2358 interactions among 1548 proteins.

Protein interactions today

The screenshot displays the IntAct database interface. At the top, there is a search bar with the text "Enter Text Here" and a "Find" button. Below the search bar is a navigation menu with options: Databases, Tools, Research, Training, Industry, About Us, and Help. The main content area shows the search results for the query "species: 'Homo sapiens'". The results indicate that 89,523 binary interactions were found in IntAct. A list of statistics is provided: 35,756 interactions are from "spoke expanded co-complexes" and should be filtered out; 68 negative interactions could match the query and should be included in the results. Below the statistics, there are options to "Select format to Download" and "Customize view".

EMBL-EBI

Enter Text Here Find Terms of Use | Privacy | Cookies

Databases Tools Research Training Industry About Us Help Site Index

IntAct

Search: species:"Homo sapiens" Search Clear Show Advanced Fields » MIQL synt

- Free text search will look by default for interactor identifier, species, interaction id, detection method, interaction type, publication identifier or author
- For a more specific search, use MIQL syntax or advanced search
- Search based on exact word matches eg. BRCA2 will not match BRCA2B
- Search for isoforms of 'P12345' by using 'P12345'

Home Search Interactions (89523) Browse Lists Interaction Details Molecule View Graph

Browse by [taxonomy](#), [gene ontology](#), [ChEBI ontology](#)

89,523 binary interactions were found in IntAct.

- 35,756 of them are originated from [spoke expanded co-complexes](#) and you may want to [filter](#) them out.
- 68 negative interactions could match the query and you may want to [include](#) them in the results. They will appear in a **pink row** and will be excluded from MITAB 2.5, RDF, Biopax, XGMML export as well as from the graph view.

> No results in other databases.

Select format to Download Download Customize view

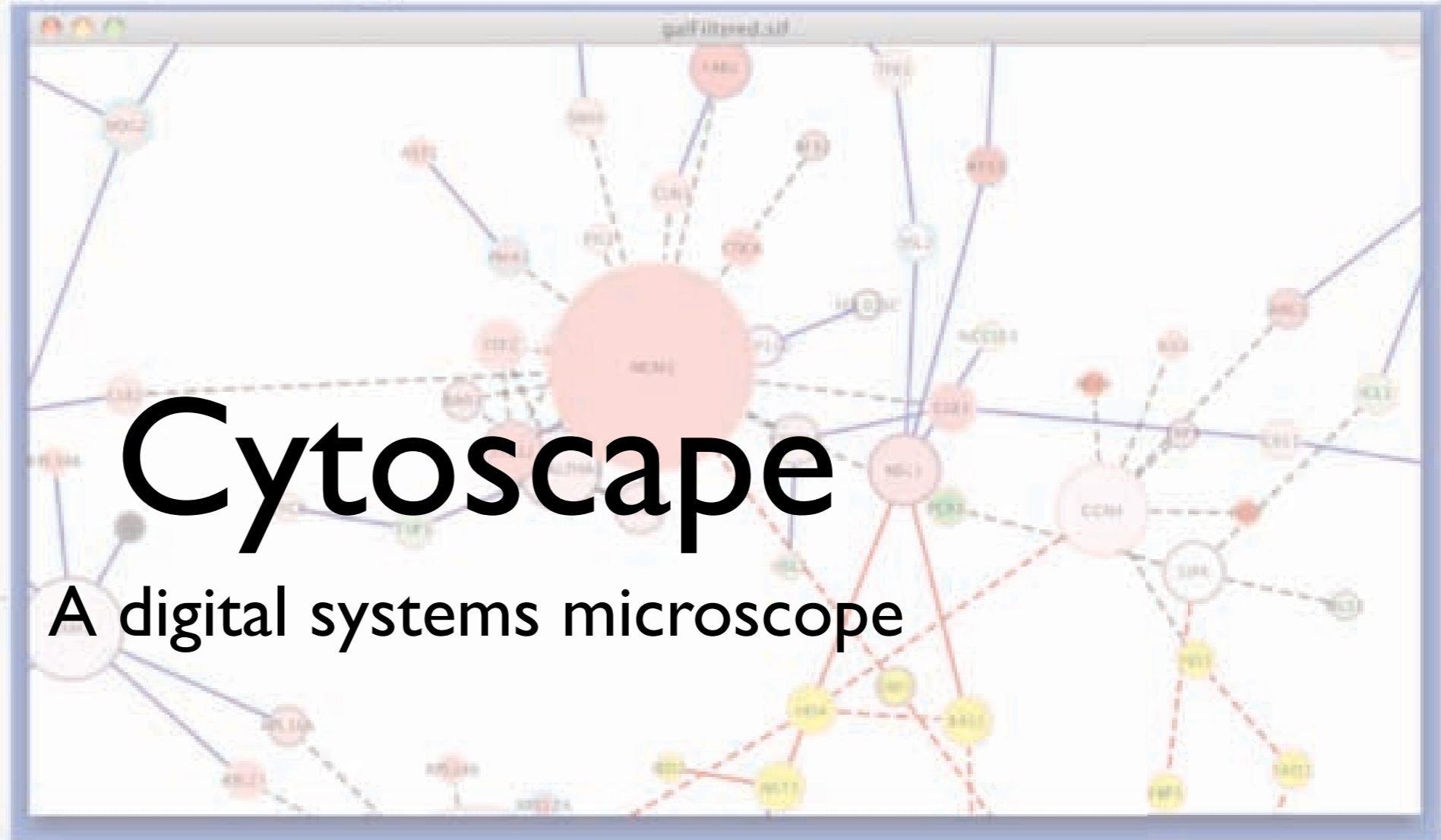
1 2 3 4 5 6 7 8 9

May 21, 2012

Nov 28, 2012

Cytoscape

A digital systems microscope



Control Panel

Network: VizMapper™

Current Visual Style: galFiltered Style

Defaults:

Visual Mapping Browser

- Edge Visual Map
- Edge Color: Interaction
- Edge Line Style: Interaction
- Node Visual Map
- Node Border Color: Family Description
- Node Color: galRGexp
- Node Label: SGD symbol
- Node Size: Degree
- Node Tooltip: Pathway

Unused Properties

- Edge Font Face
- Edge Font Size
- Edge Label
- Edge Label Color
- Edge Label Opacity
- Edge Label Width
- Edge Line Width
- Edge Opacity
- Edge Source Arrow C...

Data Panel

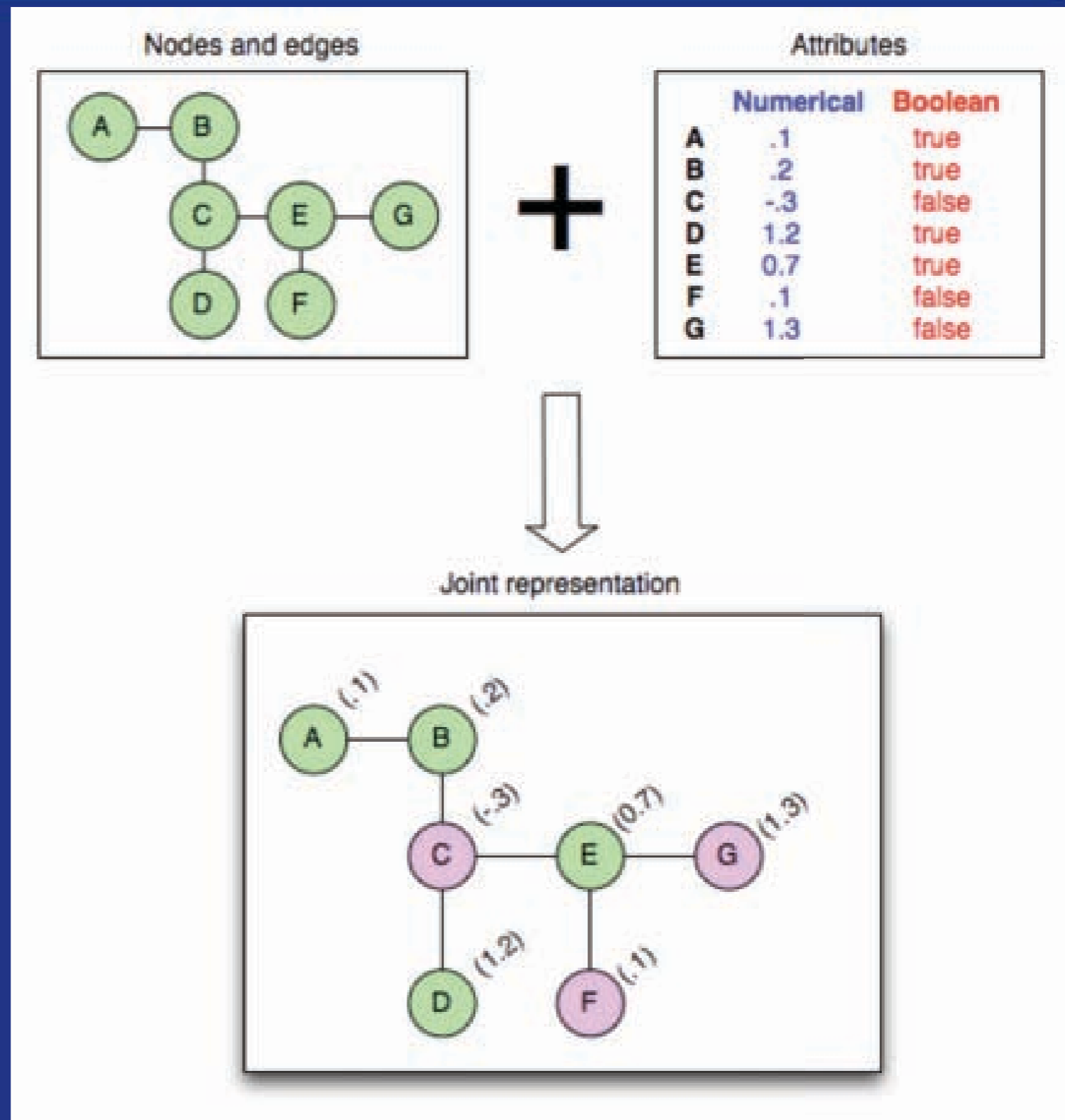
ID	EntryCase ID	Pathway	GeneID	SGD symbol	annotation:GO BIOLOGICAL_PROCESS	galRGexp
YLR177C	[851092]	[KEGG pa...	[fructose...	[FBP1]	[carbohydrate metabolic process, glu...	0.873
YCL030C	[850327]	[KEGG pa...	[]	[HIS4]	[amino acid biosynthetic process, hist...	-1.067
YDR146C	[851724]	[KEGG pa...	[]	[SWI5]	[G1-specific transcription in macroc...	-0.19
YKR099W	[853974]	[]	[The rec...	[BAS1]	[histidine biosynthetic process, meth...	0.466
YNL164C	[855557]	[]	[]	[BDI2]	[mitotic cell cycle spindle assembly c...	0.272
YDR202W	[854177]	[KEGG pa...	[Snf] prot...	[HIS3]	[amino acid biosynthetic process, hist...	-0.432
YNL167C	[855554]	[]	[The resul...	[SKO1]	[negative regulation of transcription f...	0.095

Node Attribute Browser | Edge Attribute Browser | Network Attribute Browser

Cytoscape core functionality

Data model

- Network (Graph)
- Nodes
- Edges
- Attributes



Cytoscape file formats

Sample interaction file

```
YDR216W pd YIL056W  
YDR216W pd YKR042W  
YDR216W pd YGL096W  
YDR216W pd YDR077W
```

[...]

Sample expression file

GENE DESC	exp0.sig	exp1.sig	exp0.sig	exp1.sig	
GENE0	G0	0.0	0.0	23.2	11.5
GENE1	G1	0.0	0.0	34.6	5.2
GENE2	G2	0.0	0.0	10.0	28.0
GENE3	G3	0.0	0.0	1.64	4.77

[...]

Cytoscape interface

Cytoscape Version 2.6.1 File Edit View Select Layout Plugins Help

Cytoscape Desktop (Session: galFiltered2.cys)

Search: ESP: 1532 5000000404 5000000287 5000000201 5000000039

Control Panel

Network VizMapper™ Editor Filters

Network	Nodes	Edges
galFiltered2.sif	331(15)	362(0)
Genes on MAPK Signaling Pathway	15(1)	13(0)
MAPK Signaling Pathway	178(0)	0(0)

galFiltered.sif

MAPK Signaling Pathway

Genes on MAPK Signaling Pathway

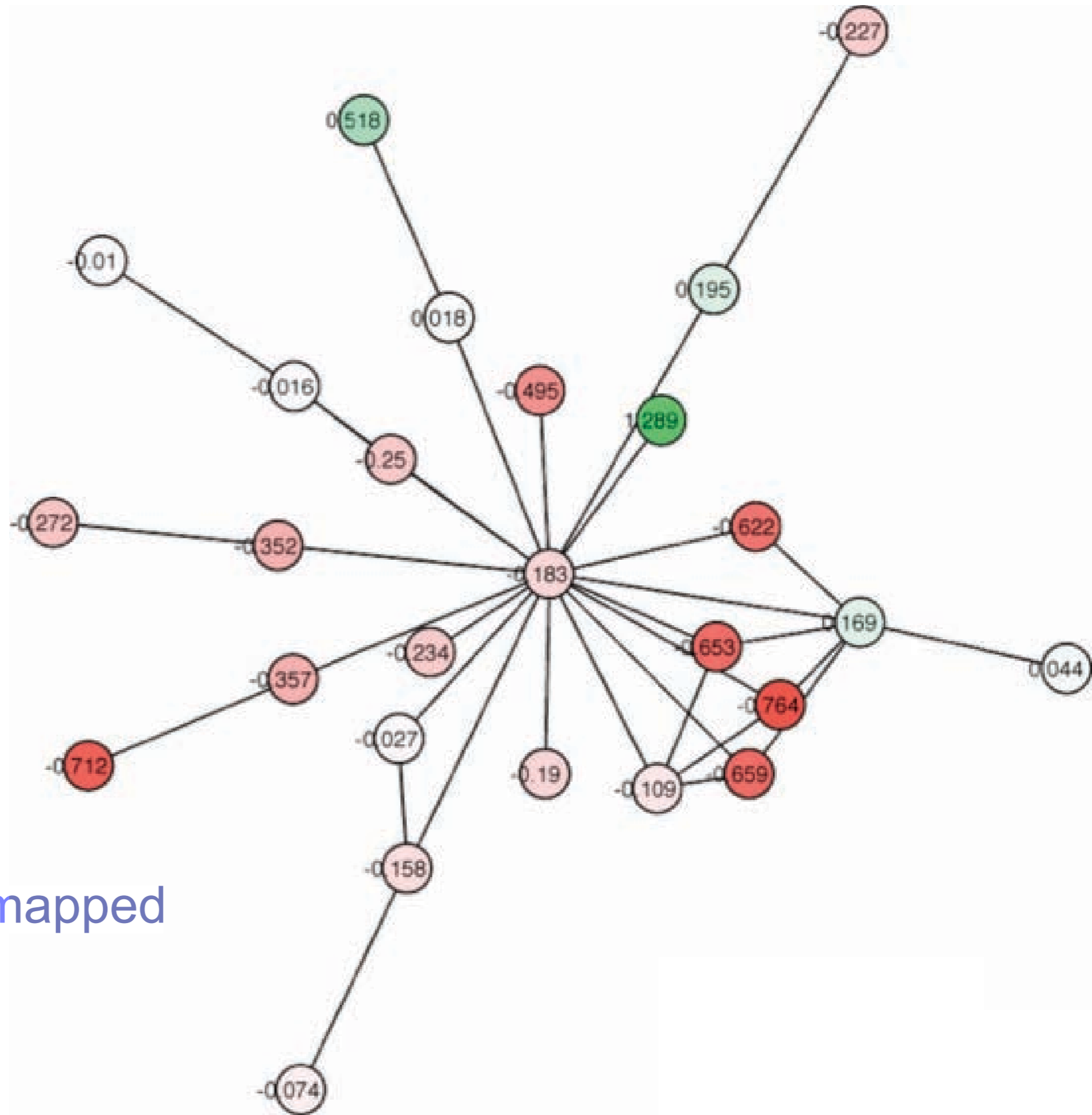
Data Panel

ID	annotation.DB_Object_ID	gal4RCexp	annotation.DB_Object_Name	annotation.GO BIOLOGICAL_PROCESS	annotation.Taxon
YMR043W	S000004646	-0.654	Transcription factor involved in cell-type-specific transcription and pherom...	YMR043W	
YHR005C	S000001047	-0.413	GTP-binding alpha subunit of the heterotrimeric G protein that couples to p...	DNA replication initiation	
YFL026W	S000001868	-0.396	Receptor for alpha-factor pheromone	cell cycle	
YER111C	S000000913	-0.105	DNA binding component of the SBF complex (Swi4p-Swi6p), a transcriptiona...	regulation of transcription from RNA polymerase II promoter	
YNL098C	S000005042	0.062	GTP-binding protein that regulates the nitrogen starvation response, sporul...	regulation of transcription, DNA-dependent	
YLR229C	S000004219	0.089	Small rho-like GTPase, essential for establishment and maintenance of cell ...	transcription	
YJL157C	S000003693	-0.803	Cyclin-dependent kinase inhibitor that mediates cell cycle arrest in respons...		
YPL089C	S000006010	-0.037	MADS-box transcription factor, component of the protein kinase C-mediate...		

Node Attribute Browser Edge Attribute Browser Network Attribute Browser

Welcome to Cytoscape 2.6.1 Right-click + drag to ZOOM Middle-click + drag to PAN

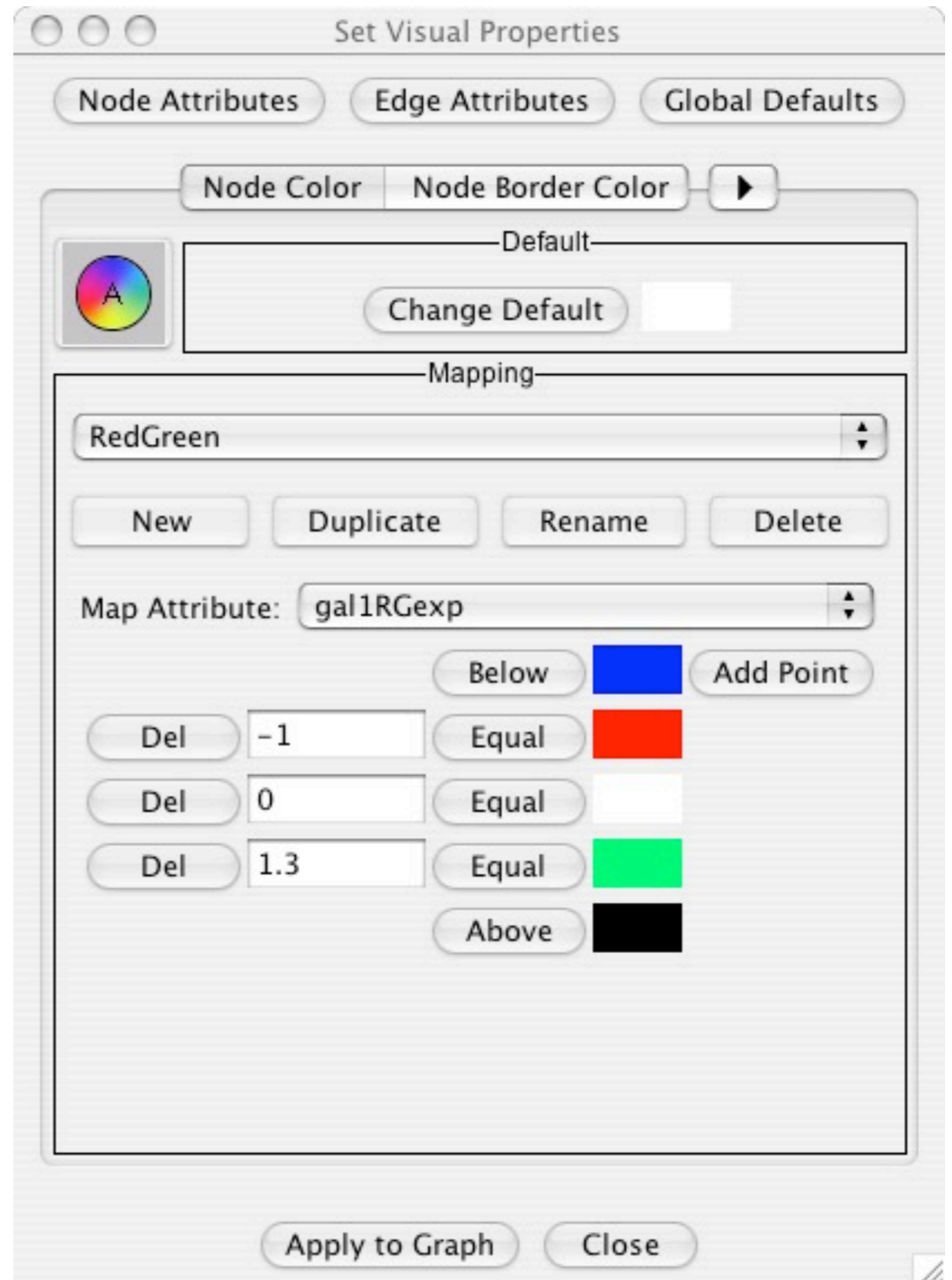
Visual Styles



Expression data mapped to node colors

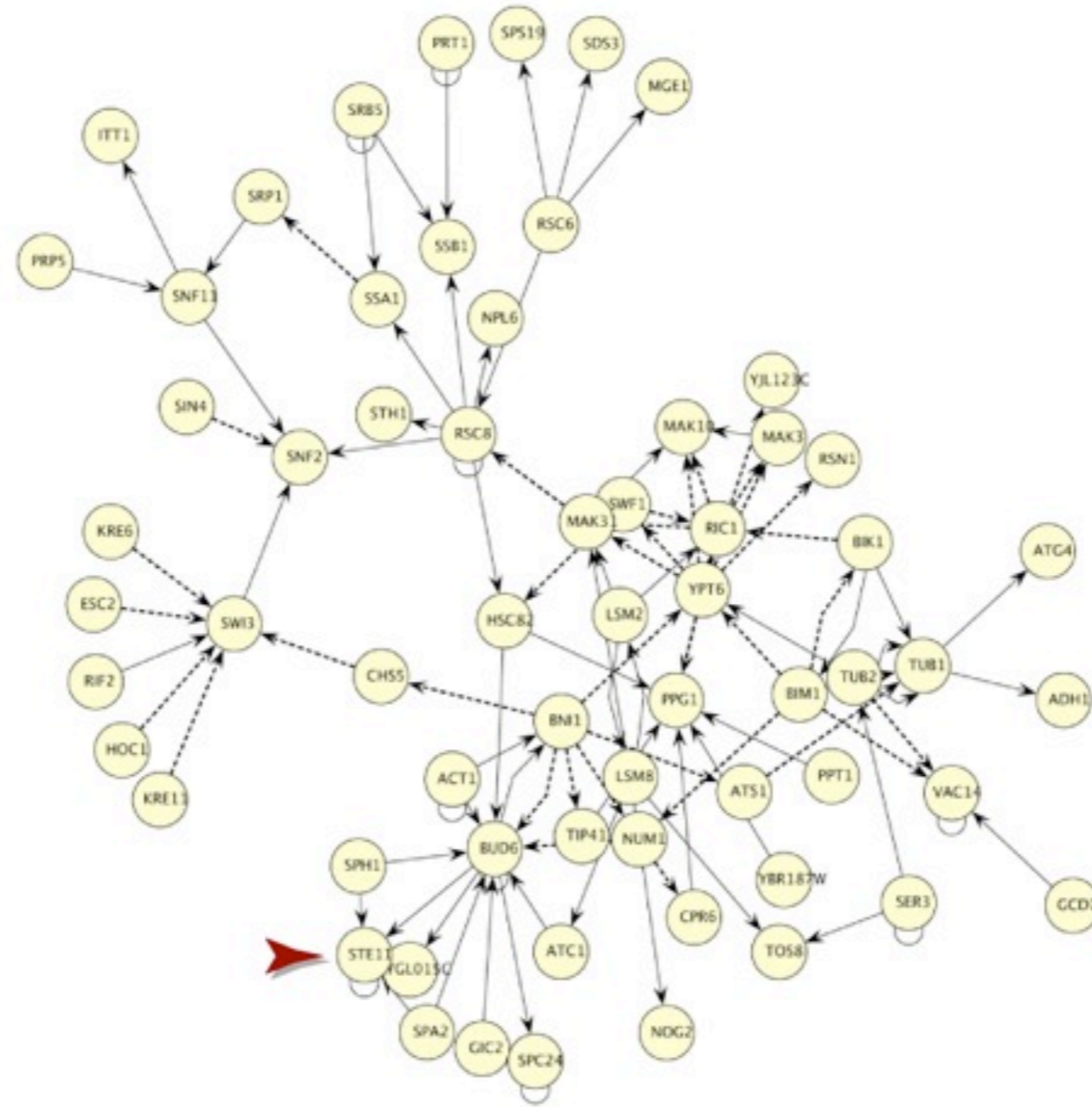
Visual Styles

Map expression values to node colors using a continuous mapper



Visual Styles

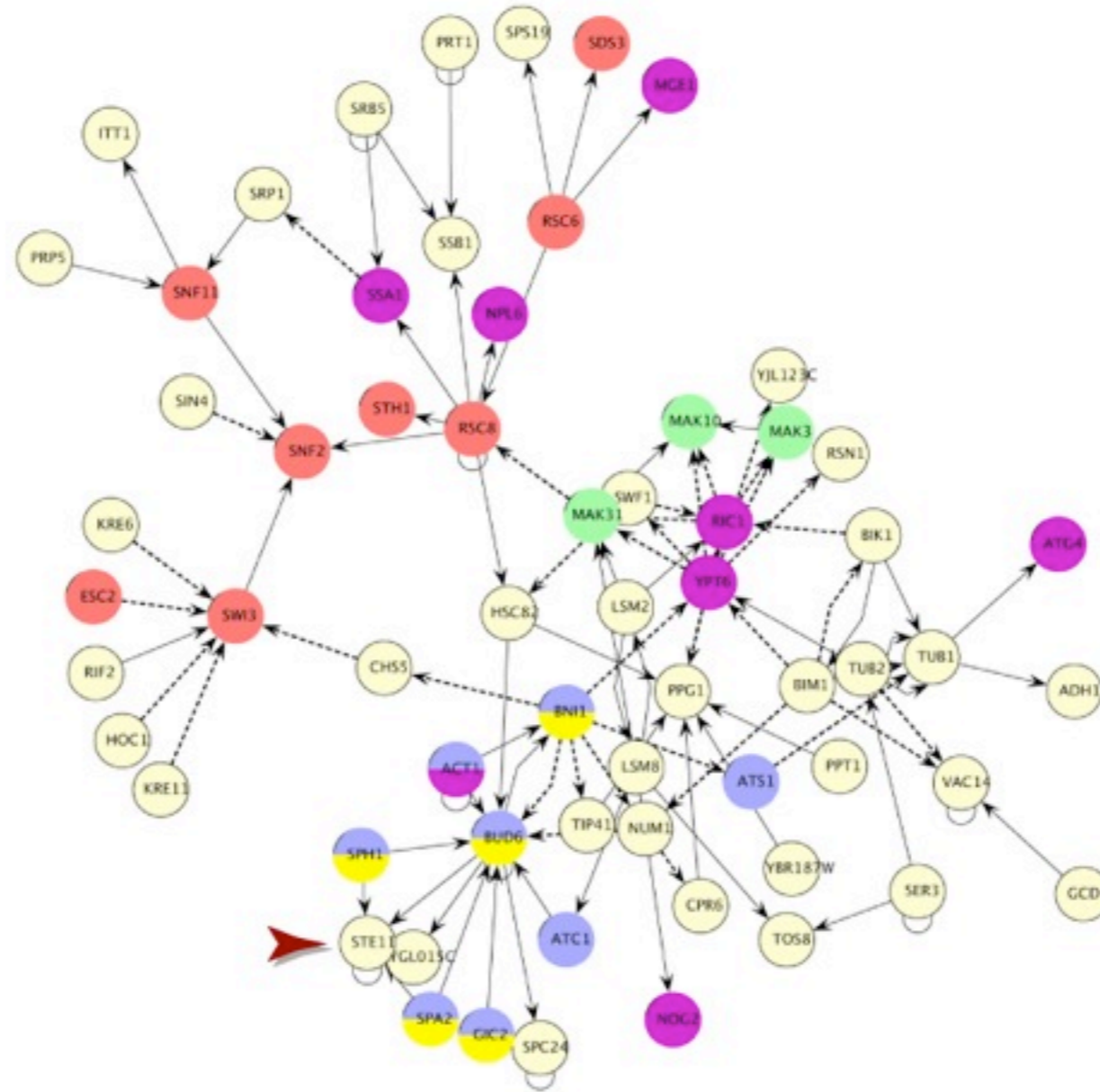
A



Spring-embedded layout

Color reflecting GO classes

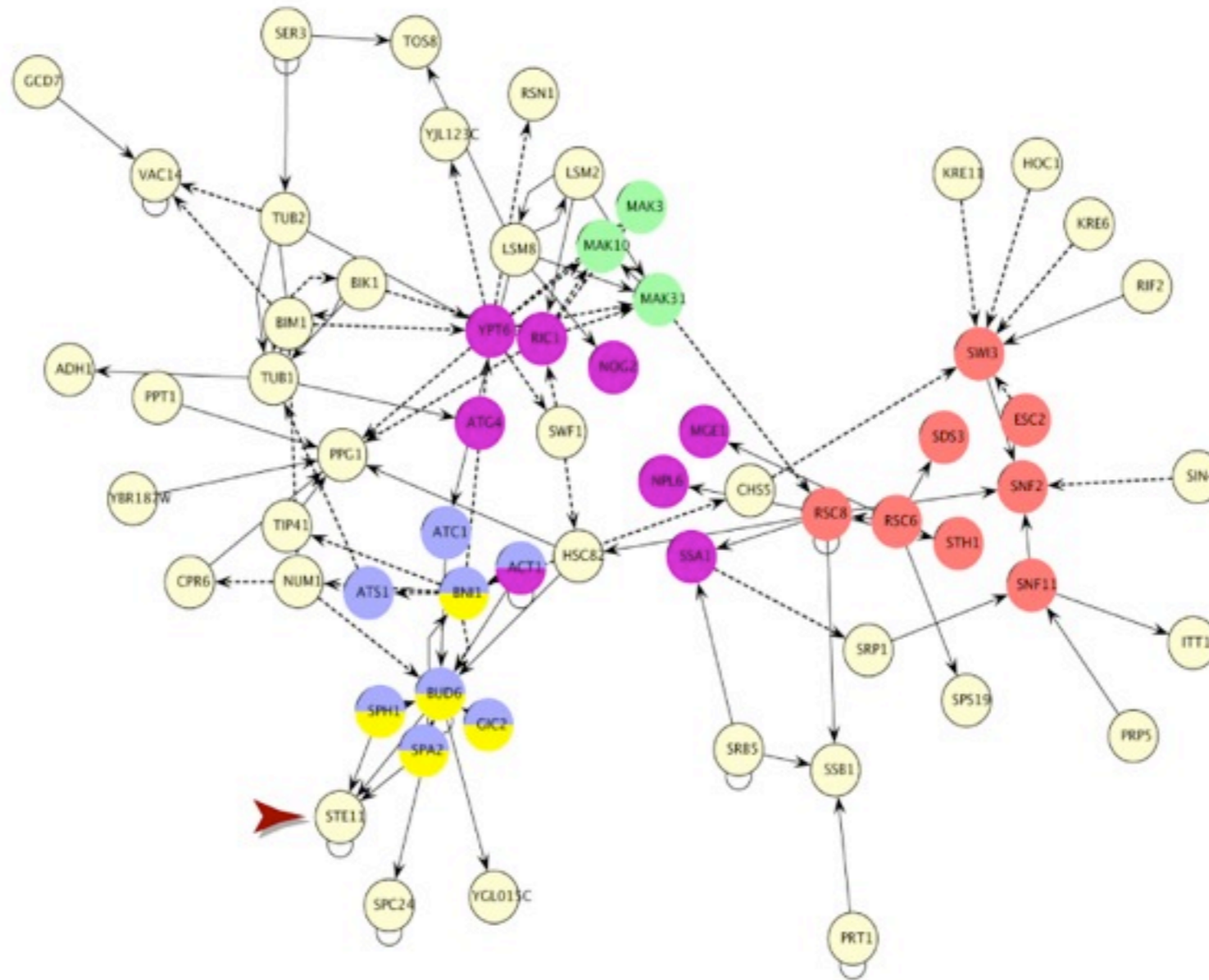
B



Spring-embedded layout, supplemented with color-coding

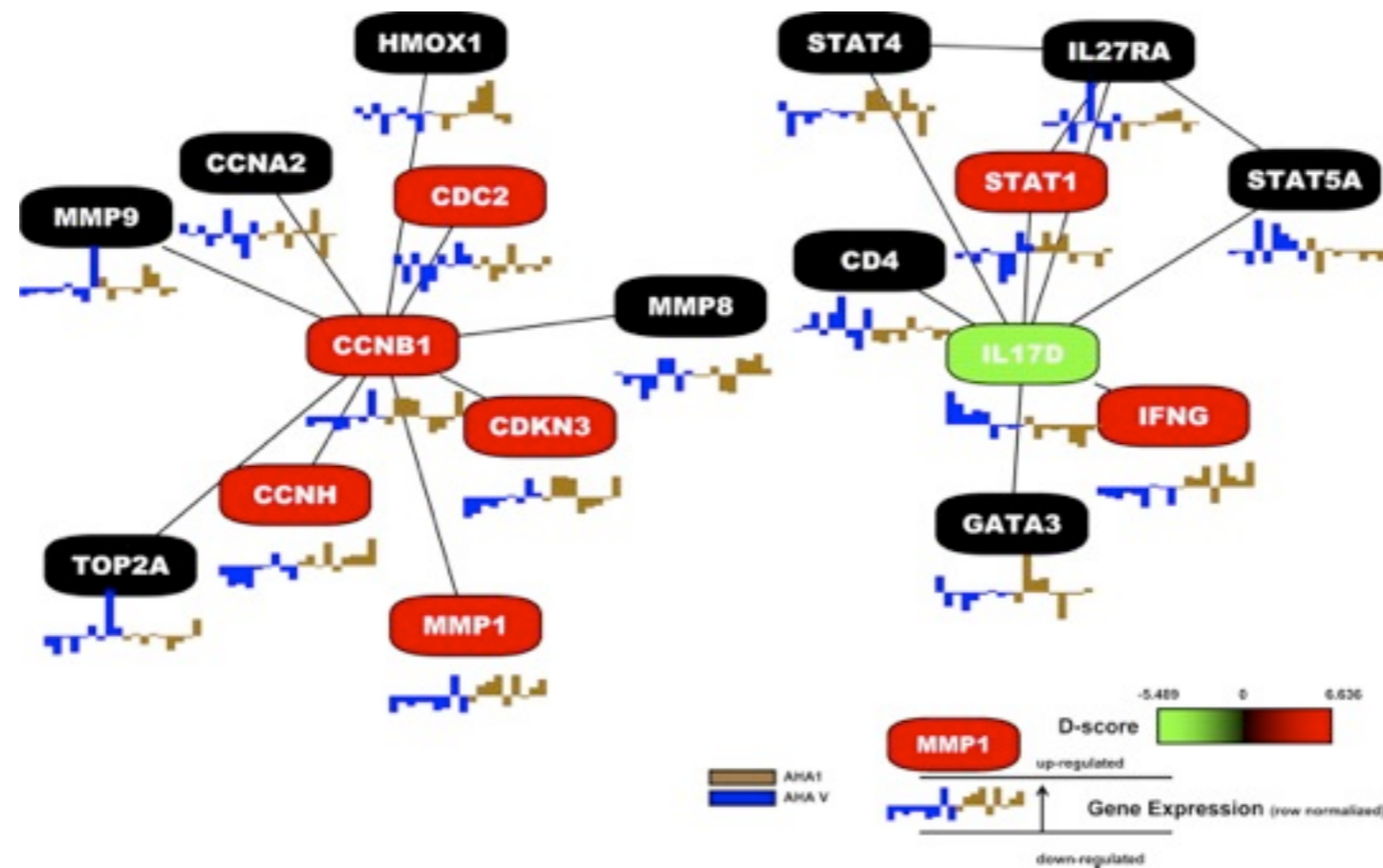
GO categories driving layout

C



GOlorize layout algorithm, informed by the Gene Ontology classes
Garcia et al. Bioinformatics 2007

Visualizing dense information



King et. al., *Physiol Genomics*. 2005 Sep 21;23(1):103-18.

Cytoscape, a digital microscope for cell biology

- Different qualitative and quantitative information accessible in a visualization and analysis platform
- Organized into interaction networks that represent systems
- Visual exploration goes hand in hand with statistical data exploration and analysis
- Simple, open-standard file formats, links with many databases
- Active community exchanging networks, know-how, and new functionality

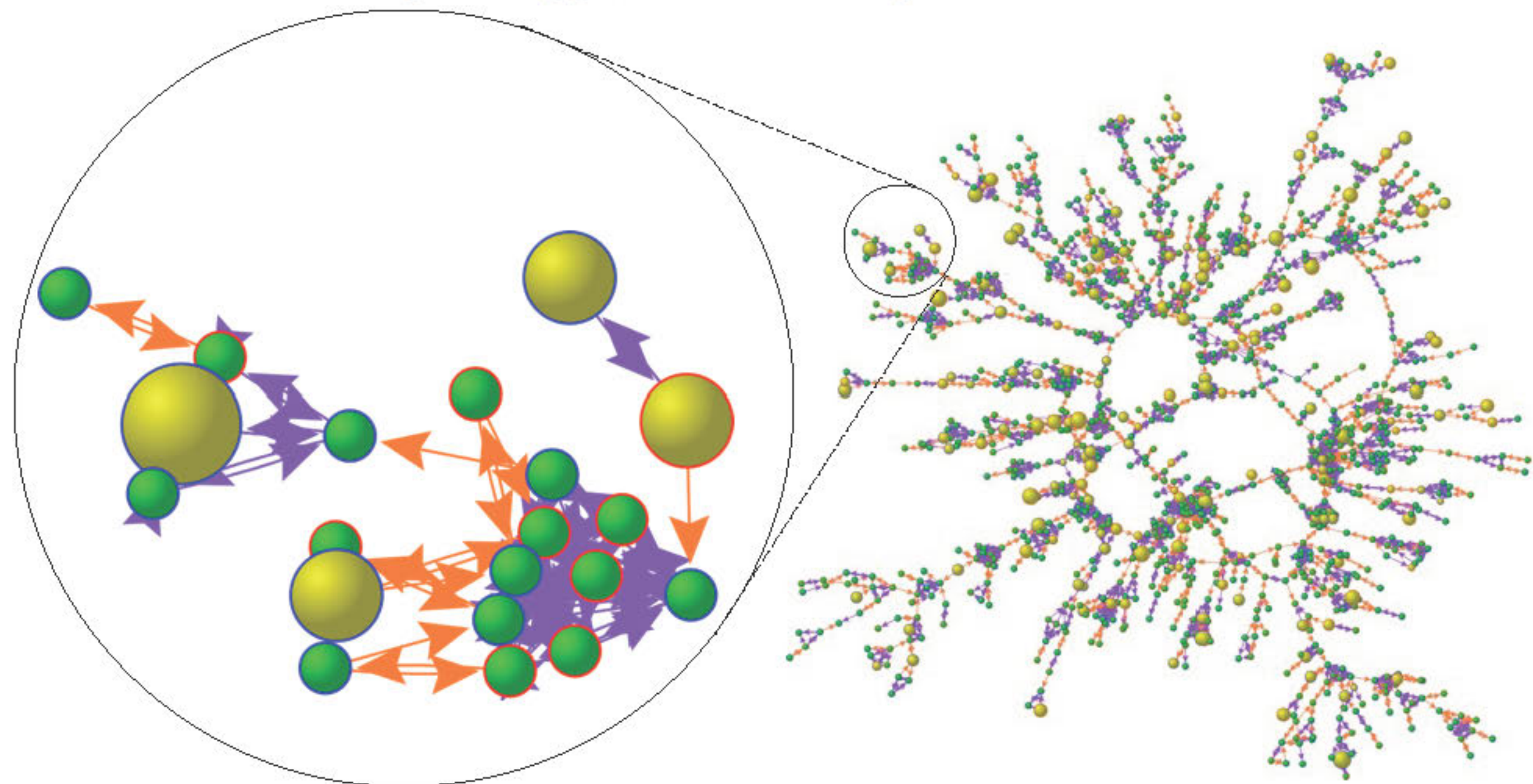
Cytoscape

- Cross-platform (Java)
- Plug-in architecture that allows external developers to easily extend core platform
- Nearly 100 plugins available through our website:
<http://cytoscape.org>
- Downloaded ~2500 times per month.
- Very popular in the Systems Biology community, but also used in other domains

The Collective Dynamics of Smoking in a Large Social Network

Nicholas A. Christakis, M.D., Ph.D., M.P.H., and James H. Fowler, Ph.D.

N ENGL J MED 358;21 WWW.NEJM.ORG MAY 22, 2008



Dissemination

- Cytoscape is released under the LGPL software license - it is **free** software available for download from our website.
- The hub of our dissemination efforts is the project Website: <http://cytoscape.org>



Cytoscape

Cytoscape: An Open Source Platform for Complex-Network Analysis and Visualization

Search...

Go



Home Introduction Download Plugins Documentation Community Report a Bug **Getting Help**

Cytoscape Desktop (New Session)

Control Panel: Network, VizMapper™, Editor, Filters

Network: Nodes: 445(93), Edges: 579(146)

Text

Cytoscape 2.8.1

Cytoscape 2.8.1 supports custom graphics, functions, and commands.

ID	GO ID	Cellular Component	Alt Name	Pathway Link	aliases	GO Evidence Code: Biological Process	Locus Tag	GeneID ID
812059	[5671, 124, 46695, 1658]	ADA2			[DMS]	[RCA, DA, MP, MP, MP, RCA, EA, I...	YDR448W	[19737915...
853827	[5678, 5634]	ASF1			[ACT3]	[DA, EA, MP, DA, DA, MP, EA, ID...	YJL081C	[19088068...
853133	[5737, 776, 5634, 48471...	CRM1			[CIA1]	[RCA, RCA, RCA, DA, DA, EA, EA, I...	YJL115W	[20048053...
855744	[16592, 5634]	CSE2			[KAP124...	[EA, MP, RCA, MP, RCA, RCA, IGL E...	YCR218W	[20485264...
853102	[31390, 3233, 43506, 56...	CTR3			[MED9]	[MP, EA, EA, DA]	YNR010W	[19077017...
					[YH131]	[RCA, EA, EA, MP, EA, RCA]	YMR078C	[19630533...

Network Data Integration, Analysis, and Visualization in a Box

Cytoscape is an open source software platform for visualizing **complex-networks** and integrating these with any type of attribute data. A lot of **plugins** are available for various kinds of problem domains, including bioinformatics, social network analysis, and semantic web.

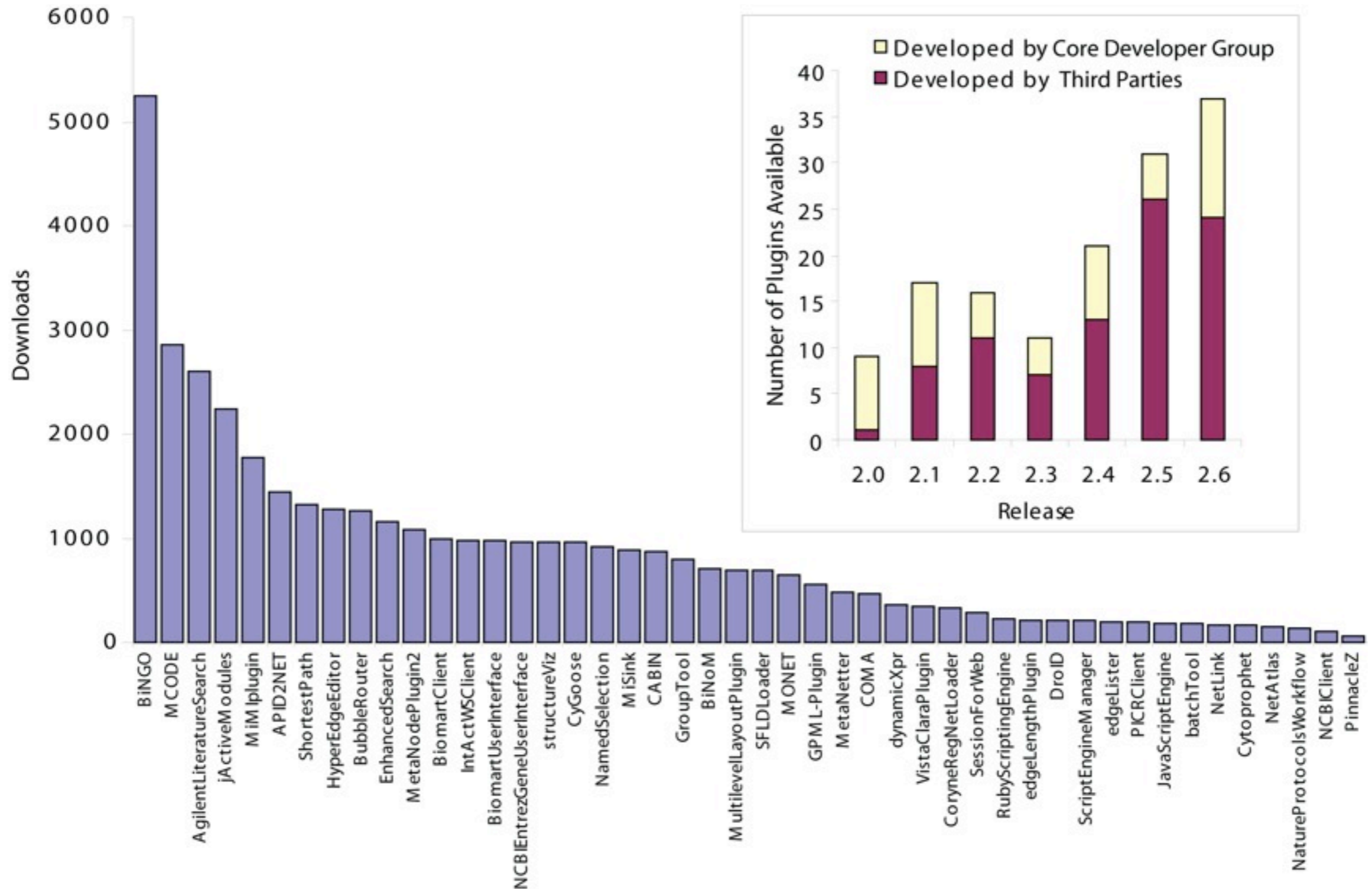
[Download Cytoscape Now](#)

[Learn More](#)

[How to Cite Cytoscape](#)

[What Can You Do With Cytoscape?](#)

Cytoscape Plugins



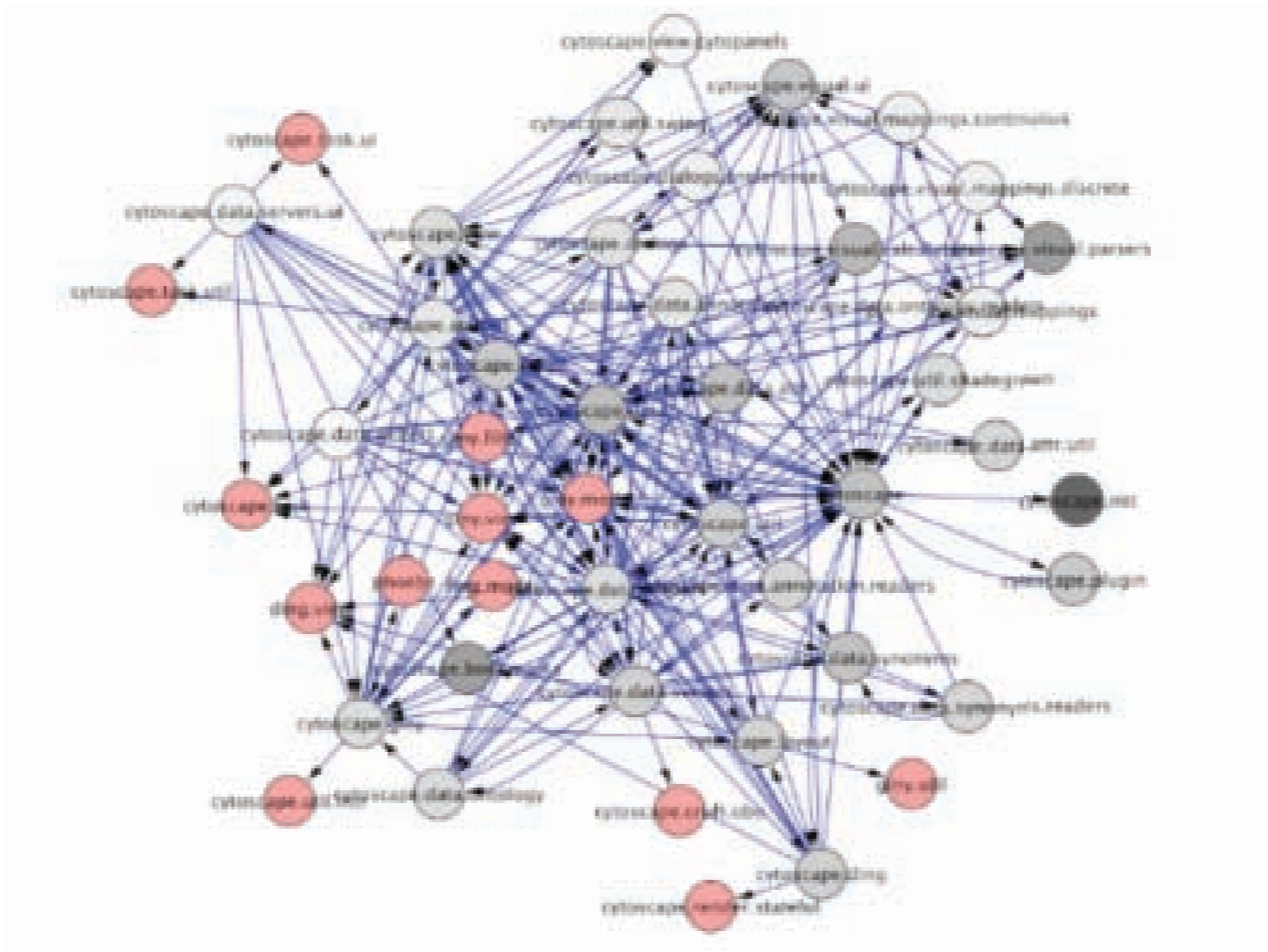
Training and Education

- Numerous tutorials and video lectures available on <http://cytoscape.org>
- Annual Symposium and Developer's retreat.
 - Held each year.
 - Features invited talks, a plugin expo, tutorials, demonstrations, and user feedback forums.
- Participation in the Google Summer of Code.
- Taught in graduate, undergraduate and other classes (e.g. UCSD, UCSF, Lund University, DTU, ISB, ...).



Cytoscape status

- The Cytoscape codebase is very feature-rich, but is becoming increasingly **difficult to maintain**, and more importantly **difficult to extend**.



What's next?

Modular Network Biology Toolkit
(aka Cytoscape 3.0)



What does this mean?

- A set of independent Java modules (jar files).
- A well defined and principled API - culmination of our team's collective experience with Cytoscape.
- Use of OSGi to support and enforce modularity.
- Use of Spring-DM to abstract away the complexities of OSGi.
- Use of Maven to facilitate distribution and integration of modules.
- Follow accepted best programming practices (information hiding, code to interfaces, dependency injection, extensive unit testing, scrum, code quality metrics, semantic versioning, thread safe, ...).



Overall Goals

Make Cytoscape...

- Easier to ***use***
 - Simple programming model = more consistent user interface.
- Easier to ***understand***
 - Well defined APIs, well defined dependencies, Maven archetypes.
- Easier to ***maintain and extend***
 - Clear APIs, separate API and implementation, semantic versioning, well understood dependencies.

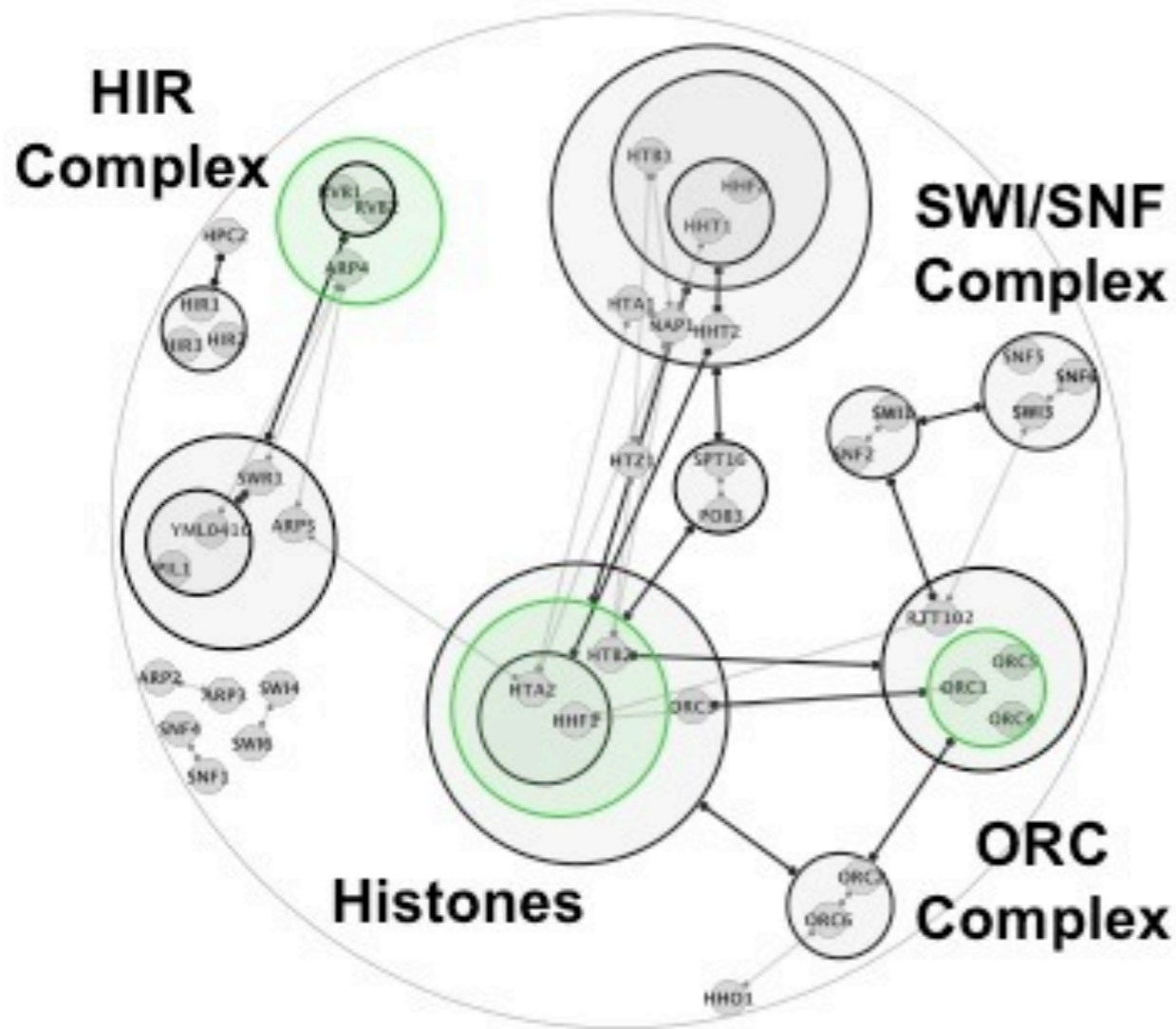


Capabilities

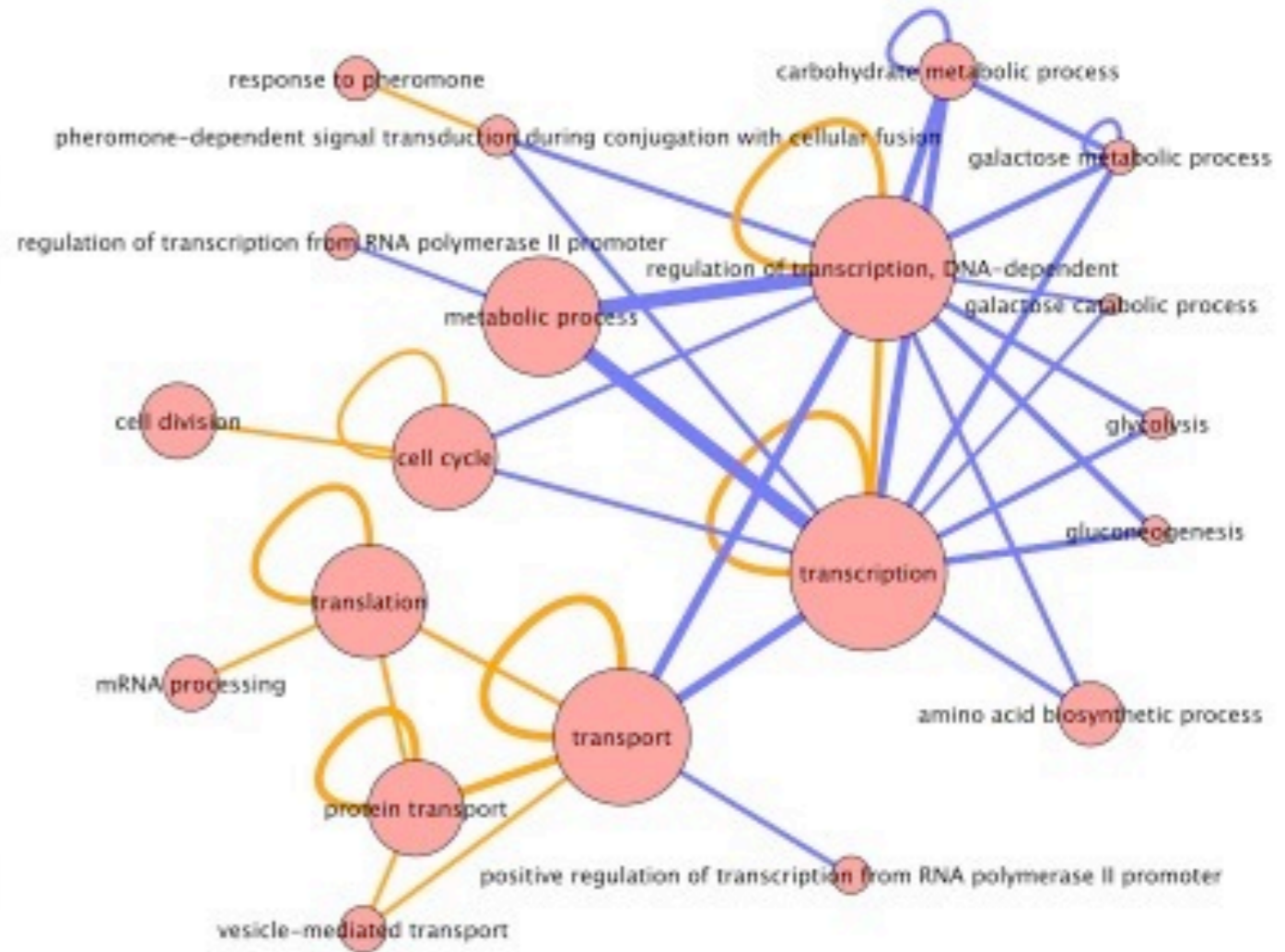
- Do everything the current desktop version of Cytoscape does.
- Run in headless mode to support batch operations.
- Run in daemon mode to support backend web services.
- Take advantage of multithreaded and/or clustered environments.
- **Many new features** (scripting in different languages, 3D rendering, custom graphics, ...).



1A. Modular Layouts and Views

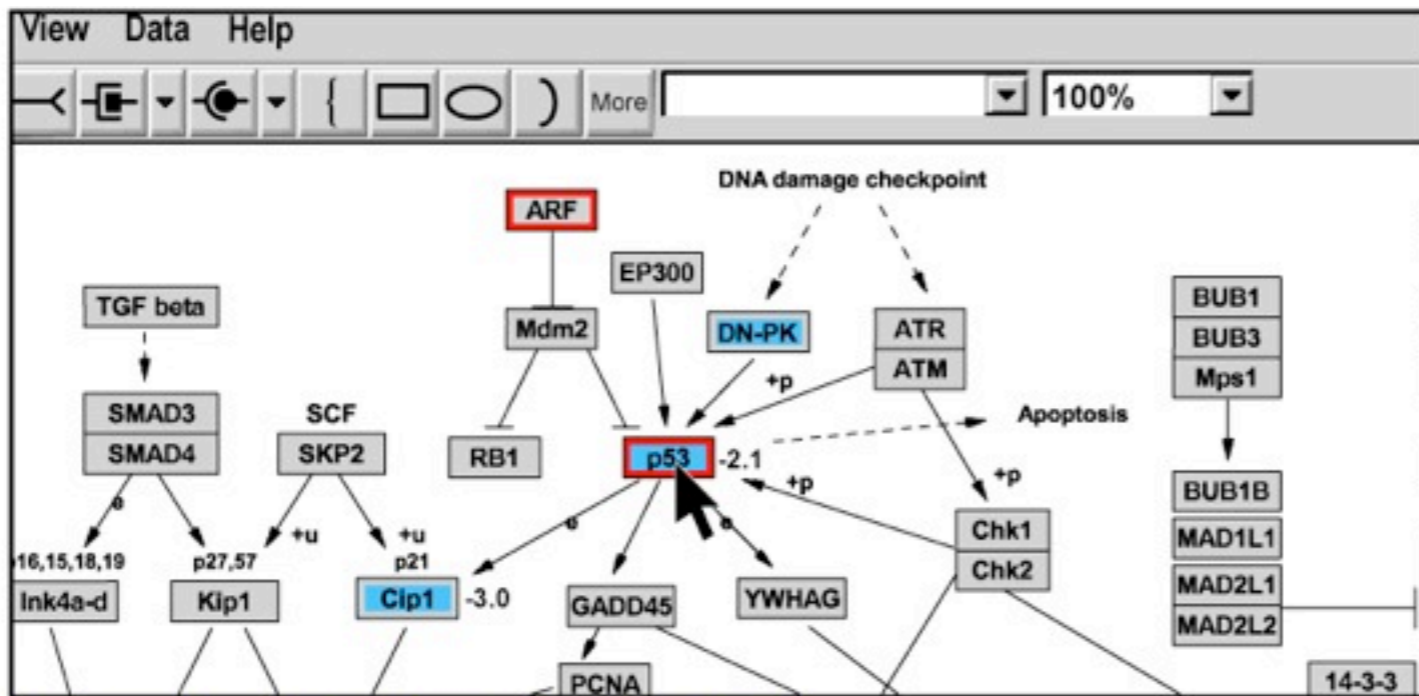


Hierarchical network view

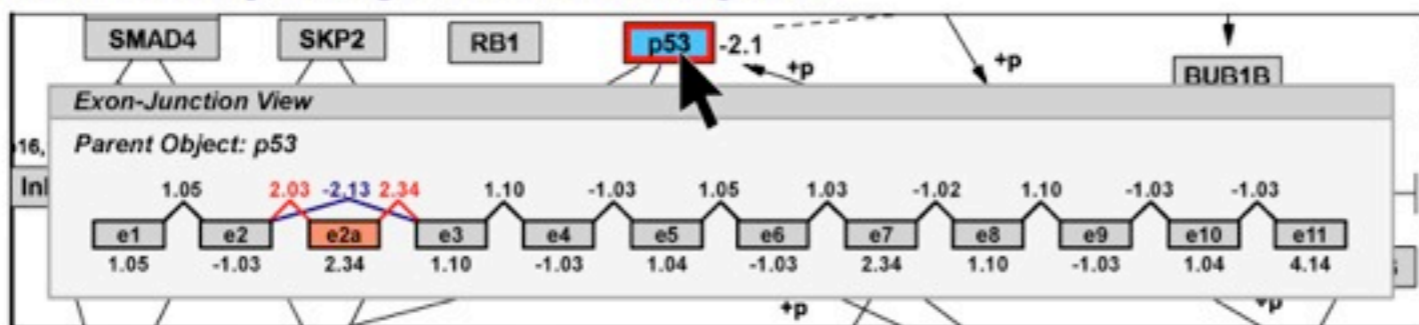


Thematic map based on node attributes

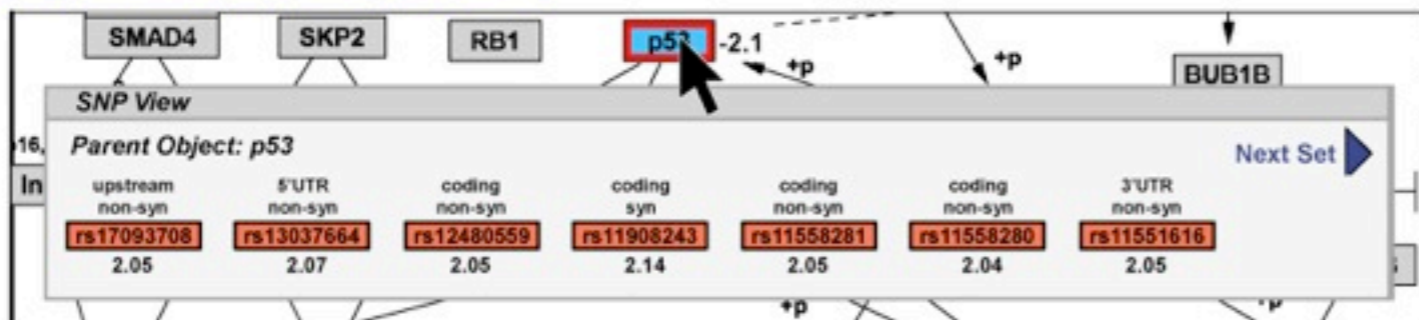
2A. Semantic Zooming: *from genes to exons*



Exon and splice junction analysis



Polymorphism analysis



Pathway ColorSets

Gene/Protein Objects

- Center Box Criterion**
 - up-regulated expression
 - down-regulated expression
 - not changed
 - not present
- Rim Criterion**
 - Differential splicing
 - No differential splicing
 - Not applicable

Child Objects

- Center Box Criterion**
 - up-regulated expression
 - down-regulated expression
 - not changed
 - not present
- Rim Criterion**
 - Rare variant SNPs present
 - No rare variants detected
 - Not applicable

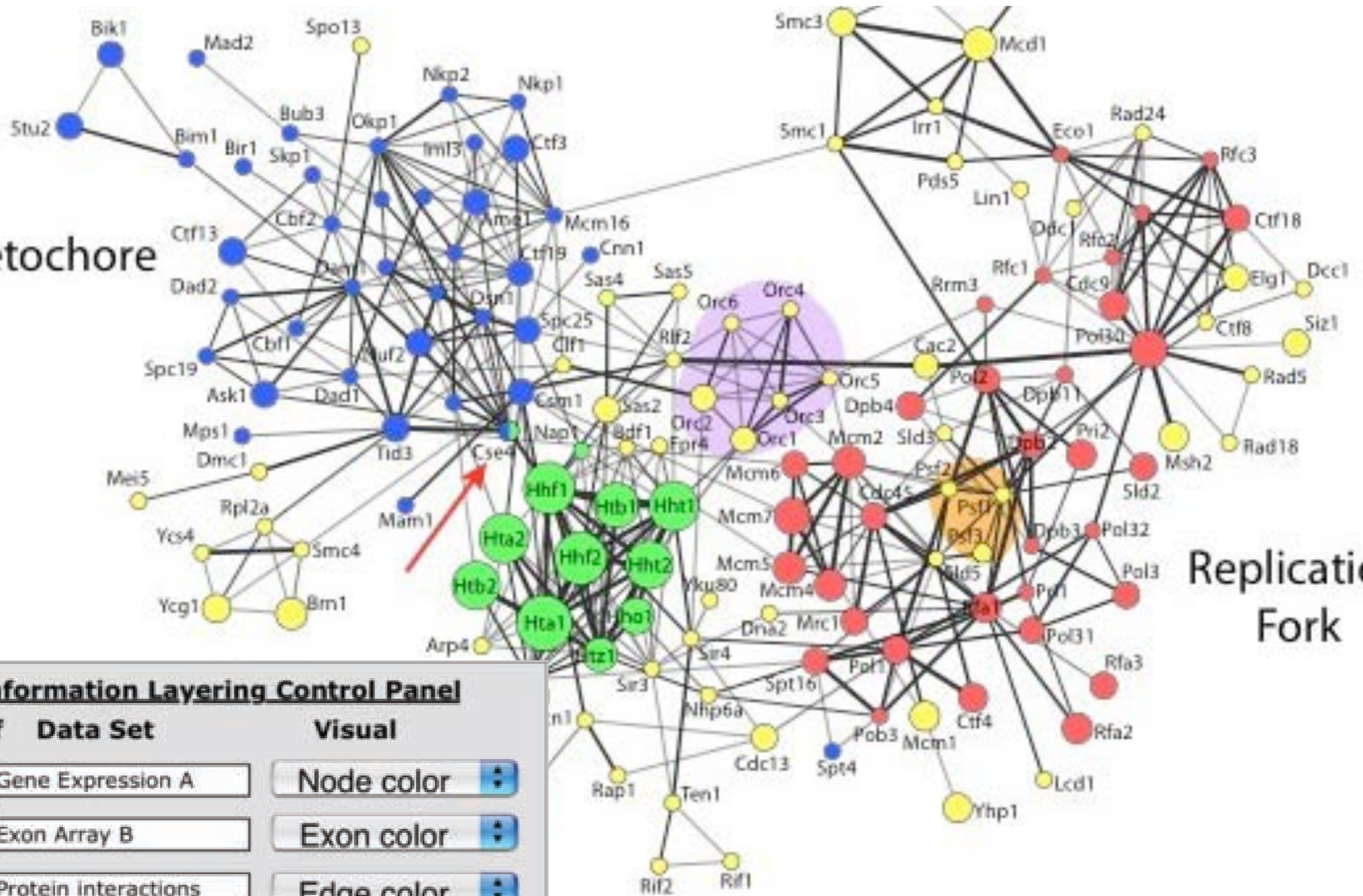
5 (v w p t t v z a

Kinetochores

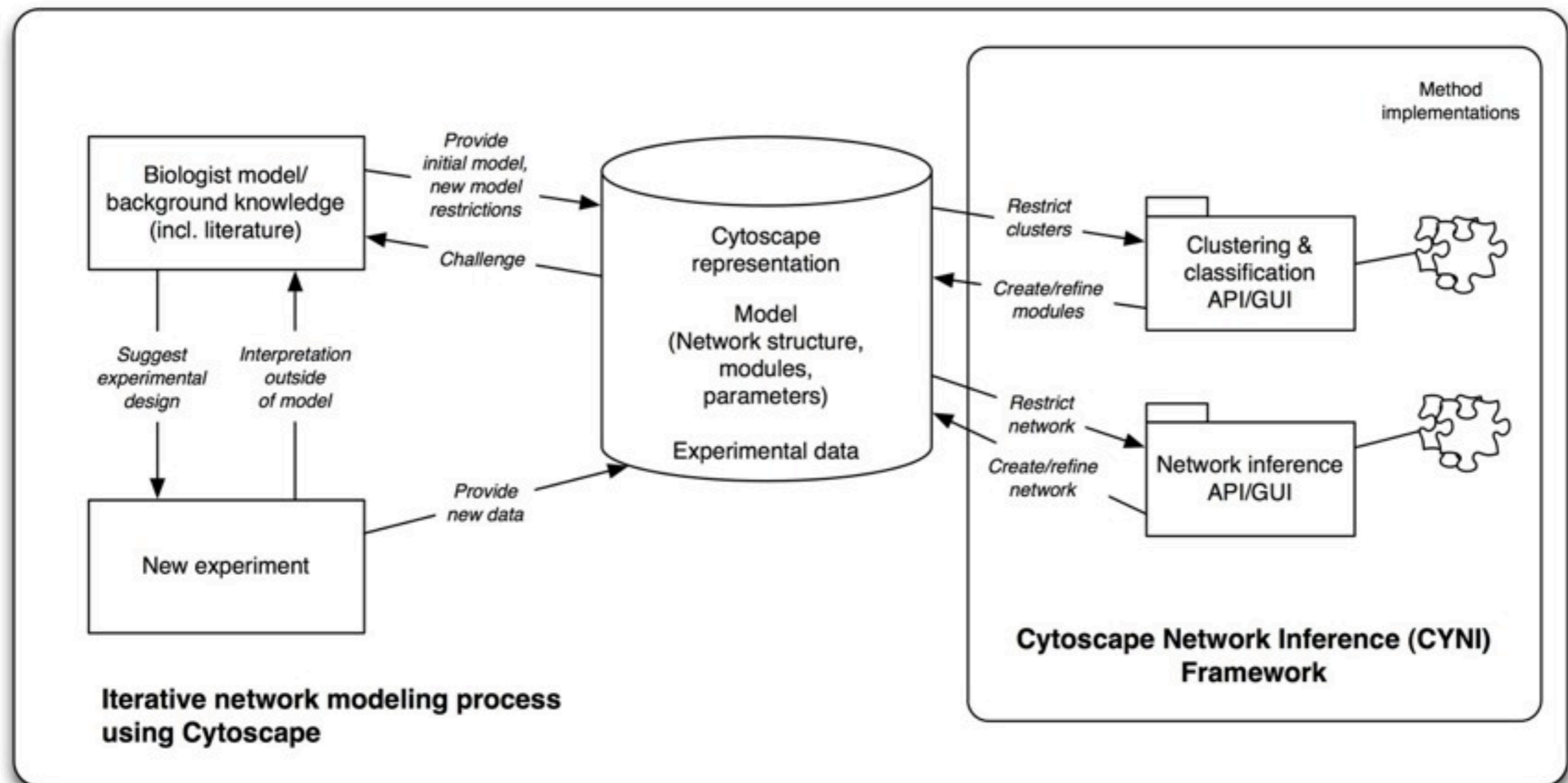
Replication Fork

Information Layering Control Panel

On/Off	Data Set	Visual
<input checked="" type="checkbox"/>	Gene Expression A	Node color
<input type="checkbox"/>	Exon Array B	Exon color
<input checked="" type="checkbox"/>	Protein interactions	Edge color
<input type="checkbox"/>	Interaction confidence	Edge width
<input type="checkbox"/>	Load data set...	Choose...



Cytoscape Network Inference (CYNI)



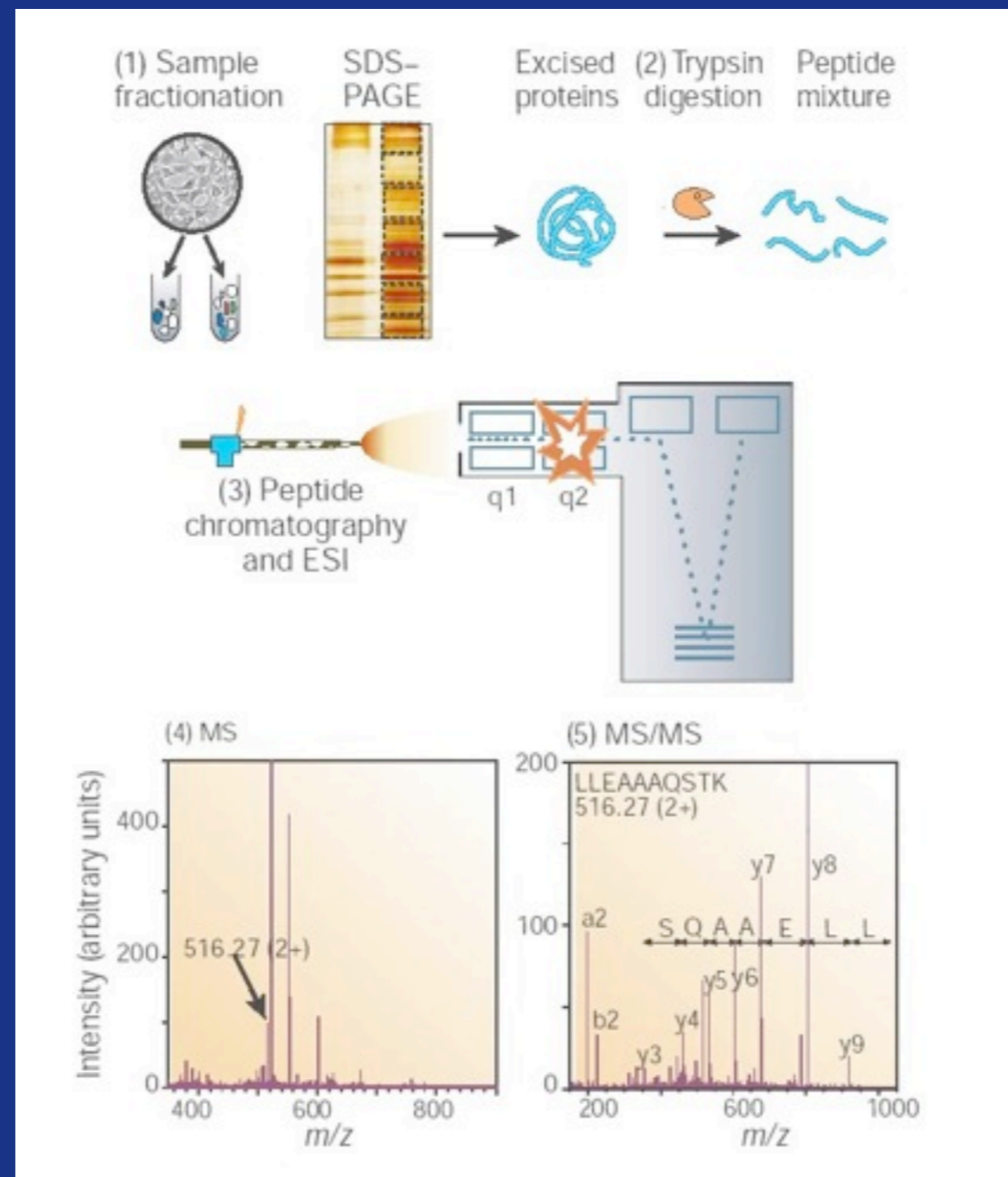
Questions we'd like biologists to ask

- What is the best network explaining the data?
- Which *parts* of this network are well-supported?
- Is there a well-supported subnetwork?
- Which experiment could be done to better distinguish different possible models?
- Given a model, which parts are consistent/inconsistent with the data?
- Which interactions could be added (removed) to make the data compatible with the model?



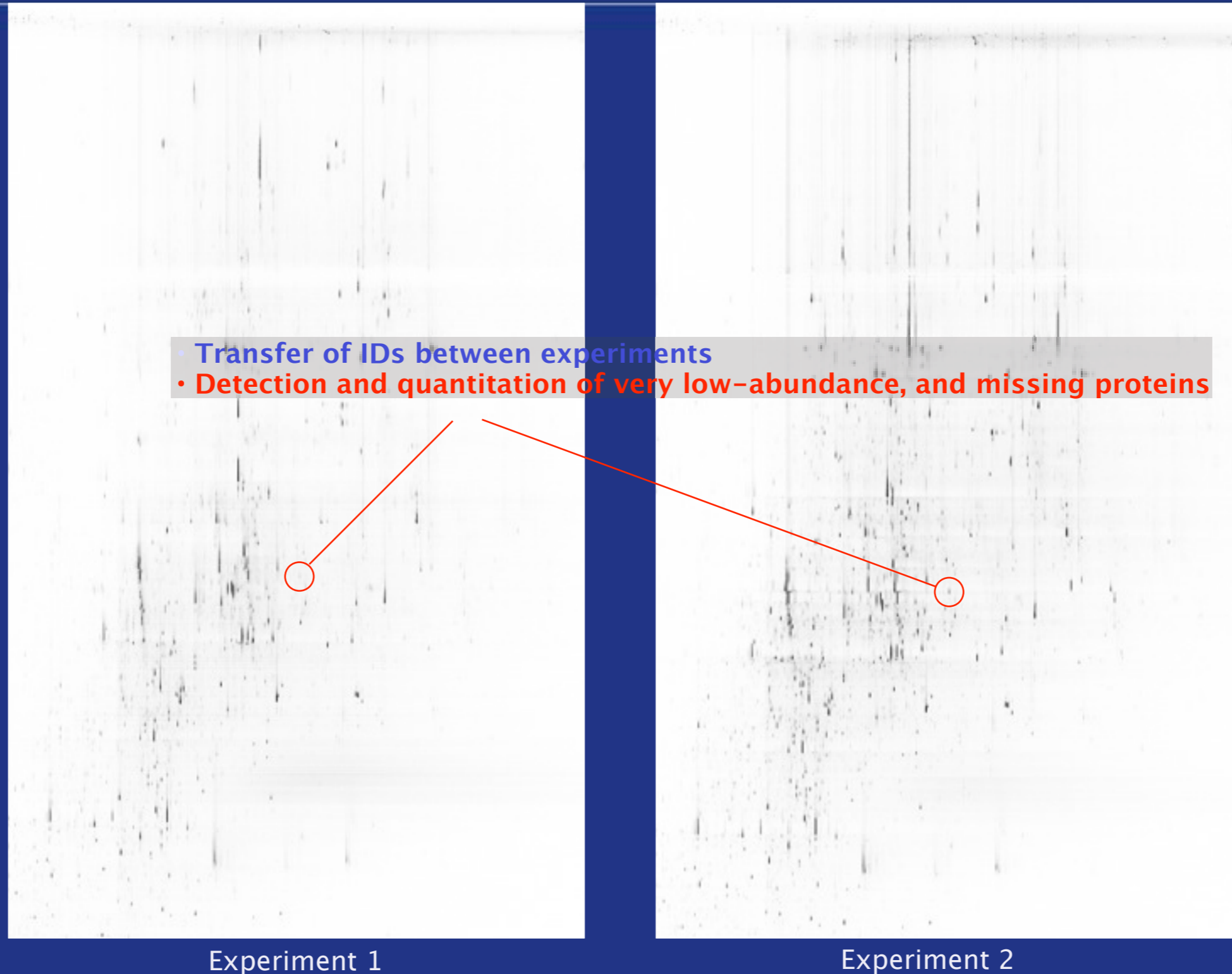
Visualization example in proteomic data analysis

LC-MS/MS is throughput-limited

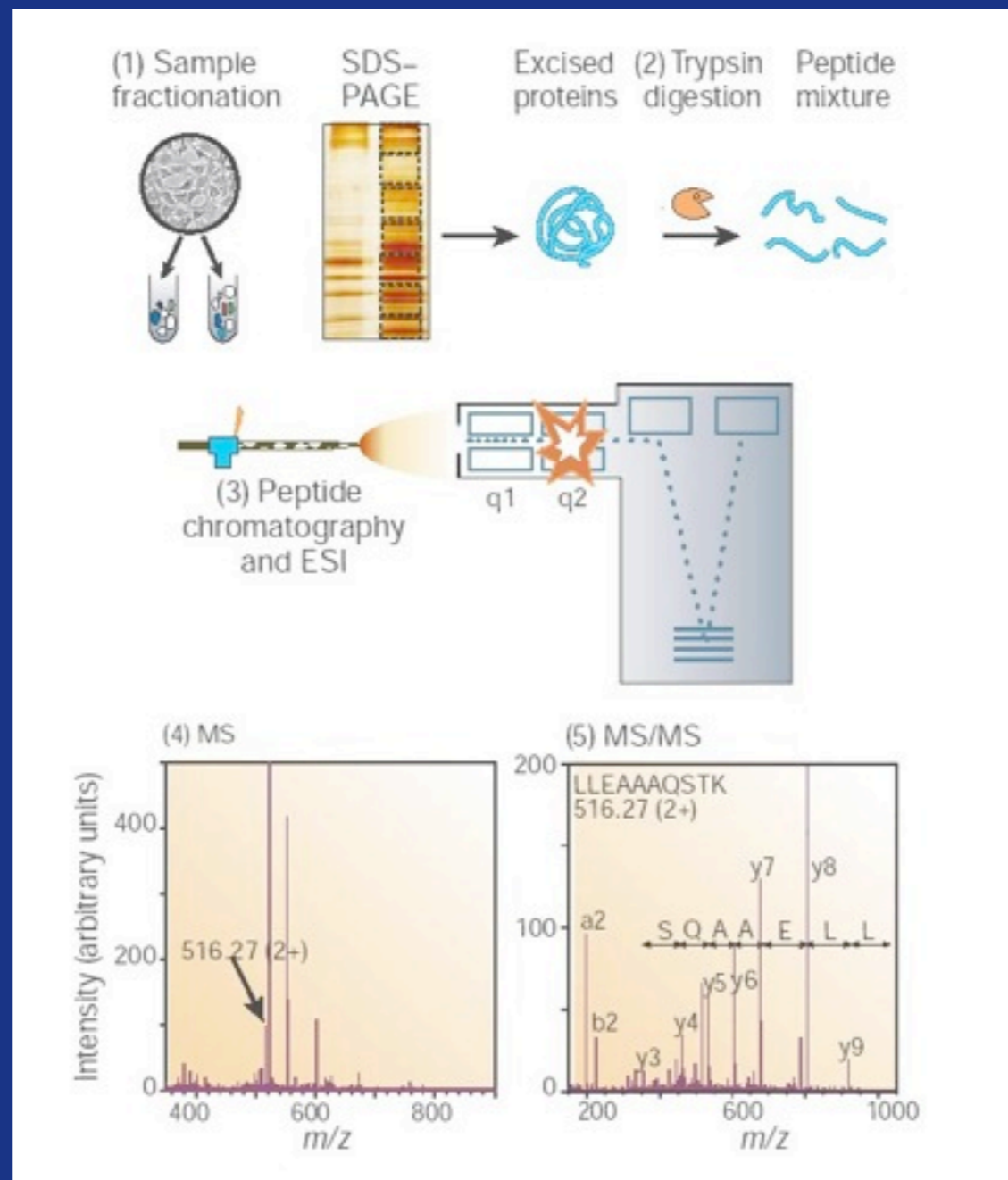


Aebersold and Mann (2003)

Label-free proteomic analysis

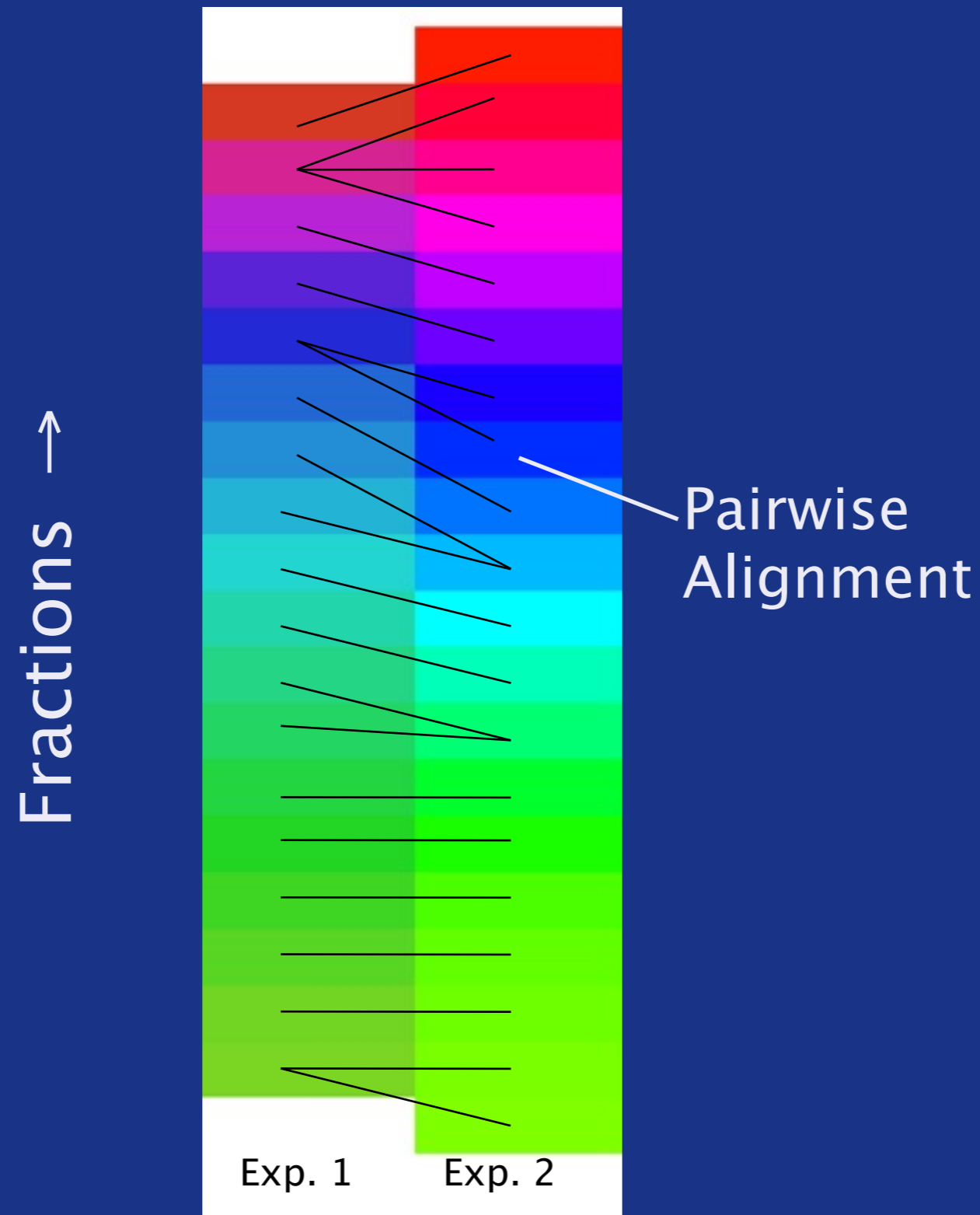


LC-MS reproducibility



From Aebersold and Mann (2003)

Implementing the comparative approach: Sequence alignment



Sequence alignment

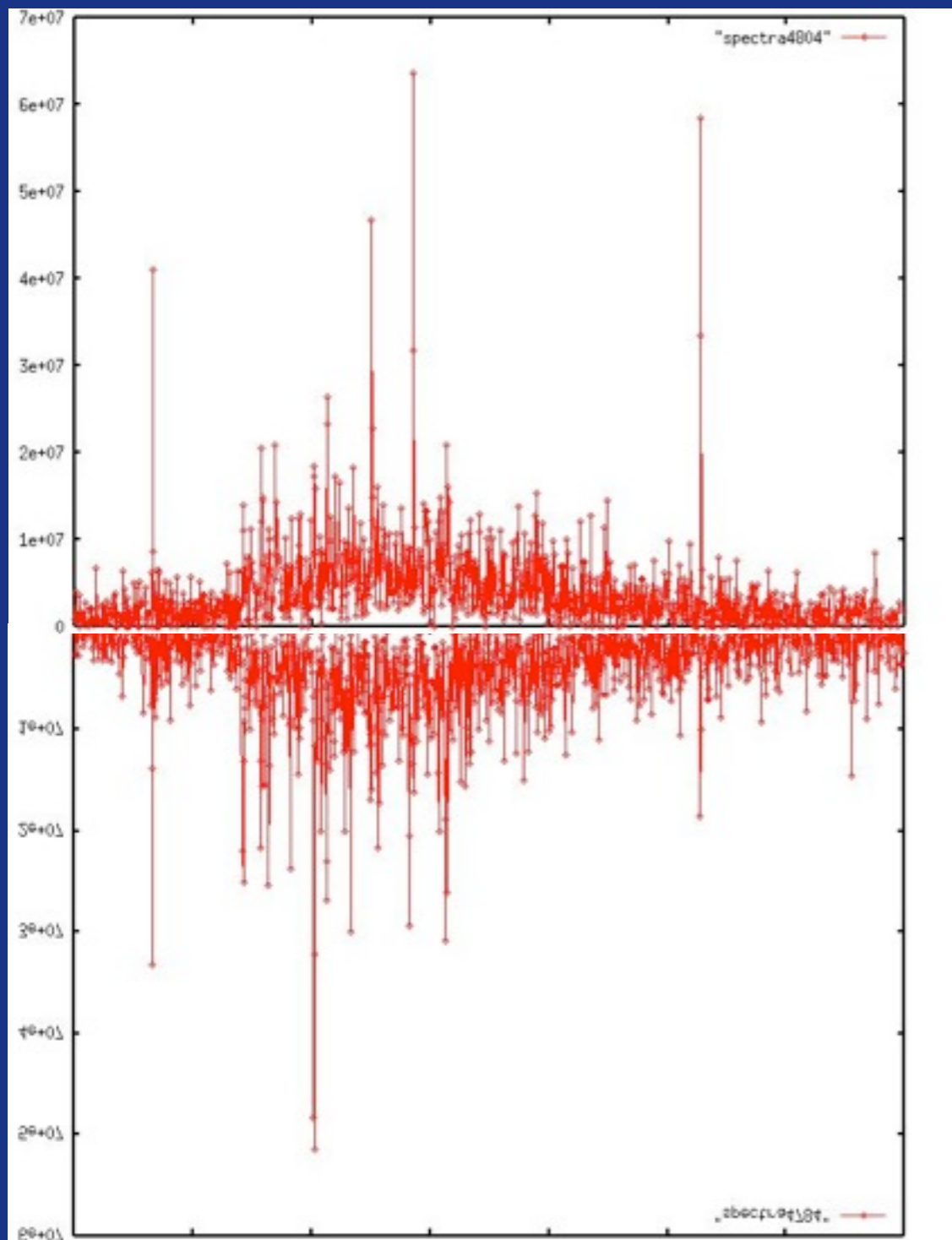
...LPGNARKMDKSTVLQKTIDE...
...LPGNARKMDKSTVLQ-EIDE...

- Scoring function BLOSUM62

BLOSUM62 (E,Z)= 5.0

BLOSUM62 (E,Z)= 1.0

The “dot product” score function for comparing two spectra

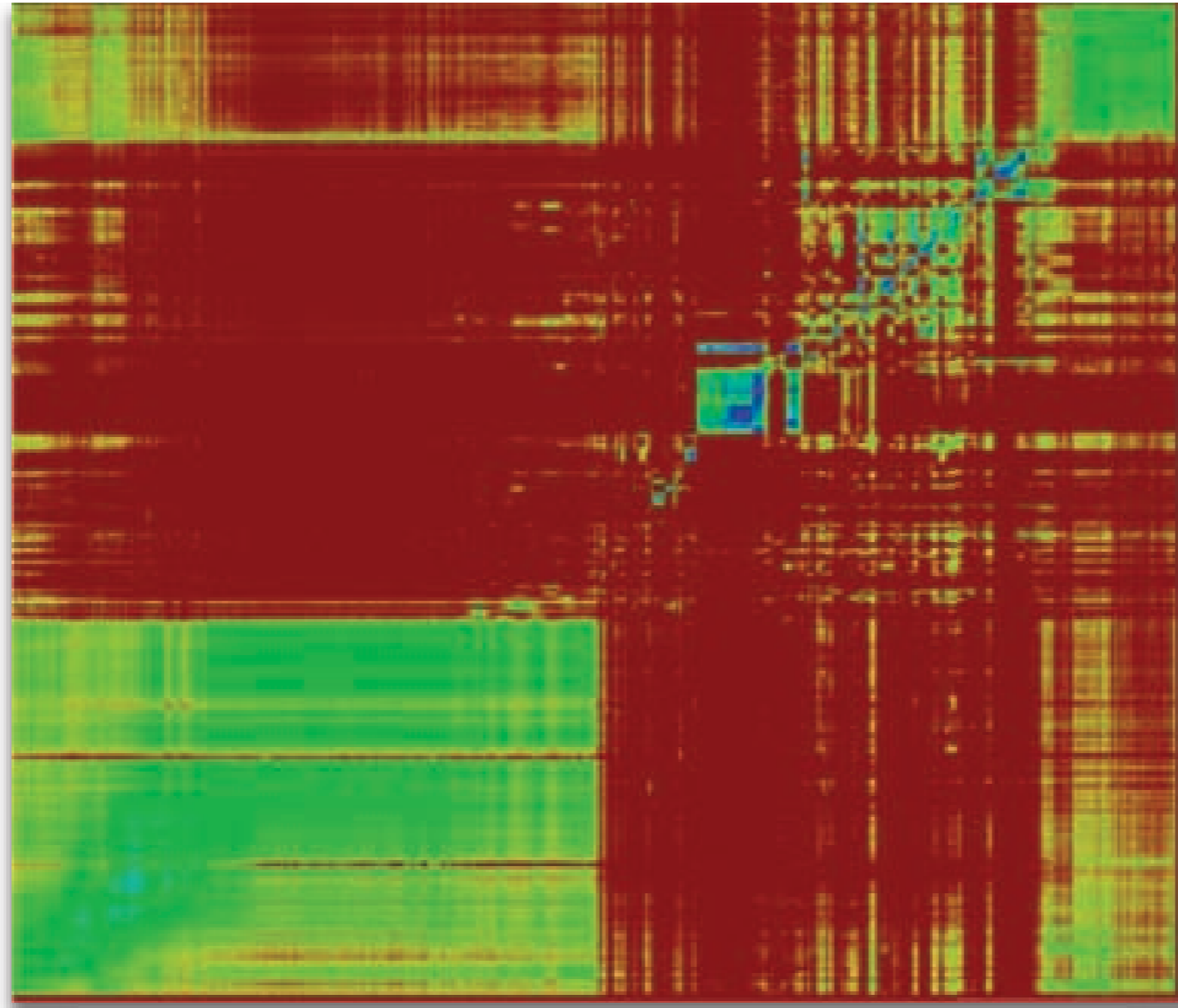


Idea

(Stein & Scott, 1994)

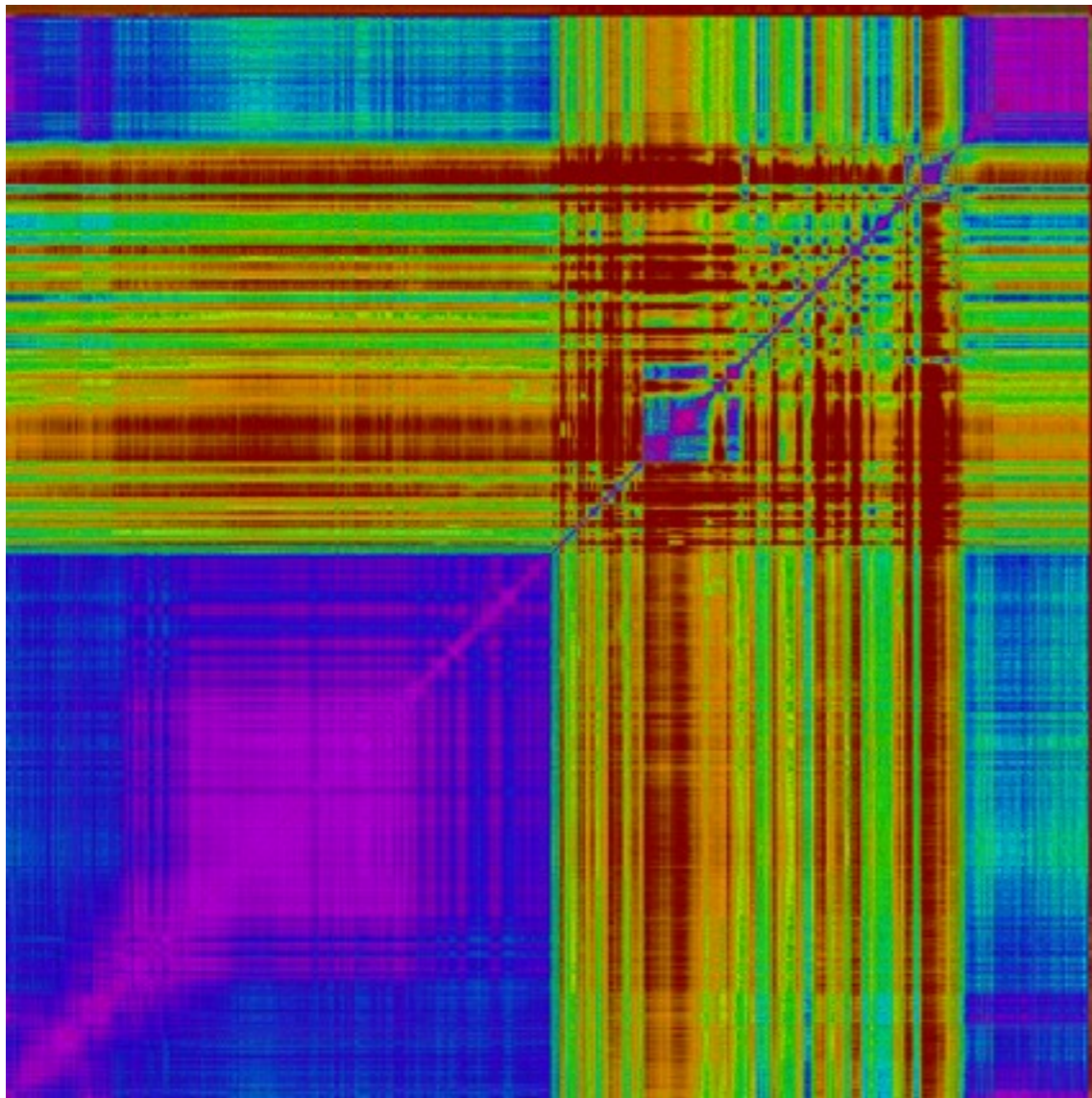
1. Reward all “close enough” peak pairs by amplitude product
2. Add over all such peak pairs
3. Normalize by total peak sum

wt n f A t k

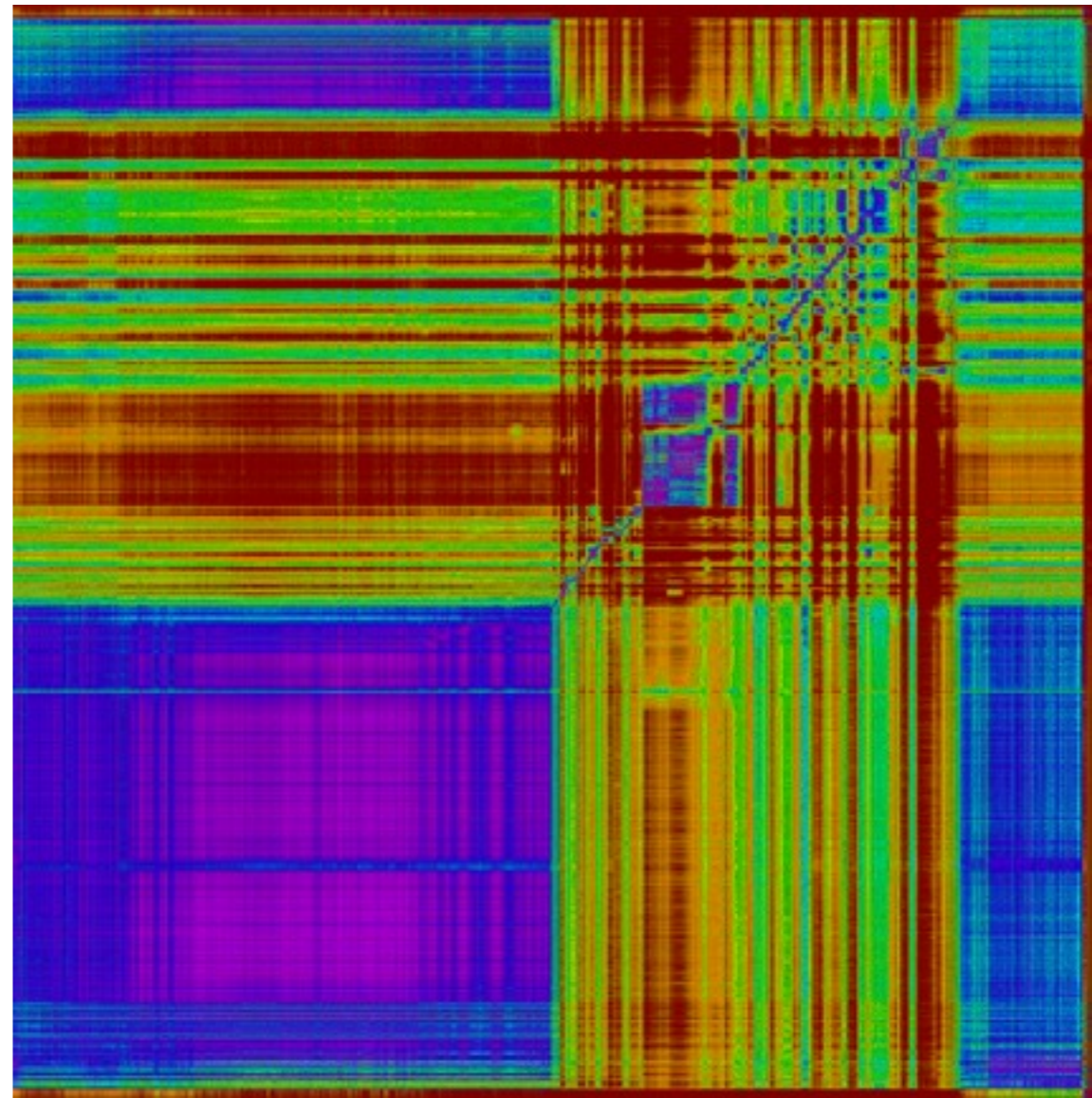


(Data from SCX fractions 23A and 24A, yeast cell cycle data, t=0, Mark Flory)

Problem: Noise



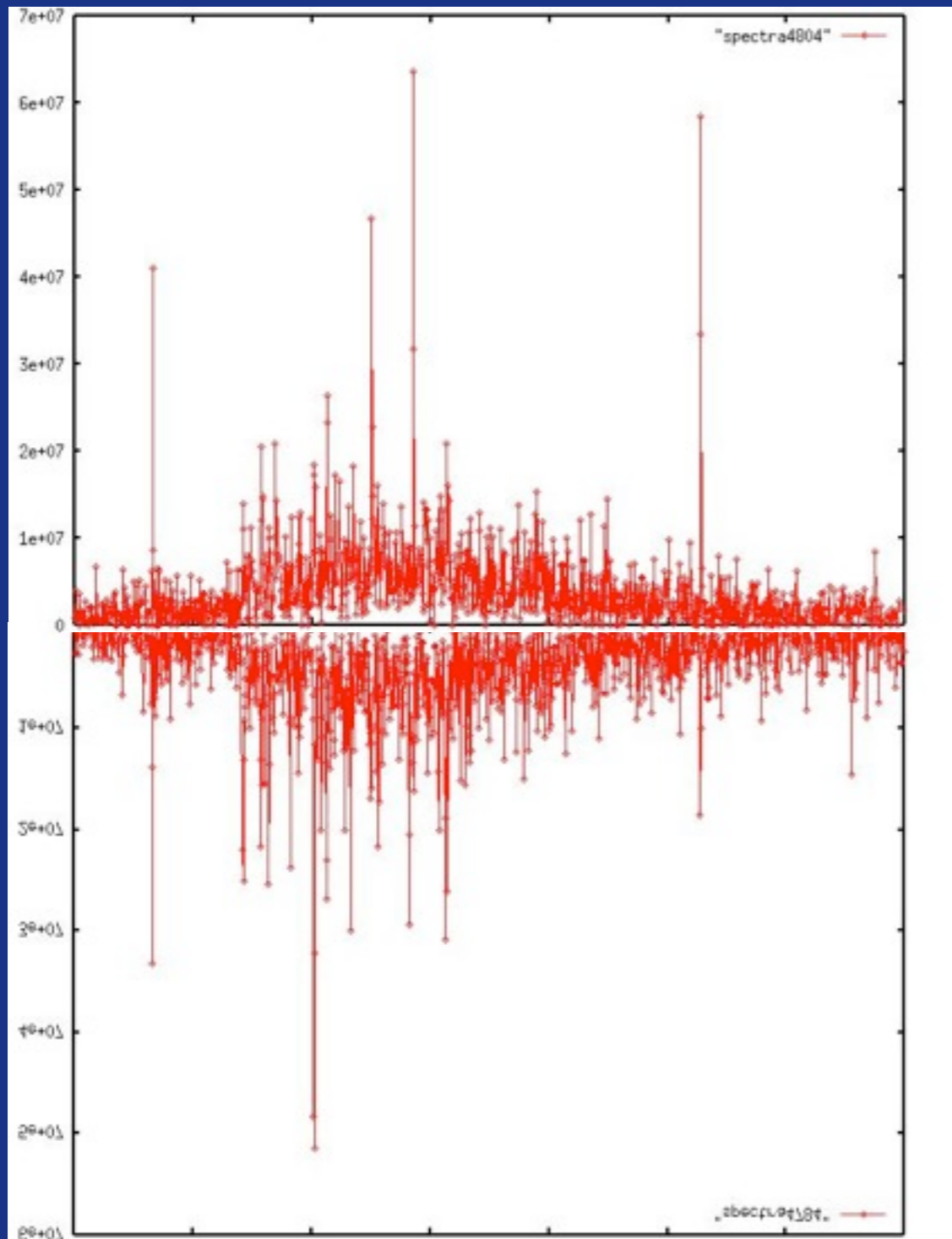
23A vs. 23A



23A vs. 23B

(Data from SCX fractions 23A and 23B, yeast cell cycle data, $t=0$, Mark Flory)

Modified score function



Modifications

- “Background subtraction”: Locally subtract spectrum “noise level” before comparison
- Subtract match score between randomized spectra before normalization, so expected value becomes 0

$$s(i, j) = \frac{M_i \times N_j - E(M_i \times N_j)}{\sqrt{(M_i \times M_i)(N_j \times N_j)}}$$

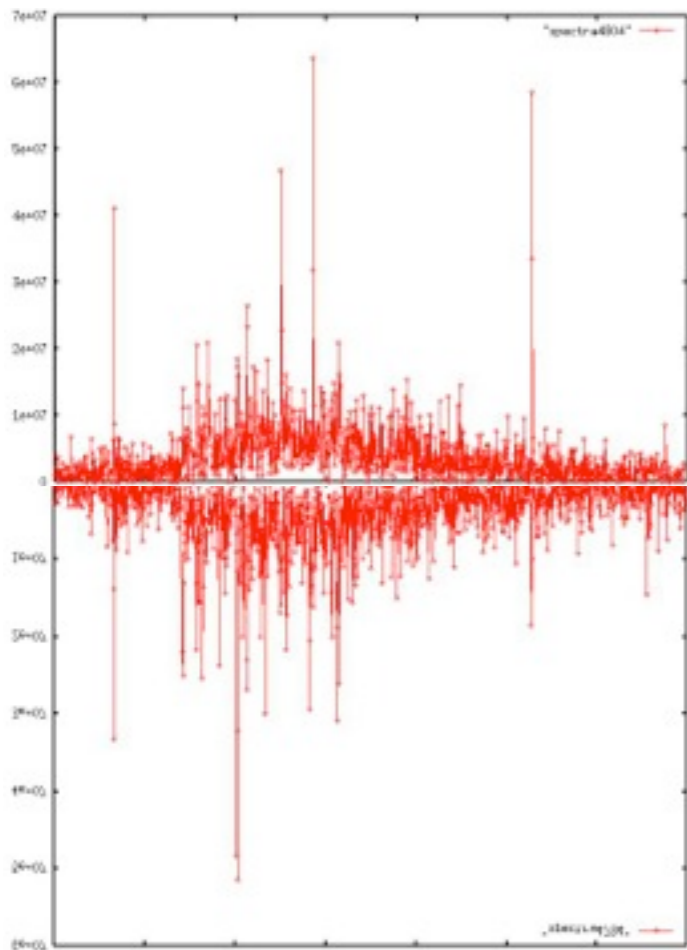
Computing the expected score

$$E(M_i \times N_j) = \sum_{\text{Peaks } s,t} p(s, t \text{ 'close enough'}) \cdot \text{int}(s) \cdot \text{int}(t)$$

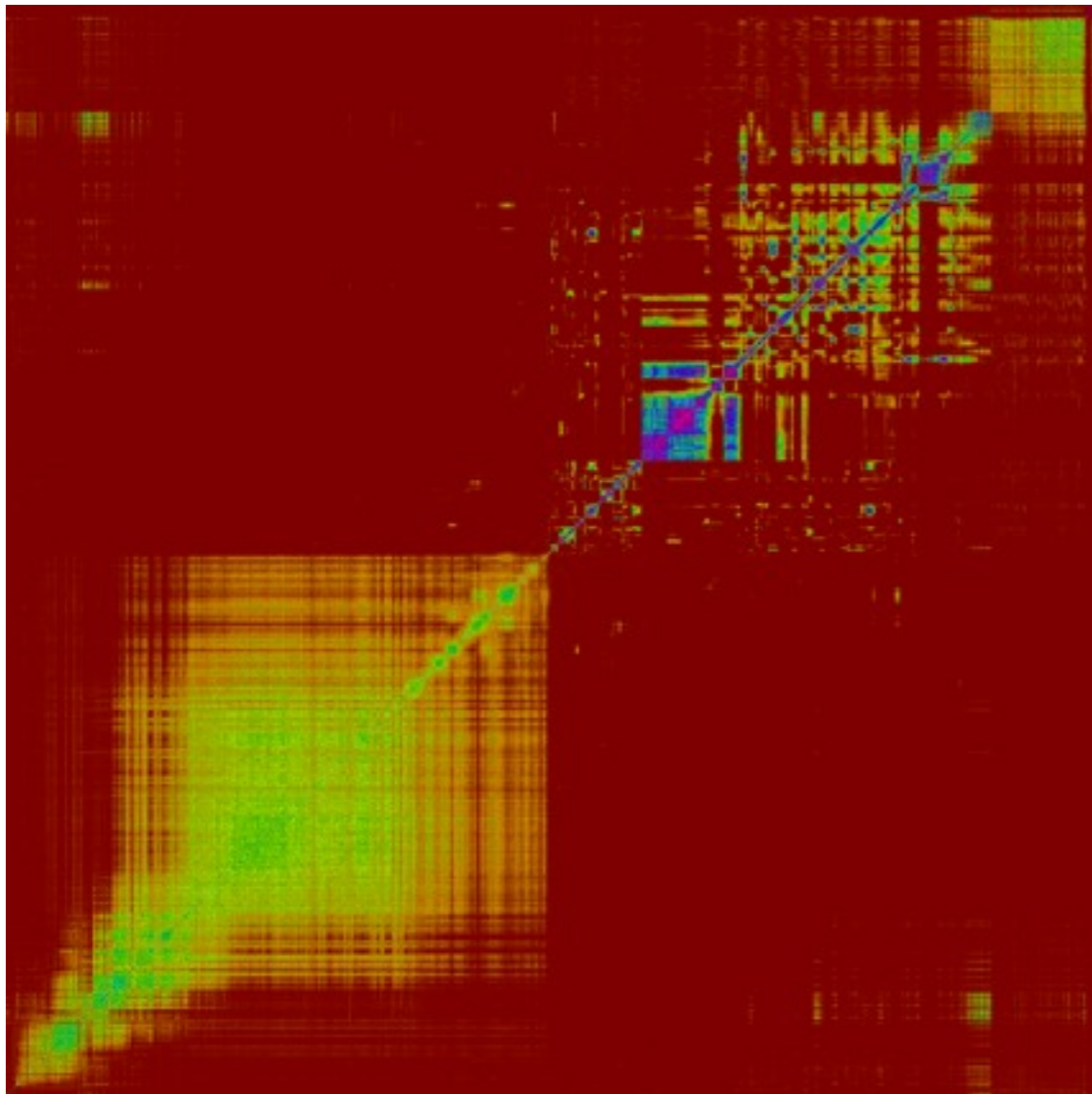
$$= \sum_{\text{Peaks } s,t} c \cdot \text{int}(s) \cdot \text{int}(t)$$

$$= c \cdot \left(\sum_s \text{int}(s) \right) \cdot \left(\sum_t \text{int}(t) \right)$$

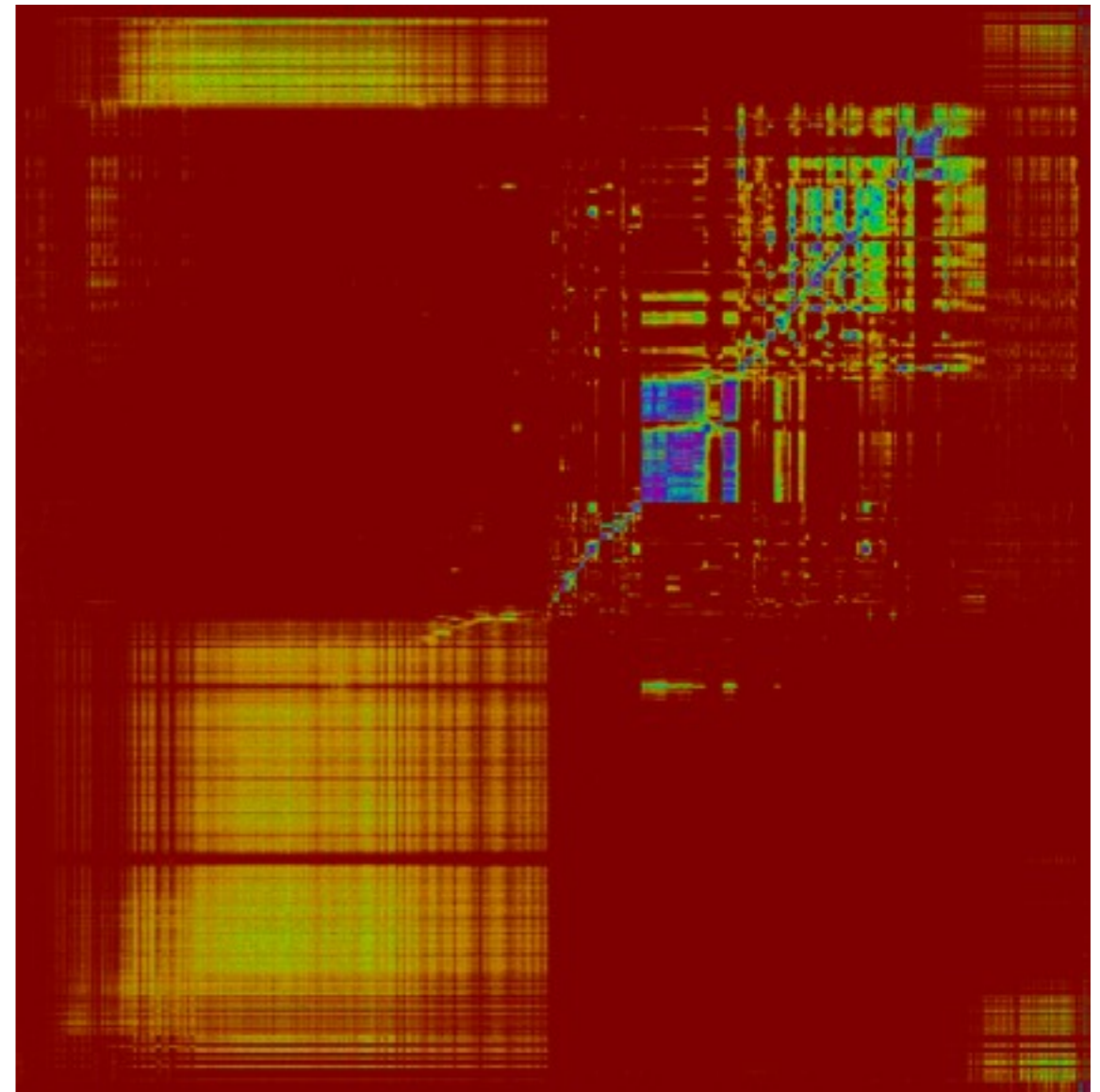
$$= c$$



Modified edit matrices



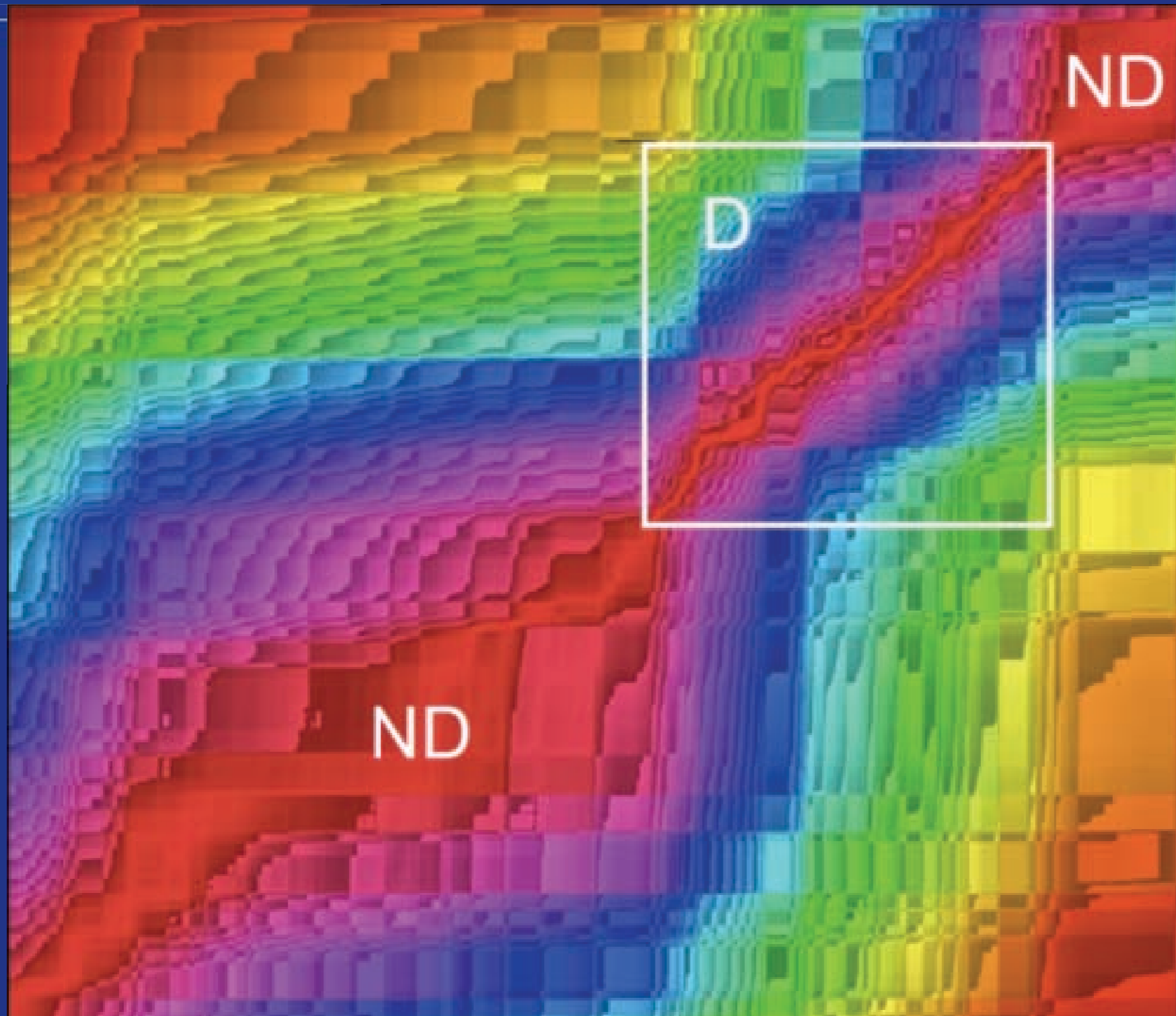
23A vs. 23A



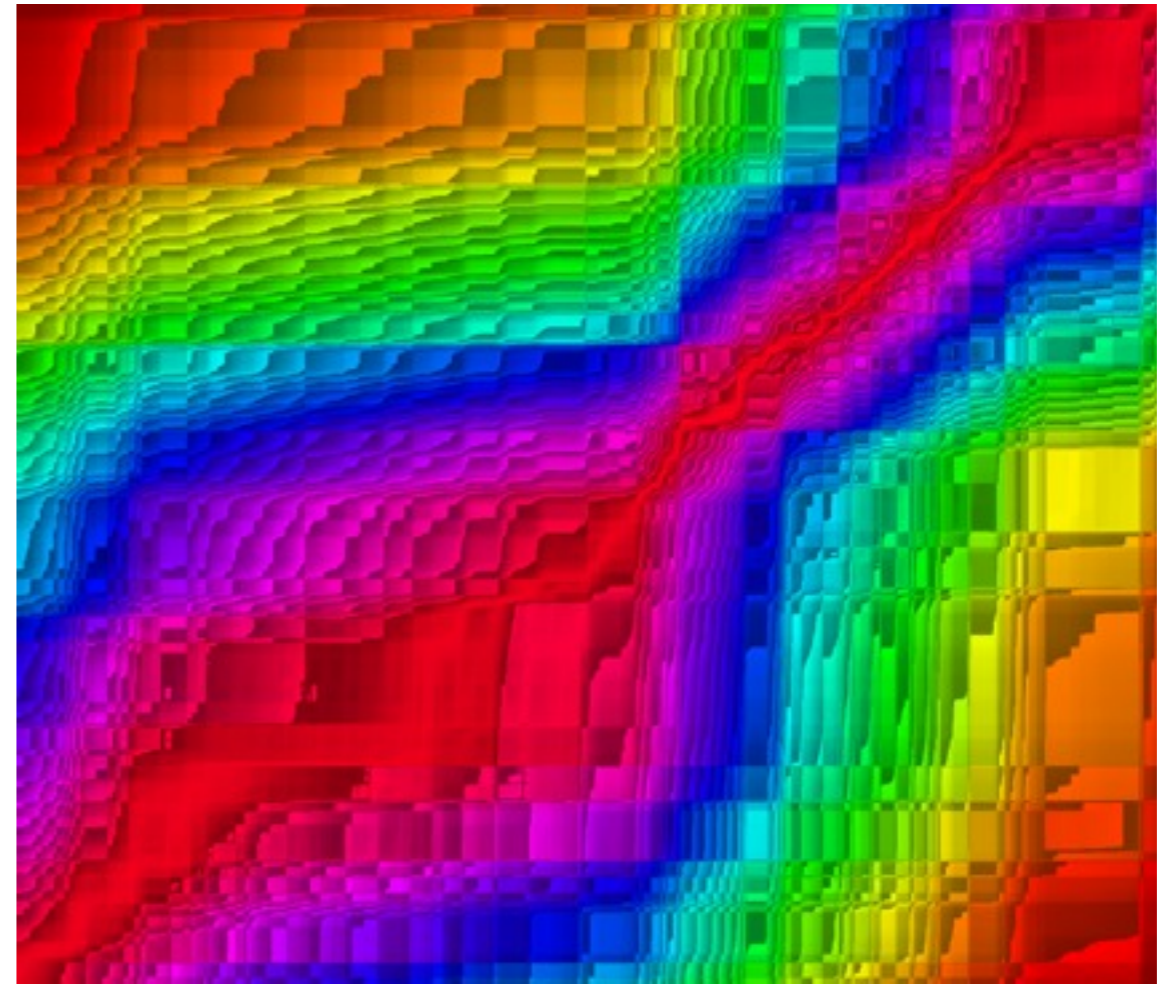
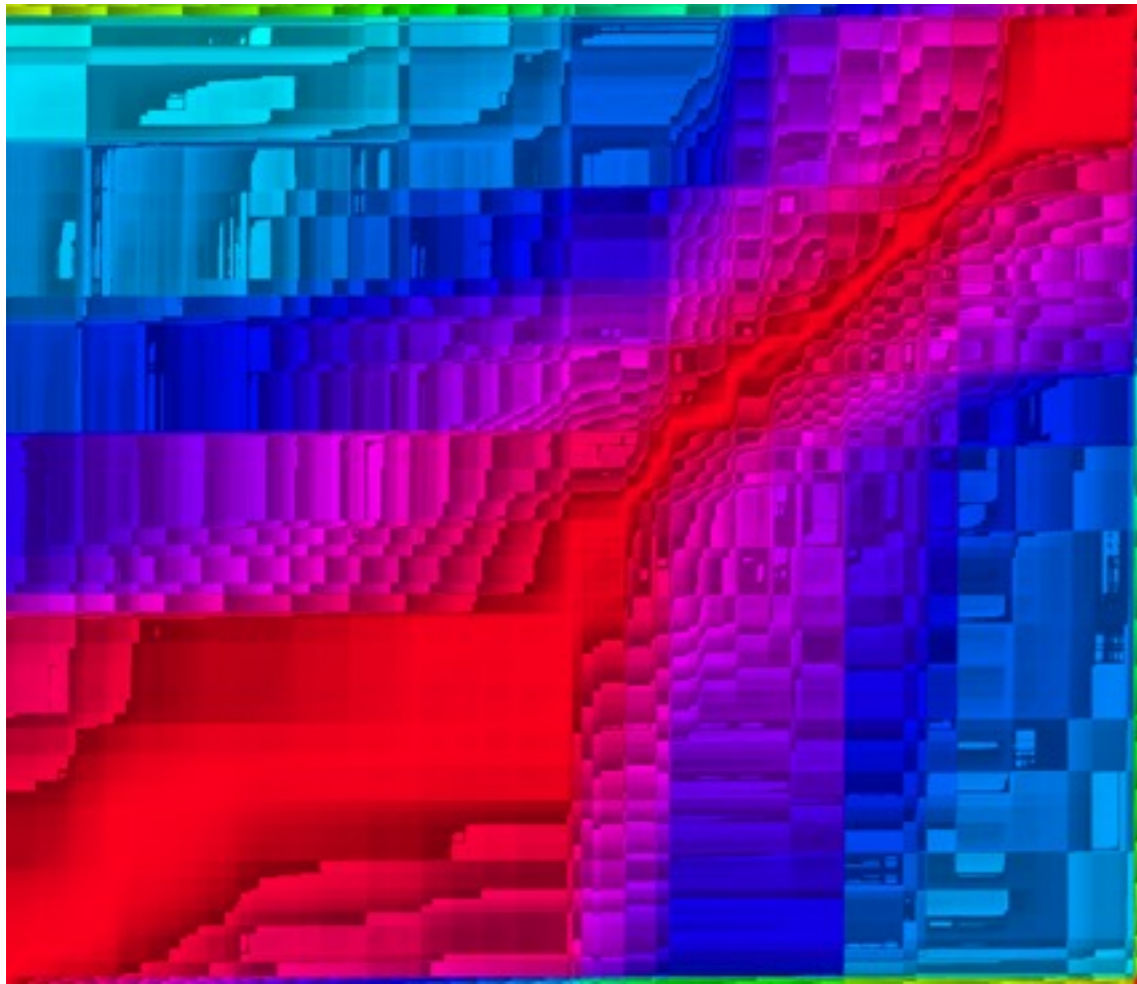
23A vs. 23B

(Data from SCX fractions 23A and 23B, yeast cell cycle data, $t=0$, Mark Flory)

Regions of optimality and suboptimality

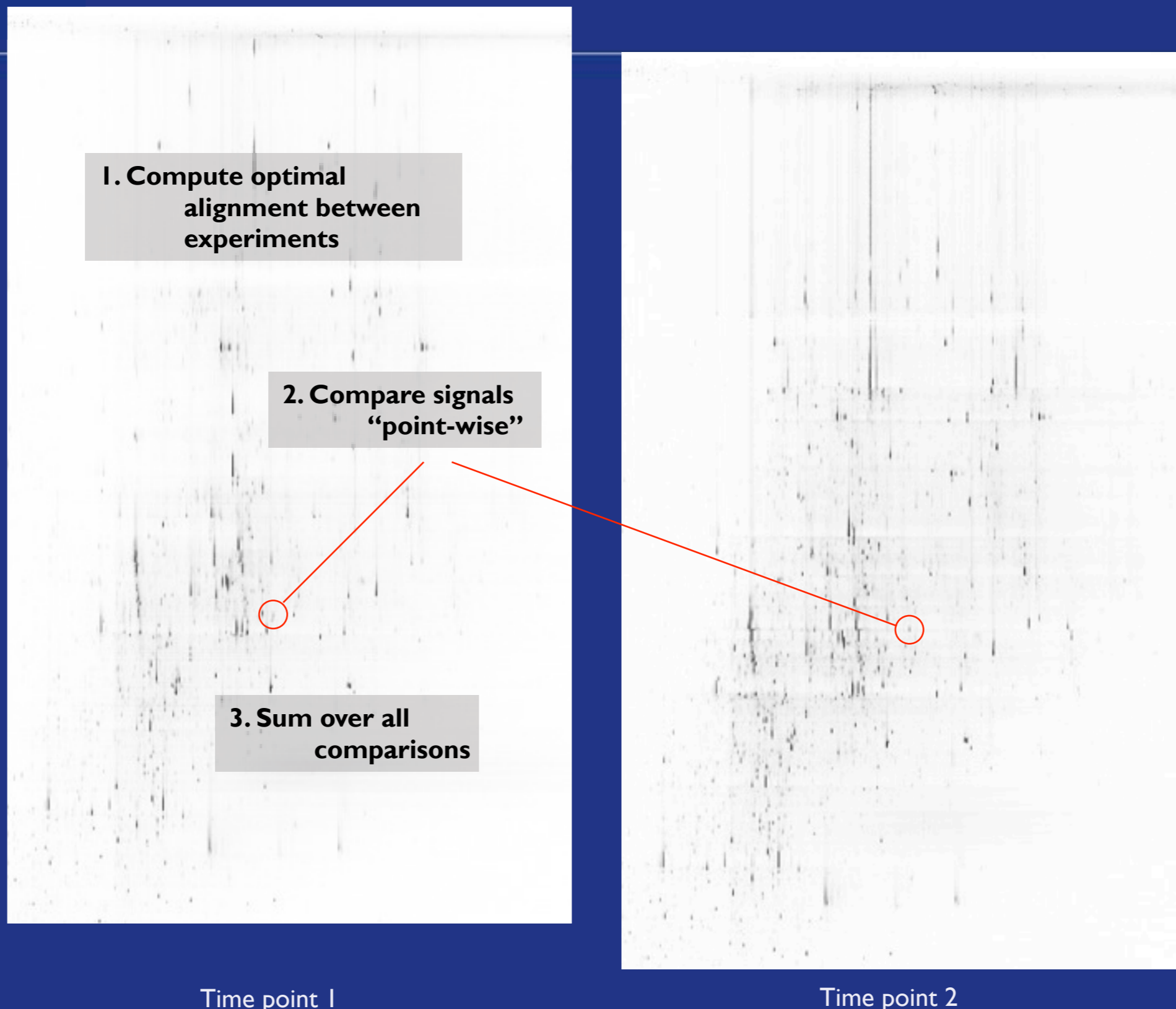


Improvement in alignment

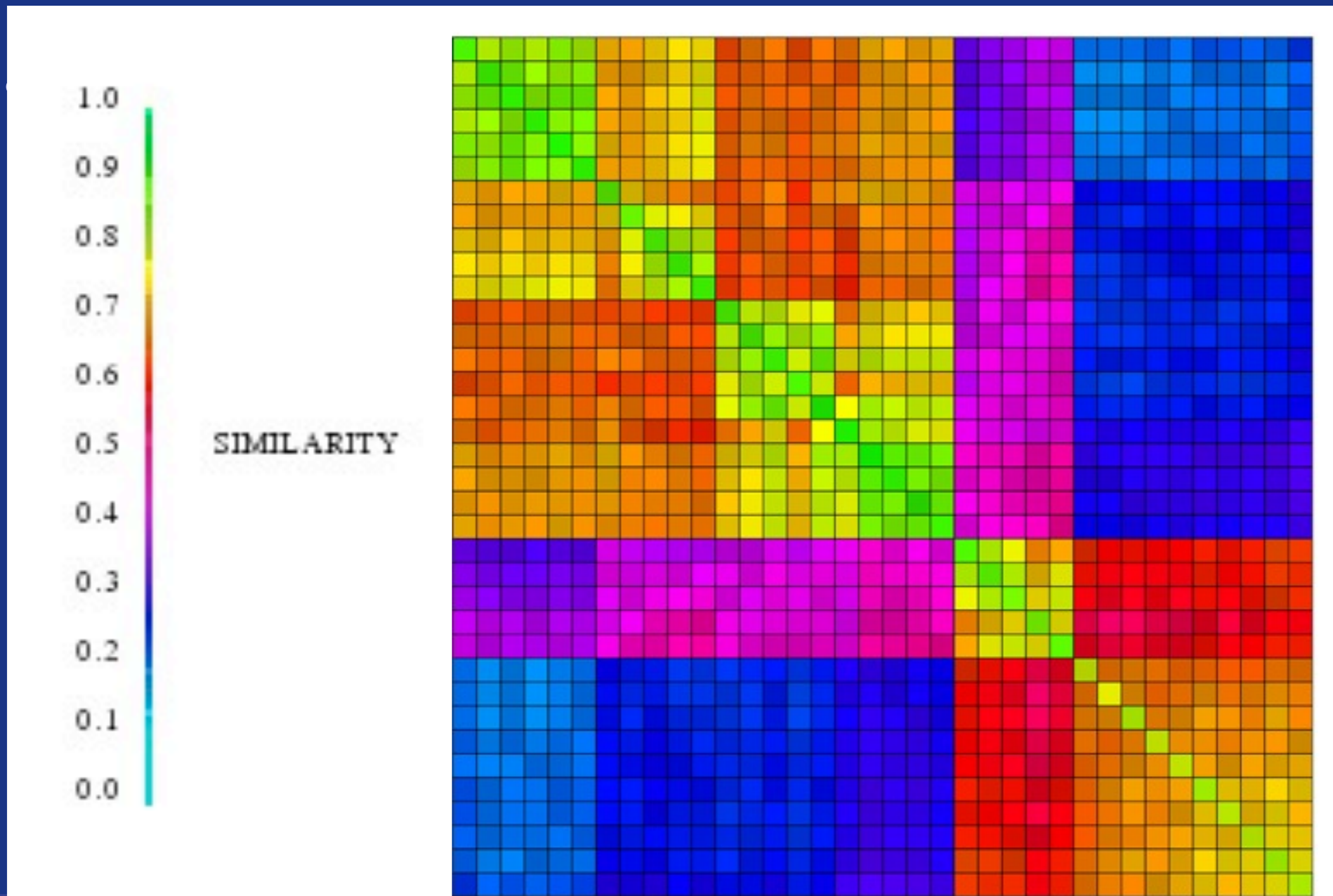


(Alignments of SCX fractions 23A and 24A, yeast cell cycle data, $t=0$, Mark Flory)

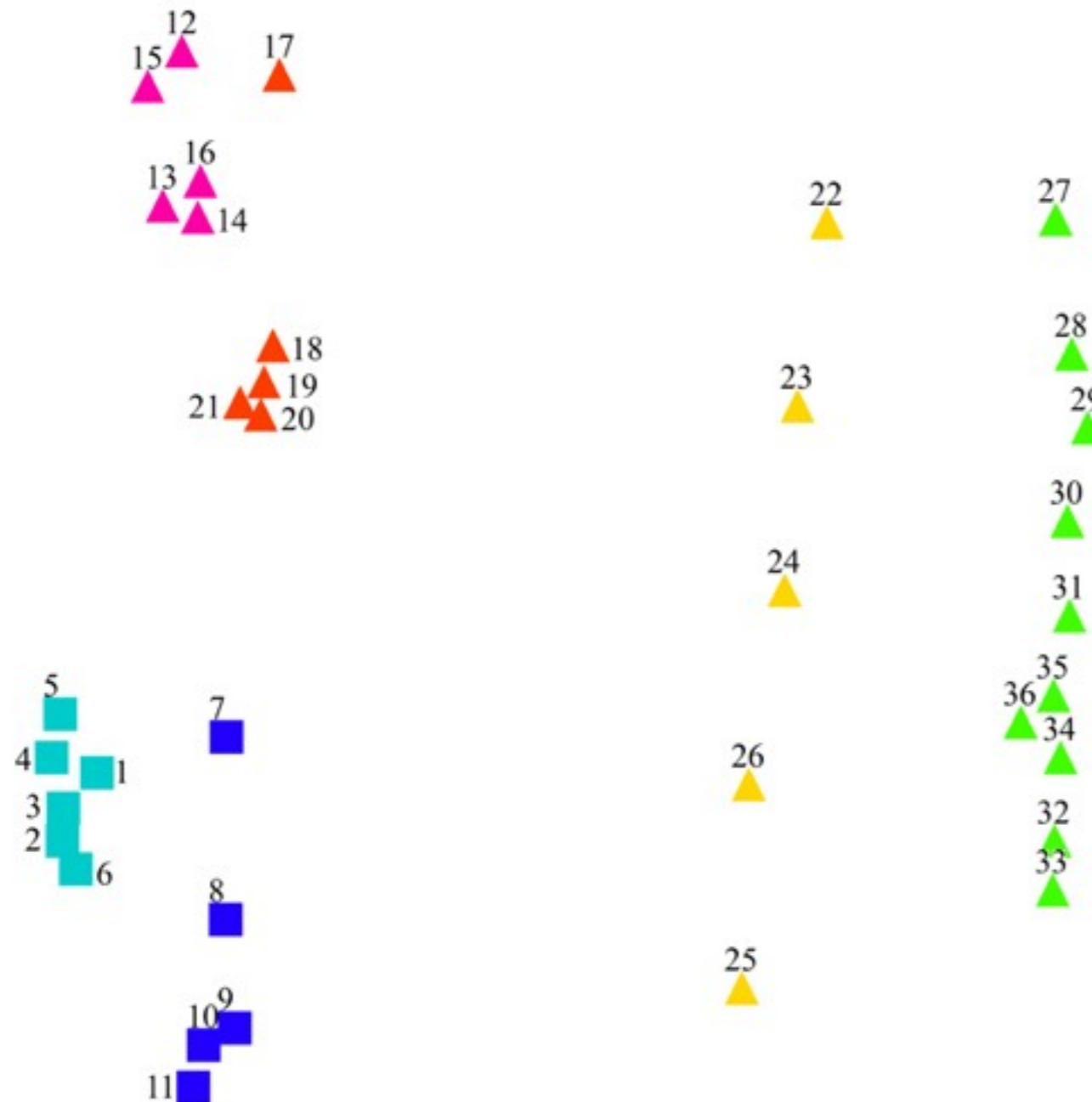
We are quantifying experimental similarity



A distance matrix between experiments



A 2D embedding



Data
“Pure” angiotensin II

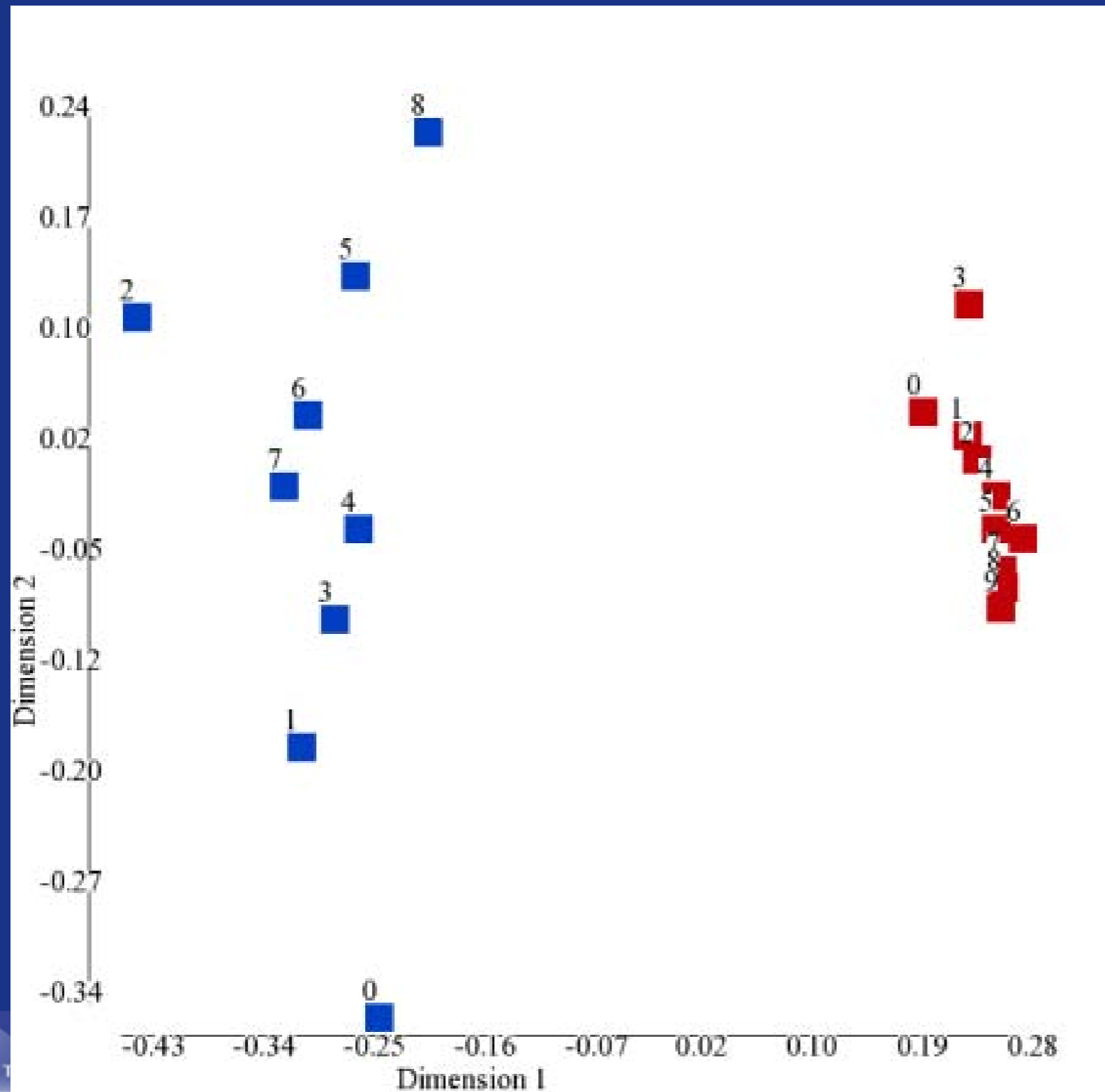
Purpose
QC

Instrument
FT-ICR

Colors
Different days

Shapes
Different LC columns

Cross-platform reproducibility



Data
Human blood serum
Identical samples

Blue/Red
QSTAR/QTOF

Numbers
Run order

Summary

- Systems Biology faces biological complexity
- Models must capture complexity along several axes
- Visualization helps...
 - Comprehend data in an integrative manner
 - Develop experimentally testable hypotheses and models
 - Comprehend complex relationships

Challenges around visualization in network biology

- Dense networks, “scrollable”
- Visualization capturing dynamic behavior
- Visualization of uncertainty (in the network)
- Standardized access to different data sources
- Many tools are not interactive
- More effective
- Development and maintenance of *tools* in an environment that rewards *publications*
- [...]

Acknowledgements

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Freddy Cliquet (IP)

*Thanks for
your attention*

<http://systemsbiology.fr>
<http://cytoscape.org>

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