Biology is Destiny:
Of Graphs and Genes

Tamara Munzner
Department of Computer Science
University of British Columbia

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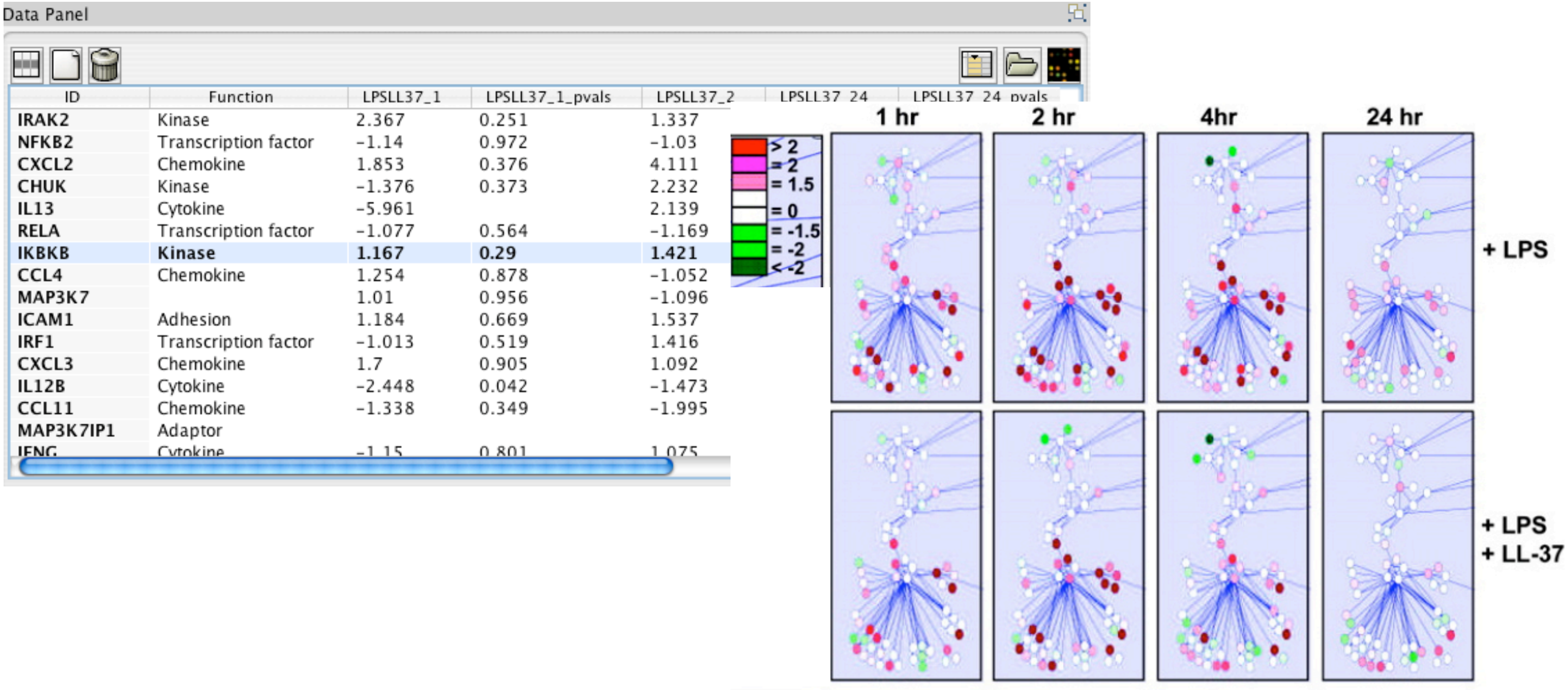
http://www.cs.ubc.ca/~tmm/talks.html#amw09

Why do visualization?

- pictures help us think
  - substitute perception for cognition
  - external memory: free up limited cognitive/memory resources for higher-level problems



Data Panel

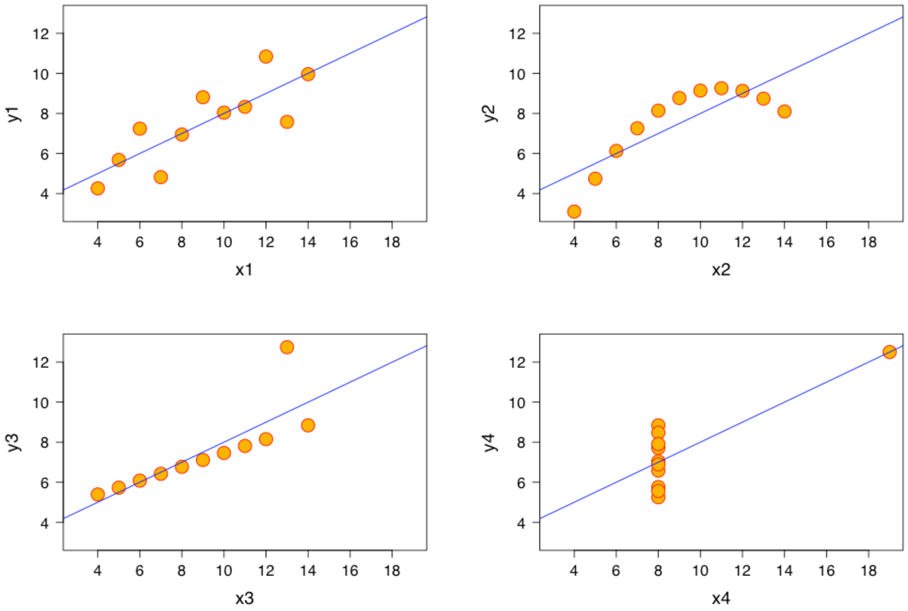
ID	Function	LPSLL37_1	LPSLL37_1_pvals	LPSLL37_2	LPSLL37_24	LPSLL37_24_pvals
IRAK2	Kinase	2.367	0.251	1.337		
NFKB2	Transcription factor	-1.14	0.972	-1.03		
CXCL2	Chemokine	1.853	0.376	4.111		
CHUK	Kinase	-1.376	0.373	2.232		
IL13	Cytokine	-5.961		2.139		
RELA	Transcription factor	-1.077	0.564	-1.169		
IKBKB	Kinase	1.167	0.29	1.421		
CCL4	Chemokine	1.254	0.878	-1.052		
MAP3K7		1.01	0.956	-1.096		
ICAM1	Adhesion	1.184	0.669	1.537		
IRF1	Transcription factor	-1.013	0.519	1.416		
CXCL3	Chemokine	1.7	0.905	1.092		
IL12B	Cytokine	-2.448	0.042	-1.473		
CCL11	Chemokine	-1.338	0.349	-1.995		
MAP3K7IP1	Adaptor					
IFNG	Cytokine	-1.15	0.801	1.075		

When should we bother doing vis?

- need a human in the loop
  - augment, not replace, human cognition
  - for problems that cannot be (completely) automated
- simple summary not adequate
  - statistics may not adequately characterize complexity of dataset distribution

Anscombe's quartet: same

  - mean
  - variance
  - correlation coefficient
  - linear regression line



http://upload.wikimedia.org/wikipedia/commons/b/b6/Anscombe.svg

What does visualization allow?

- discovery vs. confirmation
  - discovering new things
    - hypothesis discovery, “eureka moment”
  - confirming conjectured things
    - hypothesis confirmation
  - contradicting conjectured things
    - especially (inevitably?) data cleansing

- discovery vs. speedup
  - novel capabilities
    - tool supports fundamentally new operations
  - **speedup**
    - tool accelerates workflow (most common!)

Good driving problems for vis research

- need for humans in the loop
- big data
- reasonably clear questions

- many areas of science are a great match
  - biology particularly appealing

Cerebral

collaboration with researchers at UBC Hancock Lab studying innate immunity

Cerebral: Visualizing Multiple Experimental Conditions on a Graph with Biological Context

Aaron Barsky, Computer Science, UBC

Tamara Munzner, Computer Science, UBC

Jennifer Gardy, Microbiology and Immunology, UBC

Robert Kincaid, Agilent Technologies

IEEE Transactions on Visualization and Computer Graphics (Proc. InfoVis 2008) 14(6) (Nov-Dec) 2008, p 1253-1260.

http://www.cs.ubc.ca/labs/imager/tr/2008/cerebral/

http://www.cs.ubc.ca/labs/imager/th/2008/BarskyMscThesis/

open-source software download (Cytoscape plugin)

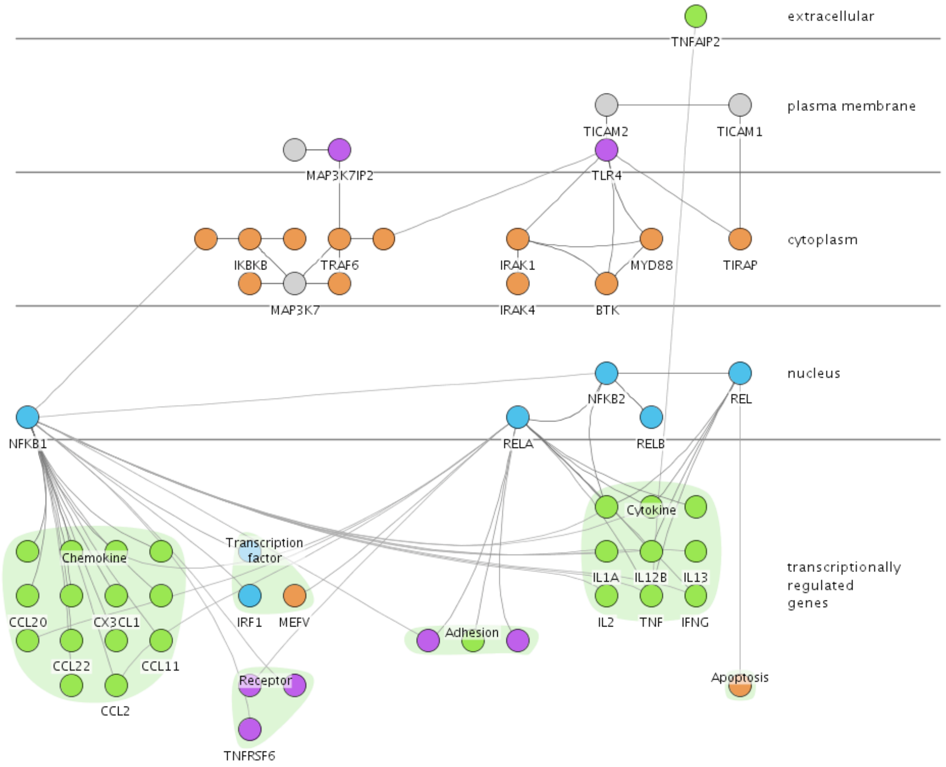
http://www.pathogenomics.ca/cerebral/

deployed in InnateDB (mammalian innate immunity database)

http://www.innatedb.ca

Systems biology model

- graph G = {V, E}
  - V: proteins, genes, DNA, RNA, tRNA, etc.
  - E: interacting molecules



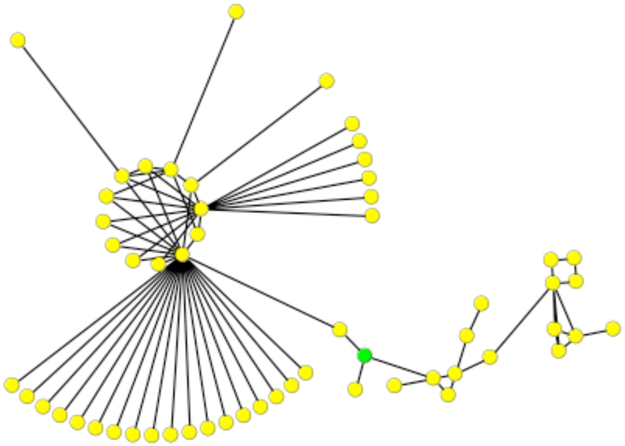
Model - Experiment cycle

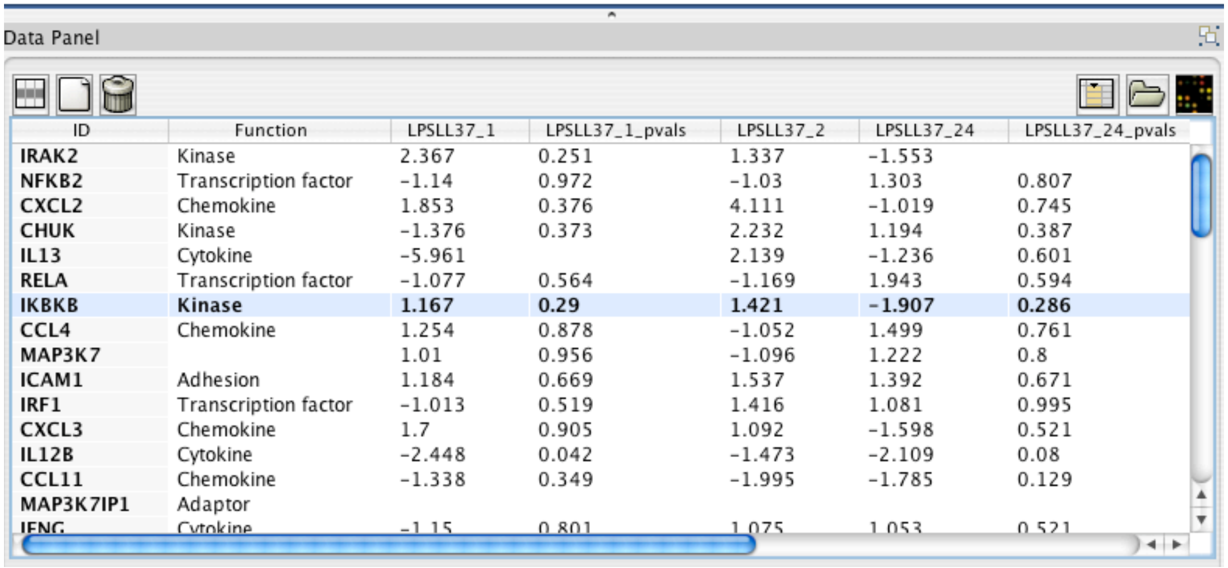
- conduct experiments on cells
- interpret results in current graph model
- propose modifications to refine model

- vis tool to accelerate workflow?

Goal: Integrate model with measurements

- system model
  - interaction graph G = {V, E}
  - meta-data for each v in V
    - labels, biological attributes
- experimental measurements
  - multiple floats for each v in V
    - microarray data





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IL13	Cytokine	-5.961		2.139	-1.236	0.601
RELA	Transcription factor	-1.077	0.564	-1.169	1.943	0.594
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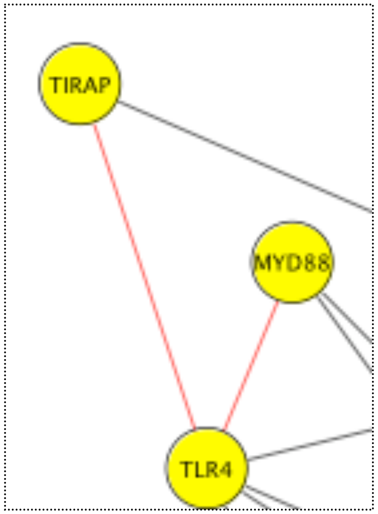
Model summarizes extensive lab work

- graphs come from hand-curated databases
  - dynamic, change with each new publication

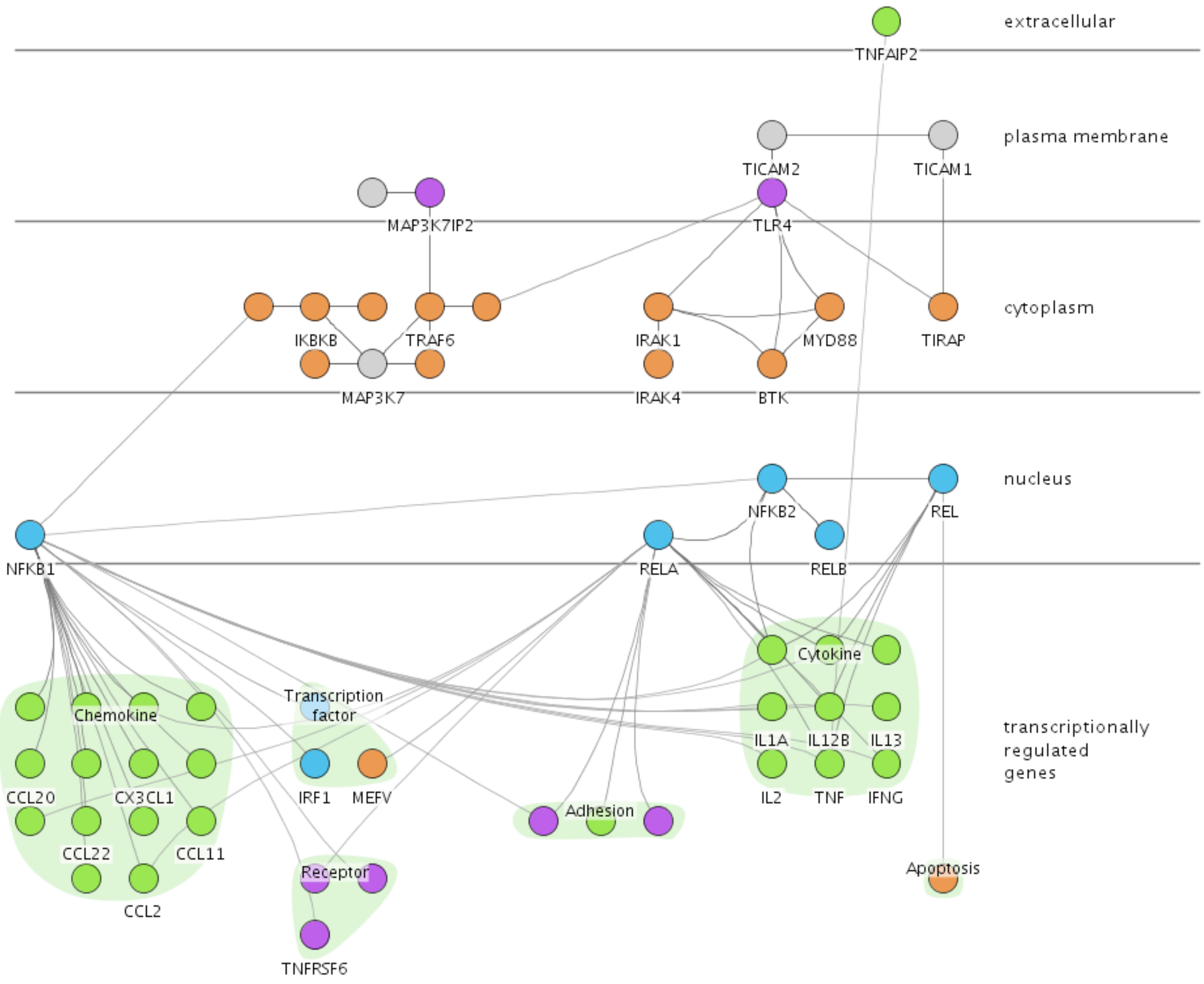
- each edge has provenance from experimental evidence
  - TIRAP: an adapter molecule in the Toll signaling pathway. *Horng T, Barton GM, Medzhitov R.*
  - Mal (MyD88-adapter-like) is required for Toll-like receptor-4 signal transduction. *Fitzgerald KA, Palsson-McDermott EM, Bowie AG, Jefferies CA, Mansell AS, Brady G, Brint E, Dunne A, Gray P, Harte MT, McMurray D, Smith DE, Sims JE, Bird TA, O'Neill LA.*



- choose scope for problem complexity

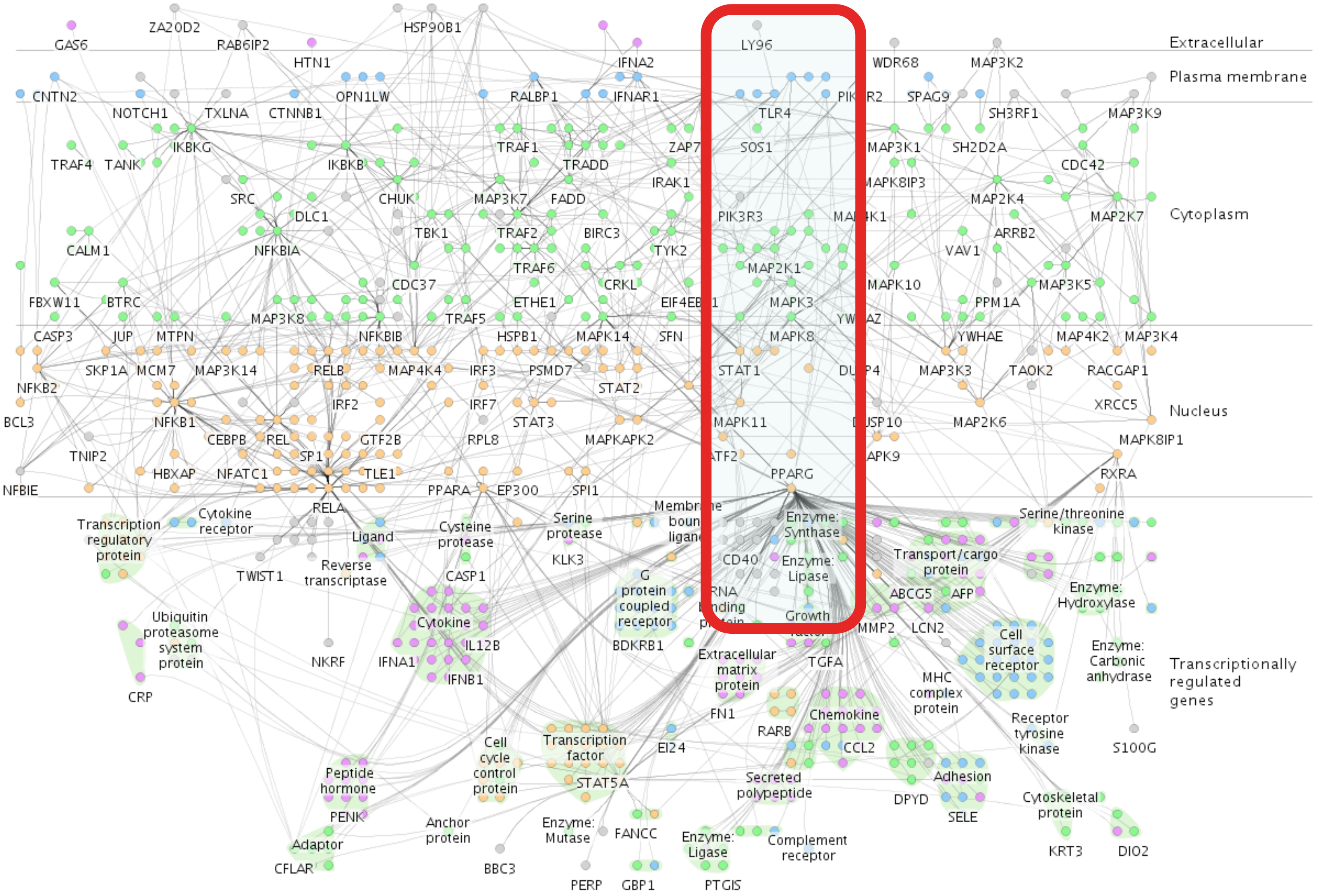
TLR4 biomolecule: E=74, V=54

- very local view



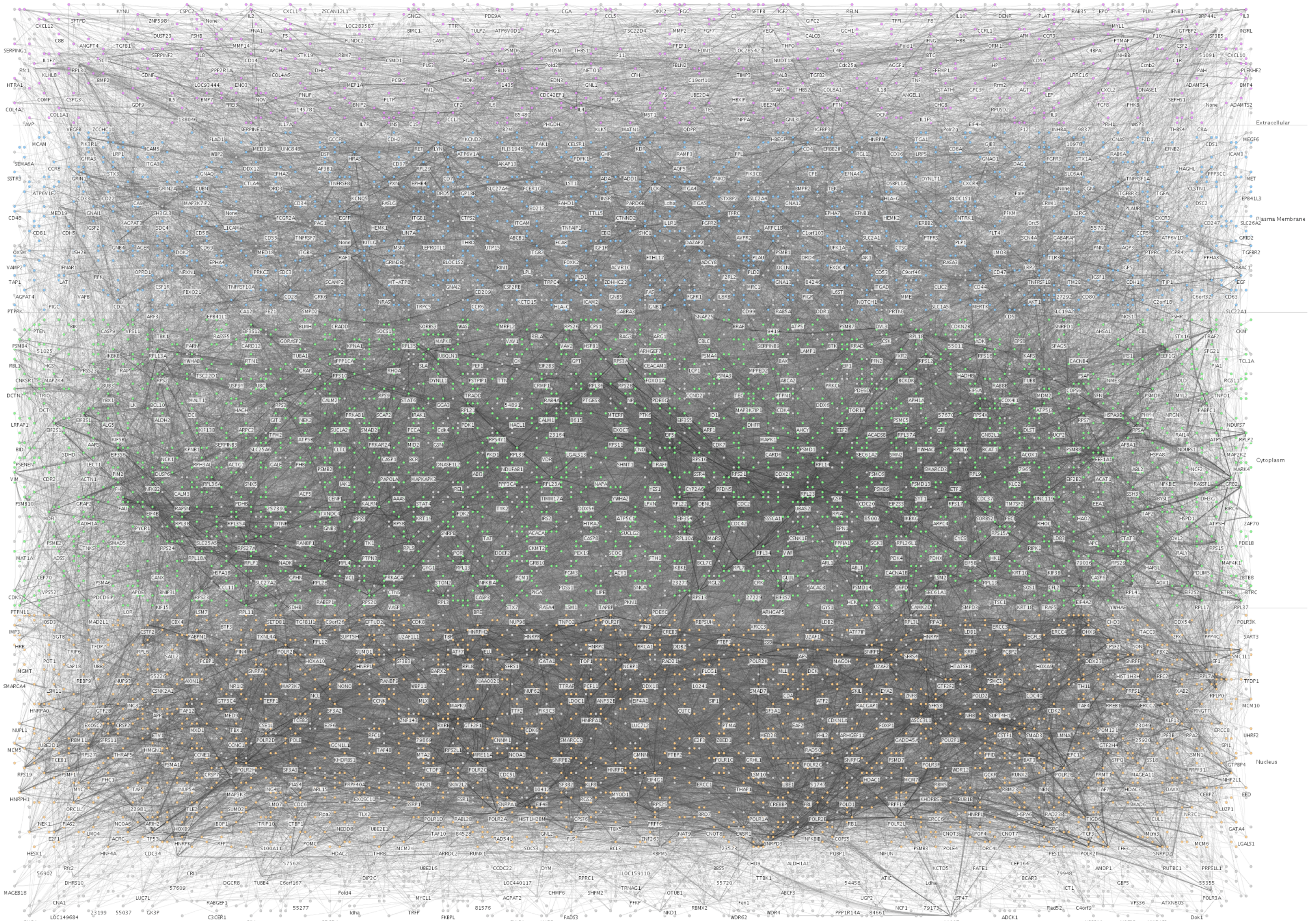
Immune system: E=1263, V=760

- bigger picture, target size for Cerebral

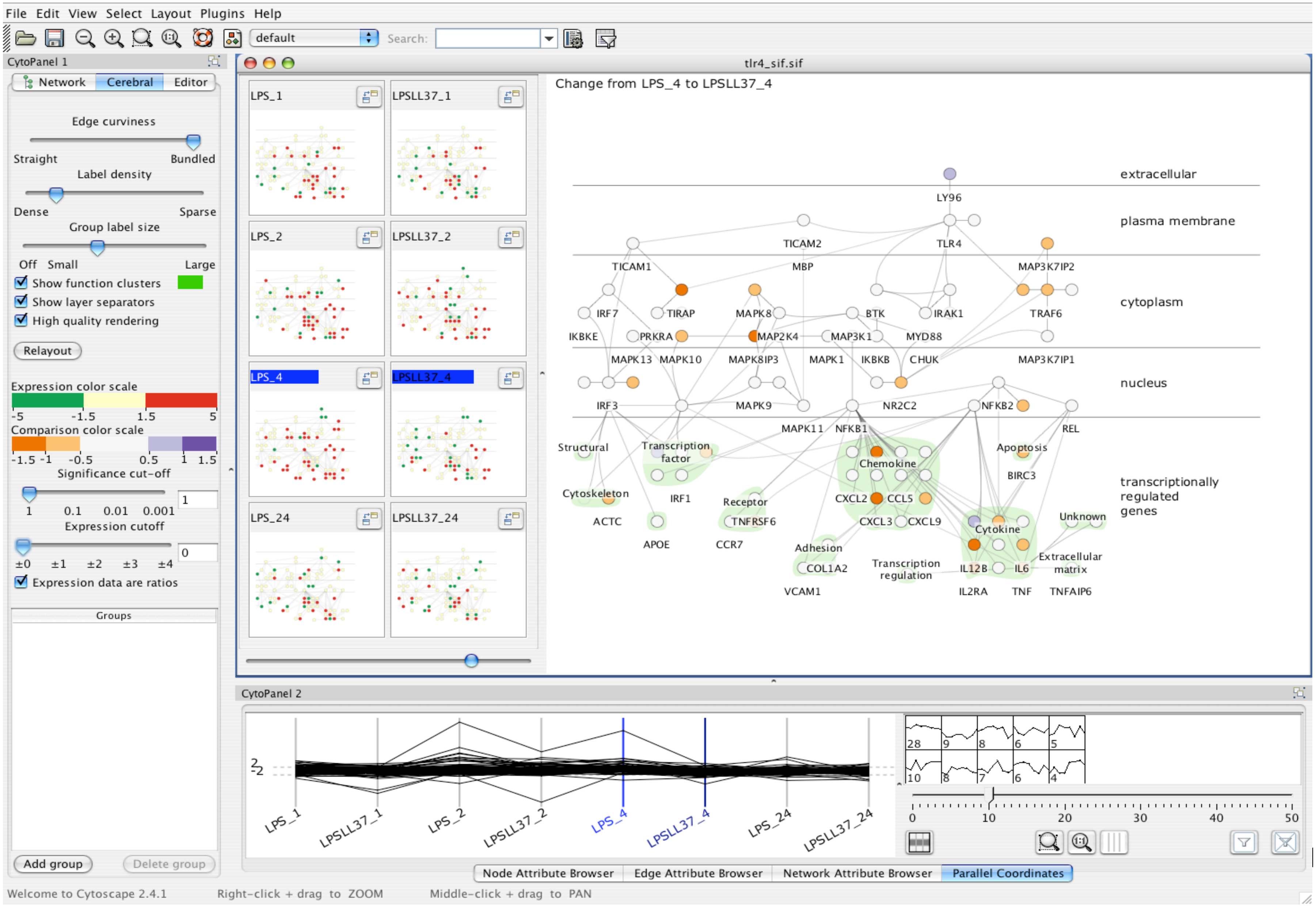


Human interactome: E~50,000, V~10,000

- too complex, beyond scope of tool



Cerebral video



Change from LPS_4 to LPSLL37_4

Edge curviness: Straight — Bundled

Label density: Dense — Sparse

Group label size: Off Small — Large

☑ Show function clusters 🟩

☑ Show layer separators

☑ High quality rendering

Significance cut-off: 1

Expression cutoff: 0

☑ Expression data are ratios

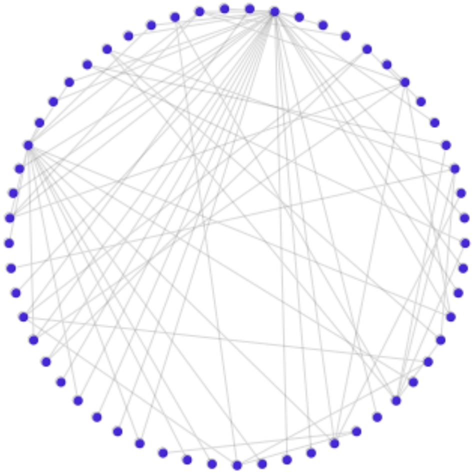
Welcome to Cytoscape 2.4.1   Right-click + drag to ZOOM   Middle-click + drag to PAN

Encoding and interaction design decisions

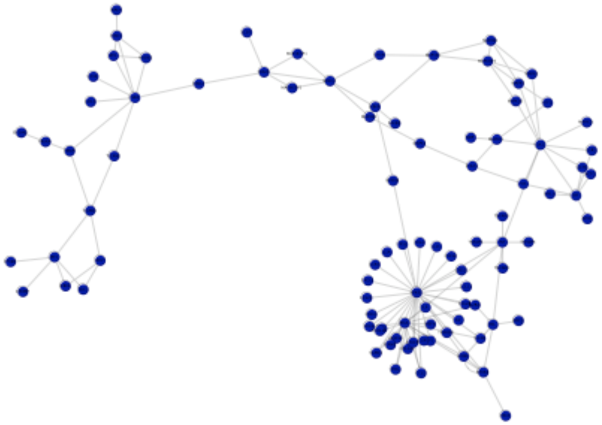
- create custom graph layout
  - guided by biological metadata
- use small multiple views
  - one view per experimental condition
- show measured data in graph context
  - not in isolation

Choice 1: Create custom graph layout

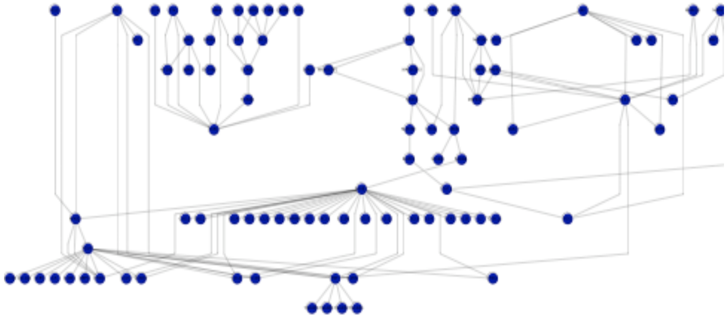
- graph layout heavily studied
    - given graph G={V,E}, create layout in 2D/3D plane
    - hundreds of papers
    - annual Graph Drawing conf.



Circular (Six and Tollis, 1999)



Force-directed
(Fruchterman and Reingold, 1991)



Hierarchical (Sugiyama 1989)

Existing layouts did not suit immunologists

- graph drawing goals
  - visualize graph structure
- biologist goals
  - visualize biological knowledge
  - some relationships happen to form a graph
  - cell location also relevant

Biological cells divided by membranes

- interactions generally occur within a compartment
- interaction location often known as part of model

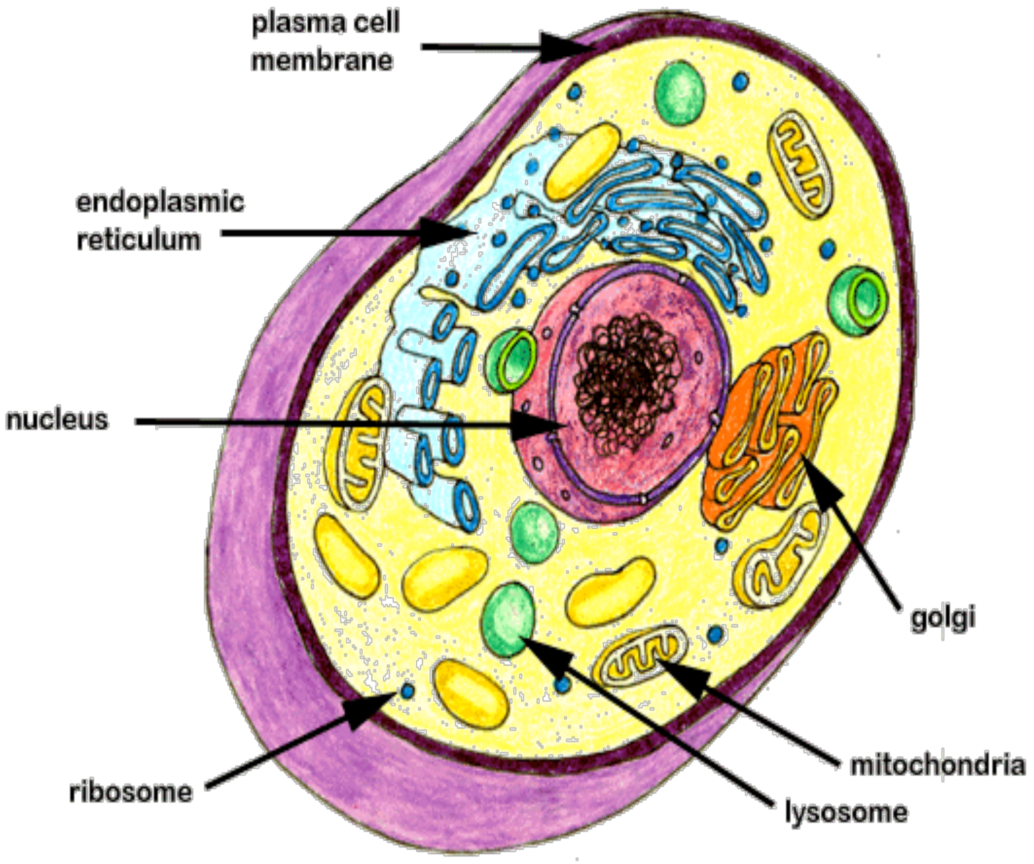
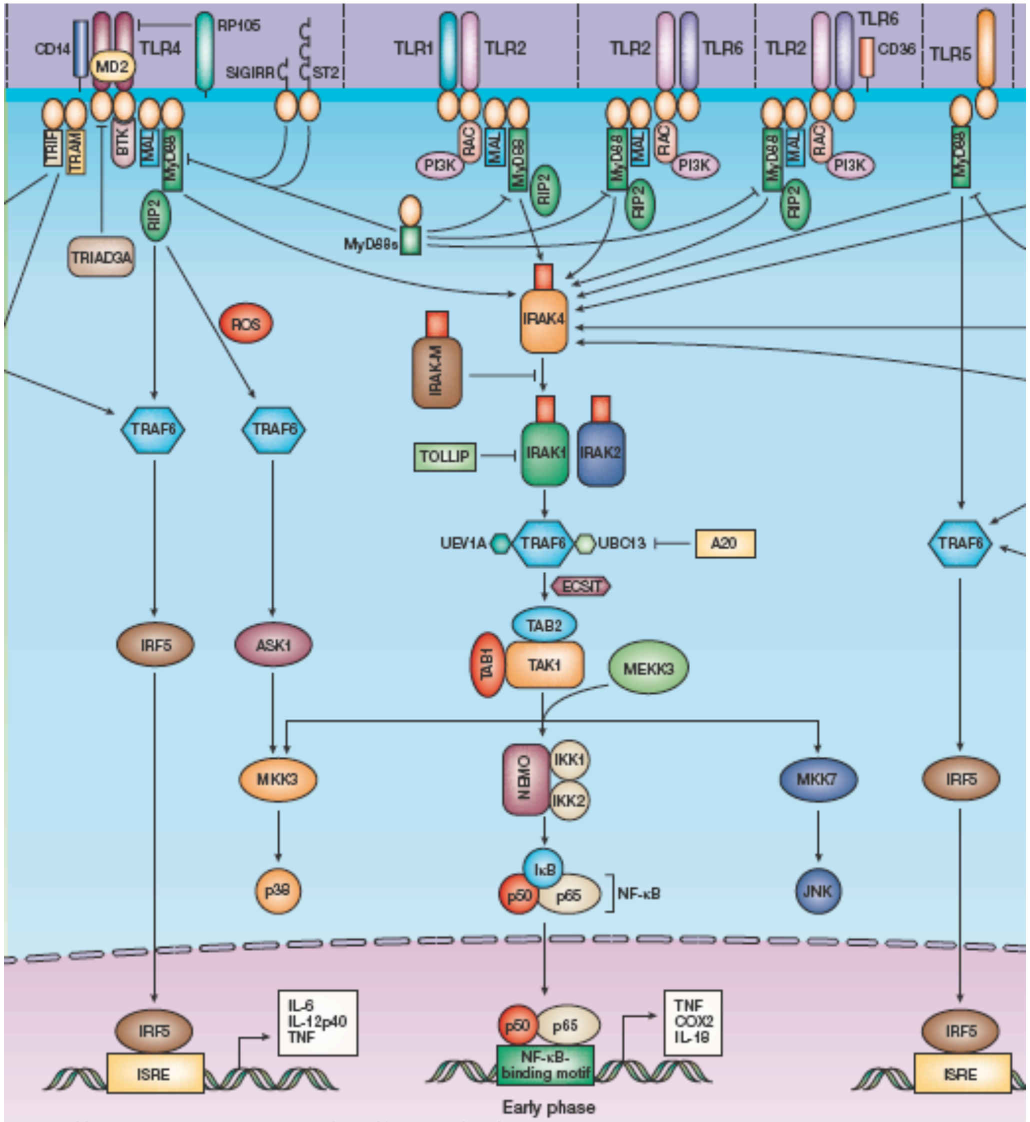


Image credit: Dr.G Weaver, Colorado University at Denver

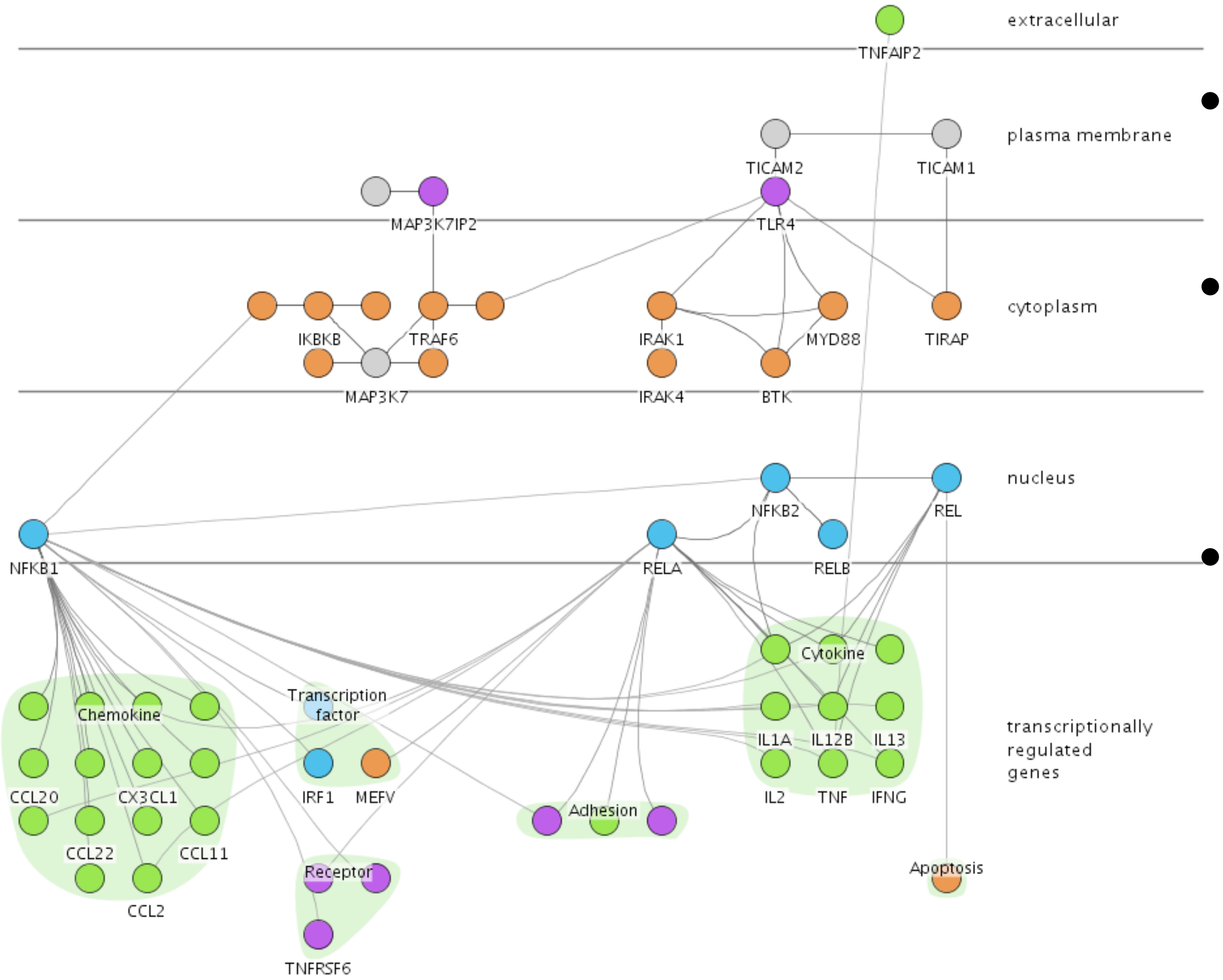
Hand-drawn diagrams



http://www.nature.com/nri/focus/tlr/nri1397.html

- cellular location spatially encoded vertically
- infeasible to create by hand in era of big data

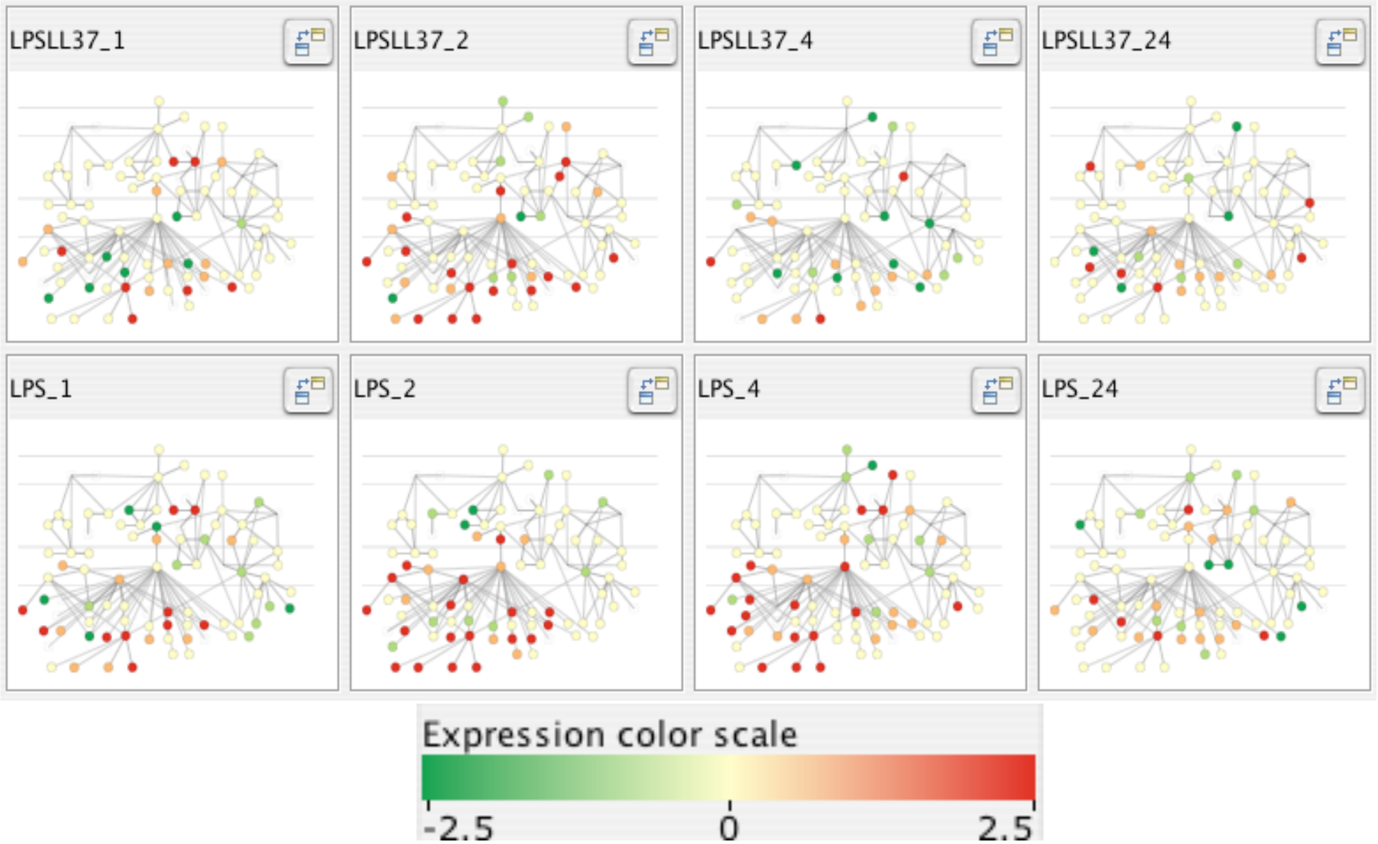
Cerebral layout using biological metadata



- similar to hand-drawn
- spatial position reveals location in cell
- simulated annealing in $O(E\sqrt{V})$ vs. $O(V^3)$ time

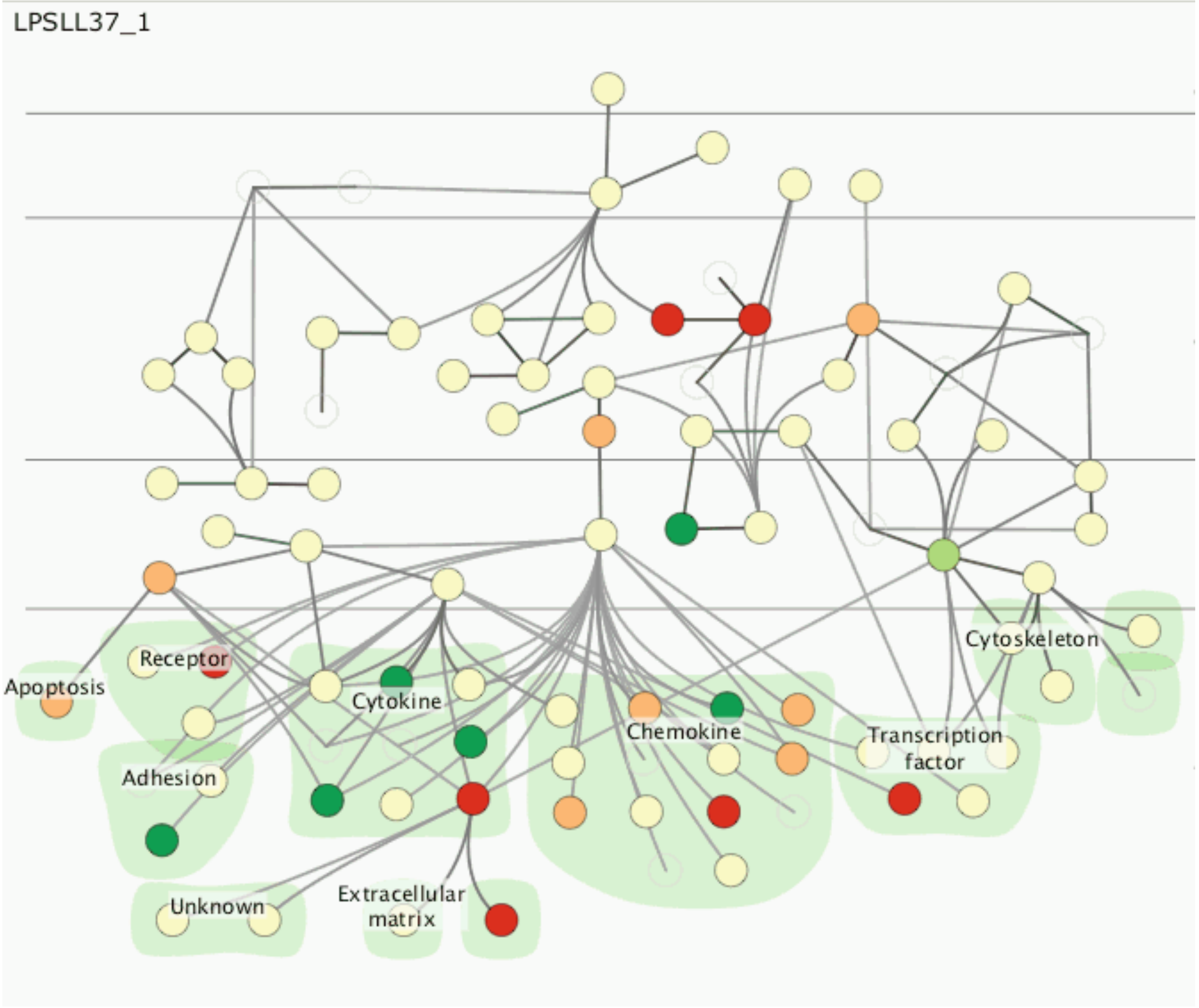
Choice 2: Use small multiple views

- one graph instance per experimental condition
  - same spatial layout
  - color differently, by condition



Why not animation?

- global comparison difficult



Why not animation?

- limits of human visual memory
  - compared to side by side visual comparison

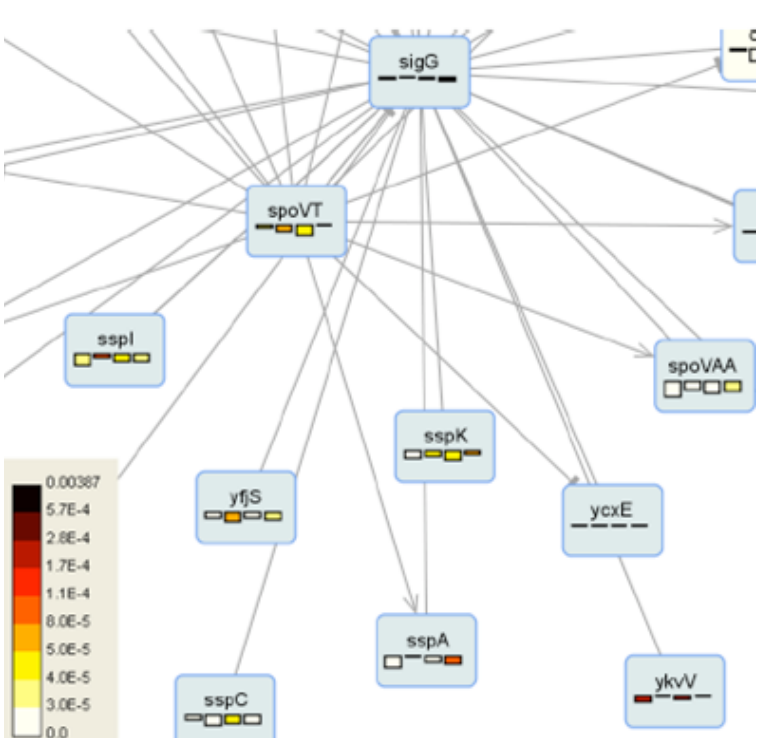
- Zooming versus multiple window interfaces: Cognitive costs of visual comparisons. Matthew Plumlee and Colin Ware. *ACM Trans. Computer-Human Interaction (ToCHI)*,13(2):179-209, 2006.

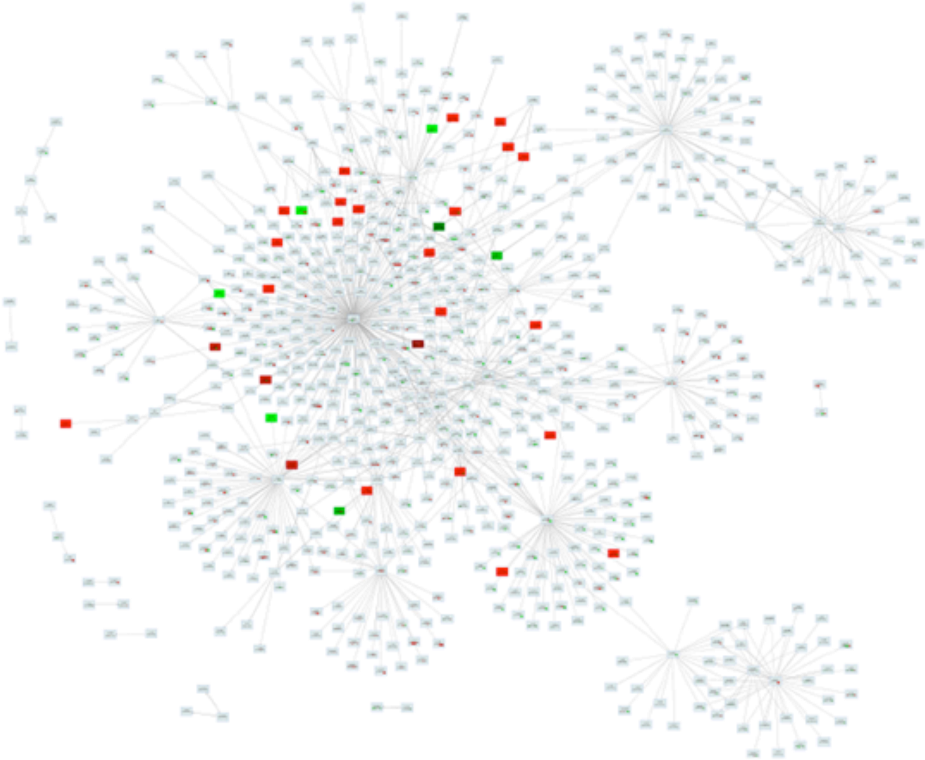
- Animation: can it facilitate? Barbara Tversky, Julie Bauer Morrison, and Mireille Betrancourt. *International Journal of Human-Computer Studies,* 57(4):247-262, 2002.

- Effectiveness of Animation in Trend Visualization. George Robertson, Roland Fernandez, Danyel Fisher, Bongshin Lee, John Stasko. IEEE Trans. Visualization and Computer Graphics 14(6):1325-1332 (Proc. InfoVis 08), 2008.

Why not glyphs?

- embed multiple conditions as a chart inside node
- clearly visible when zoomed in
- but cannot see from global view
  - only one value shown in overview

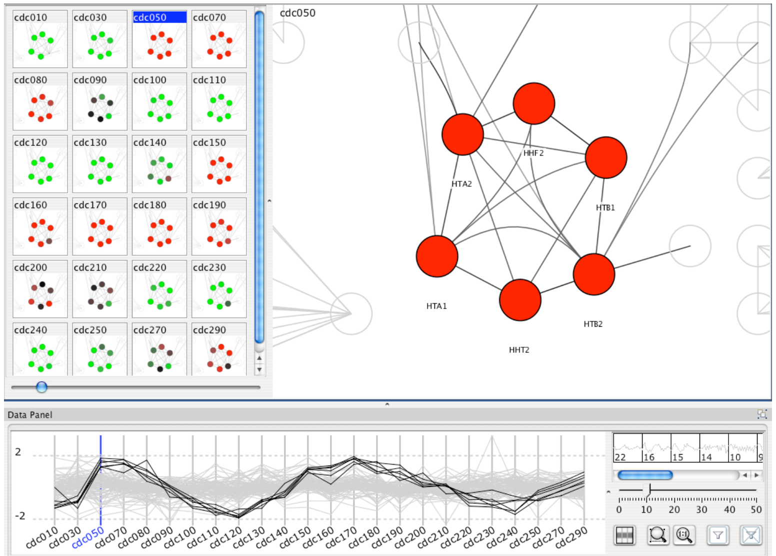




[M. A. Westenberg, S. A. F. T. van Hijum, O. P. Kuipers, J. B. T. M. Roerdink. Visualizing Genome Expression and Regulatory Network Dynamics in Genomic and Metabolic Context. Computer Graphics Forum, 27(3):887-894, 2008.]

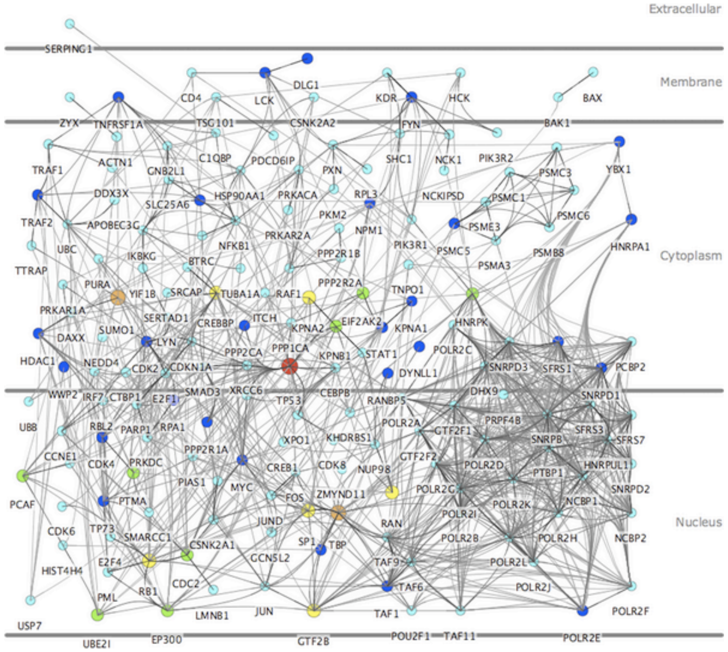
Choice 3: Show measurements and graph

- why not measurements alone?
  - data driven hypothesis: gene expression clusters indicate similar function in cell?
- clusters are often untrustworthy artifacts!
  - noisy data: different clustering alg. → different results
  - measured data alone potentially misleading
  - **show in context of graph model**

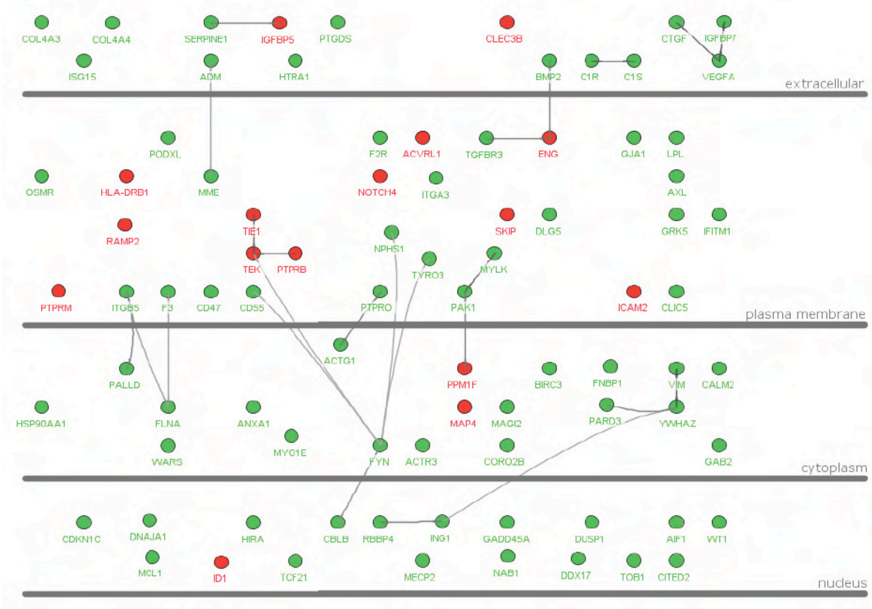


Adoption by biologists

- Matthew D Dyer, T. M Murali, and Bruno W Sobral. The landscape of human proteins interacting with viruses and other pathogens. PLoS Pathogens, 4(2):e32, 2008.

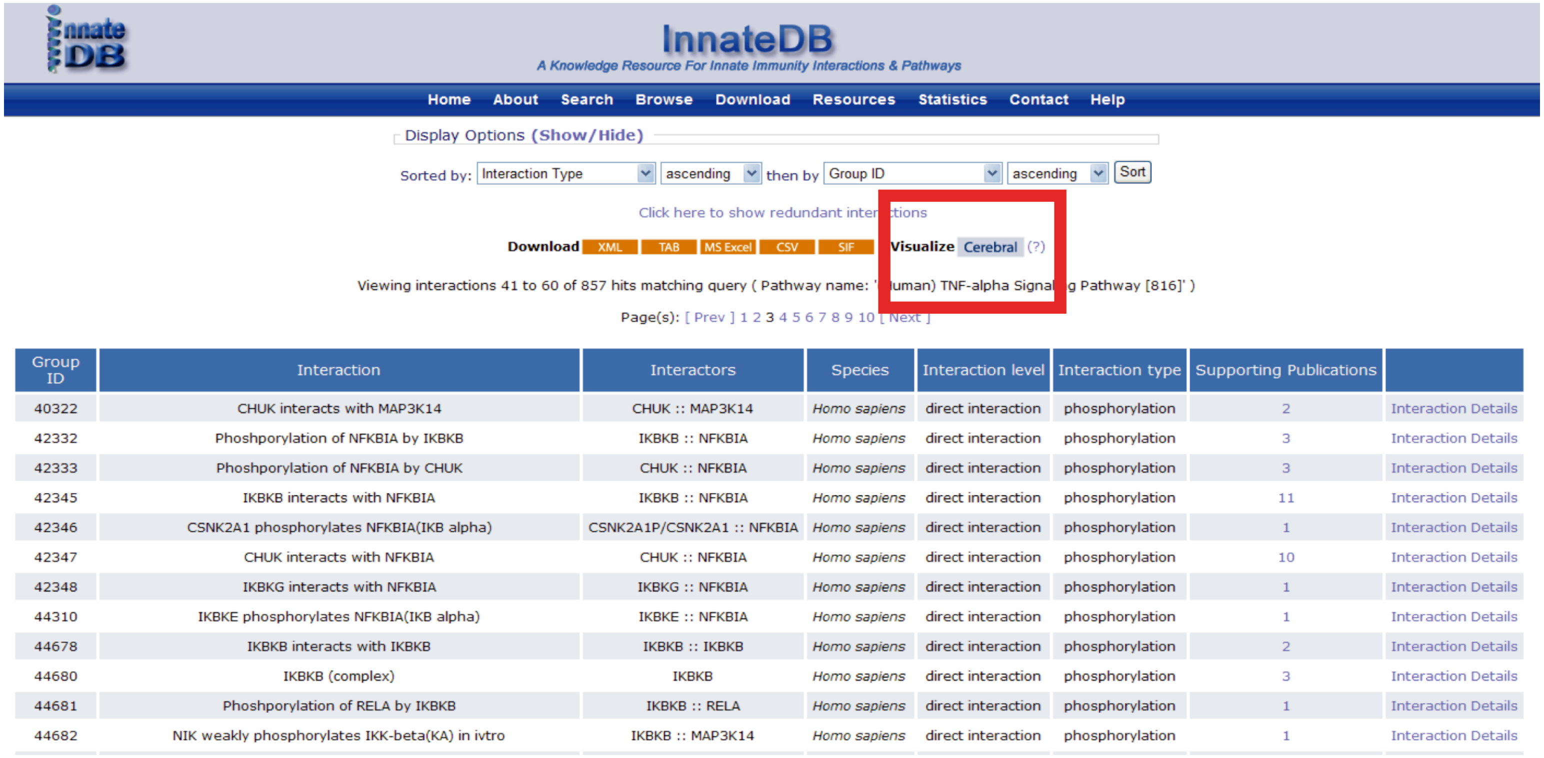


- Liqun He et al. The glomerular transcriptome and a predicted protein-protein interaction network. Journal of the American Society of Nephrology, 19(2):260-268, 2008.



InnateDB links to Cerebral

- InnateDB: facilitating systems-level analyses of the mammalian innate immune response
  - David J Lynn, Geoffrey L Winsor, Calvin Chan, Nicolas Richard, Matthew R Laird, Aaron Barsky, Jennifer L Gardy, Fiona M Roche, Timothy H W Chan, Naisha Shah, Raymond Lo, Misbah Naseer, Jaimmie Que, Melissa Yau, Michael Acab, Dan Tulpan, Matthew D Whiteside, Avinash Chikatamarla, Bernadette Mah, Tamara Munzner, Karsten Hokamp, Robert E W Hancock, Fiona S L Brinkman. Molecular Systems Biology 2008; 4:218
  - http://innatedb.ca



Sorted by: Interaction Type ascending then by Group ID ascending

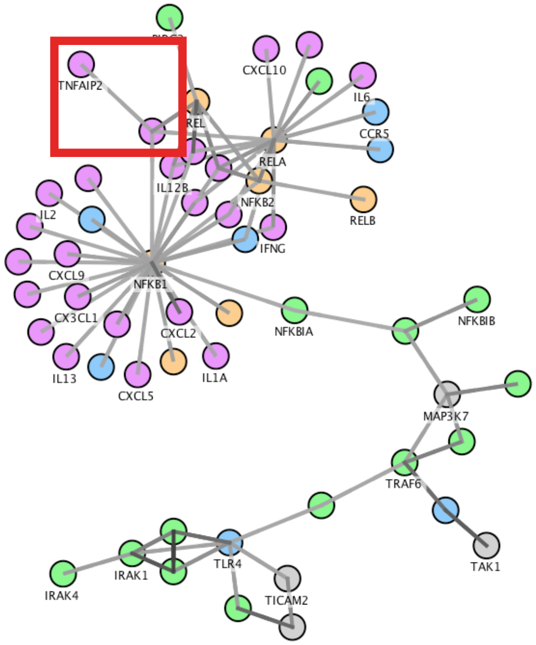
Click here to show redundant inter tions

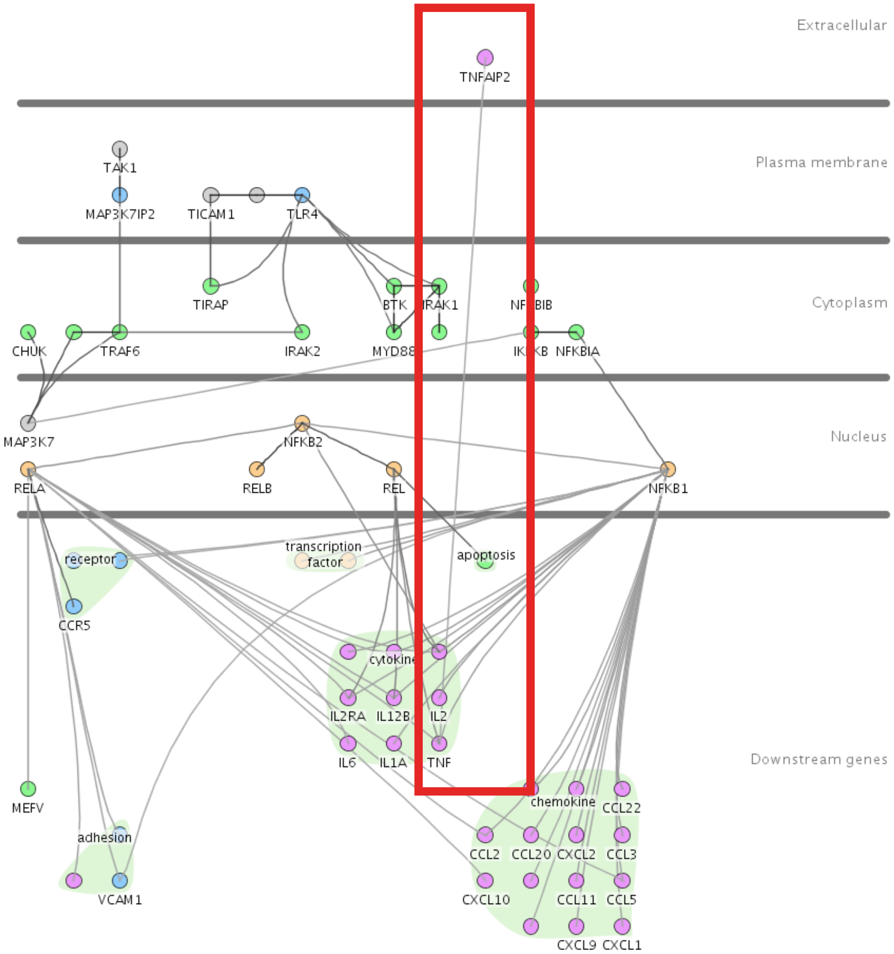
Viewing interactions 41 to 60 of 857 hits matching query (Pathway name: ' uman) TNF-alpha Signal g Pathway [816]')

Group ID	Interaction	Interactors	Species	Interaction level	Interaction type	Supporting Publications	
40322	CHUK interacts with MAP3K14	CHUK :: MAP3K14	*Homo sapiens*	direct interaction	phosphorylation	2	Interaction Details
42332	Phoshporylation of NFKBIA by IKBKB	IKBKB :: NFKBIA	*Homo sapiens*	direct interaction	phosphorylation	3	Interaction Details
42333	Phoshporylation of NFKBIA by CHUK	CHUK :: NFKBIA	*Homo sapiens*	direct interaction	phosphorylation	3	Interaction Details
42345	IKBKB interacts with NFKBIA	IKBKB :: NFKBIA	*Homo sapiens*	direct interaction	phosphorylation	11	Interaction Details
42346	CSNK2A1 phosphorylates NFKBIA(IKB alpha)	CSNK2A1P/CSNK2A1 :: NFKBIA	*Homo sapiens*	direct interaction	phosphorylation	1	Interaction Details
42347	CHUK interacts with NFKBIA	CHUK :: NFKBIA	*Homo sapiens*	direct interaction	phosphorylation	10	Interaction Details
42348	IKBKG interacts with NFKBIA	IKBKG :: NFKBIA	*Homo sapiens*	direct interaction	phosphorylation	1	Interaction Details
44310	IKBKE phosphorylates NFKBIA(IKB alpha)	IKBKE :: NFKBIA	*Homo sapiens*	direct interaction	phosphorylation	1	Interaction Details
44678	IKBKB interacts with IKBKB	IKBKB :: IKBKB	*Homo sapiens*	direct interaction	phosphorylation	2	Interaction Details
44680	IKBKB (complex)	IKBKB	*Homo sapiens*	direct interaction	phosphorylation	3	Interaction Details
44681	Phoshporylation of RELA by IKBKB	IKBKB :: RELA	*Homo sapiens*	direct interaction	phosphorylation	1	Interaction Details
44682	NIK weakly phosphorylates IKK-beta(KA) in ivtro	IKBKB :: MAP3K14	*Homo sapiens*	direct interaction	phosphorylation	1	Interaction Details

Data cleansing example

- incorrect edge across many compartments
  - in well studied dataset
  - not obvious with other layouts





Cerebral summary

- supports interactive exploration of multiple experimental conditions in graph context
- provides familiar representation by using biological metadata to guide graph layout

More information

- this talk
  http://www.cs.ubc.ca/~tmm/talks.html#amw09

- papers, videos
  http://www.cs.ubc.ca/~tmm

- software

  http://www.pathogenomics.ca/cerebral

  http://www.innatedb.ca