Supplementary Materials

Supplementary Table 1: Recommended methods for fixed gene set enrichment analysis.

(A) Recommended methods:

Method	Algorithm	Platform	Data	URL	Ref
g:Profiler	ORA+FET (modified for ordered gene lists)	WT, RP	GL	http://biit.cs.ut.ee/gprofiler	1
CAMERA	ORA+FET (corrected for gene correlation)	RP	GL, EXP	http://www.bioconductor.org/packages/release/bioc/html/limma.html	2
GO	DB	WT, DS	NA	http://geneontology.org	3
GSEA, ssGSEA	FCS+KS	DS, CL, RP	GLV	http://www.broadinstitute.org/gsea	4
GSVA	FCS+KS	RP	GLV	http://www.bioconductor.org/packages/release/bioc/html/GSVA.html	5
HumanCyc	DB	WT	NA	http://humancyc.org	6
KEGG	DB	WT, DS	NA	http://www.genome.jp/kegg/pathway.html	7
REACTOME	DB	WT, DS	NA	http://www.reactome.org	8
SLEA	FCS+Z	DS, CL	GLV	http://bg.upf.edu/slea	9

(B) Additional methods:

Method	Algorithm	Platform	Data	URL	Ref
Babelomics	ORA, FCS+FET	WT	GL	http://www.babelomics.org	10
BiNGO	ORA+HT	CP	GL	http://www.psb.ugent.be/cbd/papers/BiNGO	11
ConceptGen	ORA+FET	WT	GL	http://conceptgen.ncibi.org	12
Gitools	ORA+FET, FCS+Z	DS, CL	GL,GLV	http://www.gitools.org	13
GoMiner	ORA+FET	WT	GL	http://discover.nci.nih.gov/gominer	14
GOstats	ORA+HT	RP	GL	http://www.bioconductor.org/packages/release/bioc/html/GOstats.html	15
iPAGE	ORA+MI	DS, CL, WT	GL	https://tavazoielab.c2b2.columbia.edu/iPAGE	16
ToppGene	ORA	WT	GL	http://toppgene.cchmc.org	17

Supplementary Table 2: Recommended methods for *de novo* network construction and clustering.

(A) Recommended methods:

Method	Algorithm	Platform	Data	URL	Ref
BioGRID	DB	WT, DS	NA	http://thebiogrid.org	18
EnrichNet	RWR	DS, WT, CP	GL	http://www.enrichnet.org	19
GeneMANIA	DB, RR	CP, WT	GL	http://www.genemania.org	20
Hypermodules	GS+CC	CL,CP	GL, CD	http://apps.cytoscape.org/apps/hypermodules	21
INTACT	DB	WT,DS	NA	http://www.ebi.ac.uk/intact	22
iRefIndex	DB	DS	NA	http://irefindex.org/wiki/index.php	23
MEMo	ME	CL, DS	SSM, SNA	http://cbio.mskcc.org/tools/memo	24
NetBox	EB	CL, DS	GL	http://cbio.mskcc.org/tools/netbox	25
ReactomeFIViz	GC, FG, MCL	CP	GL, GLV	http://apps.cytoscape.org/apps/reactomefiplugin	26
ResponseNet	MCFL	CP, WT	GLV (gene weights)	http://bioinfo.bgu.ac.il/respnet	27
STRING	DB	WT, DS	NA	http://string-db.org	28

(B) Additional methods:

Method	Algorithm	Platform	Data	URL	Ref
Dendrix	ME	CP, DS, WT	SM	http://compbio.cs.brown.edu/projects/dendrix	29
iCluster+	GLV	RP	SSM, SNA, EXP	http://www.mskcc.org/research/epidemiology-biostatistics/biostatistics/iclusterplus	30
Pathifier	PDS	CL, RP	EXP	http://www.weizmann.ac.il/complex/compphys/software/yotam/pathifier	31
SIRENE	BC	ML	EXP	http://cbio.ensmp.fr/sirene	32

Supplementary Table 3: Recommended methods for network-based modeling.

(A) Recommended methods:

Method	Algorithm	Platform	Data	URL	Ref
HotNet	UD	ML	GLV	http://compbio.cs.brown.edu/projects/hotnet	33
TieDIE	UD	CL, ML	SSM, SCNA, EXP	https://sysbiowiki.soe.ucsc.edu/tiedie	34
SPIA	RW	RP	EXP	http://www.bioconductor.org/packages/devel/bioc/html/SPIA.html	35
ARACNE	DPI	CL, DS, RP	EXP	http://wiki.c2b2.columbia.edu/califanolab/index.php/Software/ARACNE	36
GENIE3	LR	ML, RC	EXP	http://homepages.inf.ed.ac.uk/vhuynht/software.html	37
PARADIGM	PGM	WT, DS, CL	SSM, SCNA, EXP, METH	http://paradigm.five3genomics.com	38
PARADIGM-Shift	PGM	DS	SSM, SCNA, EXP, METH	http:github.org/sng87/paradigmshift	39
PathOlogist	PGM	CL, ML	EXP	ftp://ftp1.nci.nih.gov/pub/pathologist	40
DataRail	BKRM	DS, RP, CP	EXP+ PD	https://code.google.com/p/sbpipeline/wiki/DataRail	41

(B) Additional methods:

Method	Algorithm	Platform	Data	URL	Ref
PSA	NF	CA	EXP, CHIP	http://apps.cytoscape.org/apps/pathwayscoringapplication	42
NetPhorest	NF	WT	GL	http://netphorest.info	43
NetworKIN	NF	WT	GL	http://networkin.info	44
CellNet-Optimizer	BKRM	DS, RP, CP	EXP+PD	http://www.cellnopt.org	45

Code for platform type:
CL: Command line tool
CP: Cytoscape plugin
DS: Downloadable software/database
ML: Matlab code available
RC: R code
RP: R package (Bioconductor)
WT: Web tool

Code for Method Type:
BC: Binary classifier
BHC: Bayesian hierarchical clustering
DB: Reference Database
EB: Edge-betweenness subnetwork detection
FCS+KS: Functional class scoring using Kolmogorov–Smirnov rank statistics
FCS+Z: Functional class scoring using z-score rank statistics
FG: Factor-graph subnetwork detection
GLV: Gaussian latent variable model subnetwork detection
LR: Linear regression
MCFL: Minimum-cost flow optimization subnetwork detection
MCL: Markov-chain clustering
MDPI: Mutual information + data processing inequality
ME: Mutually exclusive subnetworks
MIP: Mixed integer programming
NF: Network flow type, incorporates direction and inhibitory/excitatory
ORA+FET: Over-representation analysis using Fisher's exact test
ORA+MI: Over-representation analysis using mutual information statistic
PDS: Pathway deregulation score based on tumor RNA expression data
PGM: Probabilistic Graphical Model
REA: Recursive enumeration algorithm on network weighted for predicted oncogenicity of edges
RR: Ridge regression clustering
RW: Random walk
UD: Undirected diffusion; incorporates undirected links

Code for data type:
CD: Clinical data
CHIP: ChIP-seq
EXP: Gene list with RNA expression values
GL: Gene list (e.g. mutated genes, thresholded RNA fold-change)
GLV: Gene list with values (typically RNA fold-change)
SSM: Simple somatic mutations
SCNA: Somatic copy number alterations
PD: Perturbation data (e.g. small molecule screens)
METH: DNA methylation
NA: Not applicable

Supplementary references

1. Reimand, J. *et al.* g:Profiler--a web-based toolset for functional profiling of gene lists from large-scale experiments. *Nucleic Acids Res*. **35**, W193-200 (2007).
2. Wu D, Smyth GK. Camera: a competitive gene set test accounting for inter-gene correlation. *Nucleic Acids Res.* **40**, e133 (2012).
3. The Gene Ontology Consortium. The Gene Ontology in 2010: extensions and refinements. *Nucleic Acids Res.* **38**, D331-5 (2010).
4. Subramanian, A. *et al*. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A*. **102**, 15545-15550 (2005).
5. Hänzelmann, S., Castelo, R. & Guinney J. GSVA: gene set variation analysis for microarray and RNA-seq data. *BMC Bioinformatics*. **14**, 7 (2013).
6. Caspi, R. *et al.* The MetaCyc database of metabolic pathways and enzymes and the BioCyc collection of Pathway/Genome Databases. *Nucleic Acids Res.* **42**, D459-71 (2014).
7. Kanehisa, M. *et al.* Data, information, knowledge and principle: back to metabolism in KEGG. *Nucleic Acids Res.* **42**, D199-205 (2014).
8. Croft D. *et al.* The Reactome pathway knowledgebase. *Nucleic Acids Res.* **42**, D472-7 (2014).
9. Gundem, G., Lopez-Bigas, N. Sample-level enrichment analysis unravels shared stress phenotypes among multiple cancer types. *Genome Med*. **4**, 28 (2012).
10. Medina, I. *et al*. Babelomics: an integrative platform for the analysis of transcriptomics, proteomics and genomic data with advanced functional profiling. *Nucleic Acids Res*. **38**, W210-213 (2010).
11. Maere, S., Heymans, K., Kuiper, M. BiNGO: a Cytoscape plugin to assess overrepresentation of gene ontology categories in biological networks. *Bioinformatics* **21**, 3448-3449 (2005).
12. Sartor, M.A. *et al*. ConceptGen: a gene set enrichment and gene set relation mapping tool. *Bioinformatics* **26**, 456-463 (2010).
13. Perez-Llamas, C., Lopez-Bigas, N. Gitools: analysis and visualisation of genomic data using interactive heat-maps. *PLoS One*. **6**, e19541 (2011).
14. Zeeberg, B.R. *et al*. GoMiner: a resource for biological interpretation of genomic and proteomic data. *Genome Biol*. **4**, R28 (2003).
15. Falcon, S., Gentleman, R. Using GOstats to test gene lists for GO term association. *Bioinformatics* **23**, 257-258 (2007).
16. Goodarzi, H., Elemento, O., Tavazoie, S. Revealing Global Regulatory Perturbations across Human Cancers. *Molecular Cell*. **36**, 900-911 (2009).
17. Chen, J., Bardes, E. E., Aronow, B. J., Jegga, A. G. ToppGene Suite for gene list enrichment analysis and candidate gene prioritization. *Nucleic Acids Res*. **37**, W305-W311 (2009).
18. Chatr-Aryamontri, A. *et al*. The BioGRID interaction database: *Nucleic Acids Res*., pii: gku1204 (2015).
19. Glaab, E., Baudot, A., Krasnogor, N., Schneider, R., Valencia A. EnrichNet: network-based gene set enrichment analysis. *Bioinformatics* **28**, i451-i457 (2012).
20. Warde-Farley, D. *et al*. The GeneMANIA prediction server: biological network integration for gene prioritization and predicting gene function. *Nucleic Acids Res*. **38**, W214-20 (2010).
21. Leung, A., Bader G.D., Reimand J. HyperModules: identifying clinically and phenotypically significant network modules with disease mutations for biomarker discovery. *Bioinformatics*. **30**, 2230-2 (2014).
22. Kerrien, S. *et al*. The IntAct molecular interaction database in 2012. *Nucleic Acids Res*. **40**, D841-6 (2012).
23. Razick, S., Magklaras, G., Donaldson, I.M. iRefIndex: a consolidated protein interaction database with provenance. *BMC Bioinformatics*. **30**, 1471-2105 (2008).
24. Ciriello, G., Cera, E., Sander C, Schultz, N. Mutual exclusivity analysis identifies oncogenic network modules. *Genome Res*. **22**, 398-406 (2012).
25. Cerami, E., Demir, E., Schultz, N., Taylor, B.S., Sander, C. Automated network analysis identifies core pathways in glioblastoma. *PLoS One*. **5**, e8918 (2010).
26. Wu ,G., Dawson, E., Duong, A., Haw, R., Stein, L. ReactomeFIViz: a Cytoscape app for pathway and network-based data analysis. *F1000Res*. **3**, doi: 10.12688/f1000research.4431.2. eCollection (2014).
27. Lan, A. *et al*. ResponseNet: revealing signaling and regulatory networks linking genetic and transcriptomic screening data. *Nucleic Acids Res*. **39**, W424-9 (2011).

28. Szklarczyk, D. *et al*. STRING v10: protein-protein interaction networks, integrated over the tree of life. *Nucleic Acids Res*. **28**, pii: gku1003 (2014).

29. Vandin, F., Upfal, E., Raphael B.J. De novo discovery of mutated driver pathways in cancer. *Genome Res*. **22**, 375-85 (2012).

30. Mo, Q. *et al.* Pattern discovery and cancer gene identification in integrated cancer genomic data. *Proc Natl Acad Sci U S A.* **110**, 4245-50 (2013).

31. Drier, Y., Sheffer, M., Domany E. Pathway-based personalized analysis of cancer. *Proc Natl Acad Sci U S A.* **110**, 6388-93 (2013).

32. Mordelet, F., Vert, J.P. SIRENE: supervised inference of regulatory networks. *Bioinformatics* **24**, i76-82 (2008).

33.Vandin, F., Upfal, E., Raphael B.J. Algorithms for detecting significantly mutated pathways in cancer. *J Comput Biol.* **18**, 507-22 (2011).

34. Paull, E.O. *et al*. Discovering causal pathways linking genomic events to transcriptional states using Tied Diffusion Through Interacting Events (TieDIE). *Bioinformatics* **29**, 2757-64 (2013).

35. Tarca, A.L. *et al.* A novel signaling pathway impact analysis. *Bioinformatics* **25**, 75-82 (2009).

36. Margolin, A.A. *et al.* ARACNE: an algorithm for the reconstruction of gene regulatory networks in a mammalian cellular context. *BMC Bioinformatics* **7**, S7 (2006).

37. Huynh-Thu, V.A., Irrthum, A., Wehenkel, L., Geurts P. Inferring regulatory networks from expression data using tree-based methods. *PLoS One* **5**, e12776 (2010).

38. Vaske, C.J. *et al.* Inference of patient-specific pathway activities from multi-dimensional cancer genomics data using PARADIGM. *Bioinformatics* **26**, i237-45 (2010).

39. Ng, S. *et al.* PARADIGM-SHIFT predicts the function of mutations in multiple cancers using pathway impact analysis. *Bioinformatics* **28**, i640-i646 (2012).

40. Greenblum, S.I., Efroni, S., Schaefer, C.F., Buetow, KH. The PathOlogist: an automated tool for pathway-centric analysis. *BMC Bioinformatics* **12**,133 (2011).

41. Saez-Rodriguez, J. *et al.* Flexible informatics for linking experimental data to mathematical models via DataRail. *Bioinformatics* **24**, 840-7 (2008).

42. Isik, Z., Ersahin, T., Atalay, V., Aykanat, C., Cetin-Atalay, R. A signal transduction score flow algorithm for cyclic cellular pathway analysis, which combines transcriptome and ChIP-seq data. *Mol Biosyst*. **8**, 3224-31 (2012).

43. Miller, M.L. *et al.* Linear motif atlas for phosphorylation-dependent signaling. *Sci Signal*. **1**, ra2 (2008).

44. Linding, R. *et al.* Systematic discovery of in vivo phosphorylation networks. *Cell*. **129**, 1415-26 (2007).

45. Klamt, S., Saez-Rodriguez, J., Gilles, E.D. Structural and functional analysis of cellular networks with CellNetAnalyzer. *BMC Syst Biol*. **1**, 2 (2007).