SUPPLEMENTARY MATERIALS

Clustering algorithms

We compared the *MGclus* method to a set of popular graph clustering methods including *MCL* [1], *CFinder* [2], *FastCommunity* [3], *MCode* [4], *MINE* [5], *NEMO* [6], *SPICi* [7], and *Cohtop* [8]. A common problem for non-expert users is that many graph clustering methods have a variety of user adjustable parameters, that can greatly influence their performance. However, without knowing the optimal clustering beforehand it is impossible to know how to set certain parameters. Therefore, it is extremely important that methods have reasonable and robust standard parameters. To allow a fair comparison we ran all methods with their default parameters. The two methods *MCode* and *NeMo* are only available as Cytoscape plugin. We set the size of the Java heap space for Cytoscape to 12Gb when running those two methods.

Briefly, we ran the *MCL* method with an inflation factor of 2. For the *CFinder* method we considered all *k*-clique percolation clusters for *k* >= 3. The *FastCommunity* method was run twice setting the "maximum modularity" value in the second run to the value reported after the first run. The *MCode, MINE,* and *NEMO* methods have a lot of user adjustable parameters. *MCode* was run with the following parameter settings: "degree cutoff" 2, "include loops" false, "node score cutoff" 0.2, "k-core" 2, "max. depth from seed" 100, "haircut" true, and "fluff" false. For *MINE* the following parameters were used: "include loops" false, "degree cutoff" 2, "node score cutoff" 0.2, "modularity score cutoff" 0.1, "complex merge score cutoff" 0.5, "haircut" true, "fluff" false, and "max. depth from seed" 100. *NEMO* has similar parameters that we set as follows: "include loops" false, "degree cutoff" 2, "node score cutoff" 0.2, "haircut" true, "fluff" false, "k-core" 2, and "max. depth from seed" 100. For *SPICi* we used the following parameter settings: "minimum density threshold for output clusters" 0.5, "minimum cluster size" 2, and "minimum increment ratio" 0.5. The *Cohtop* method has no user-adjustable parameters.

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Figures

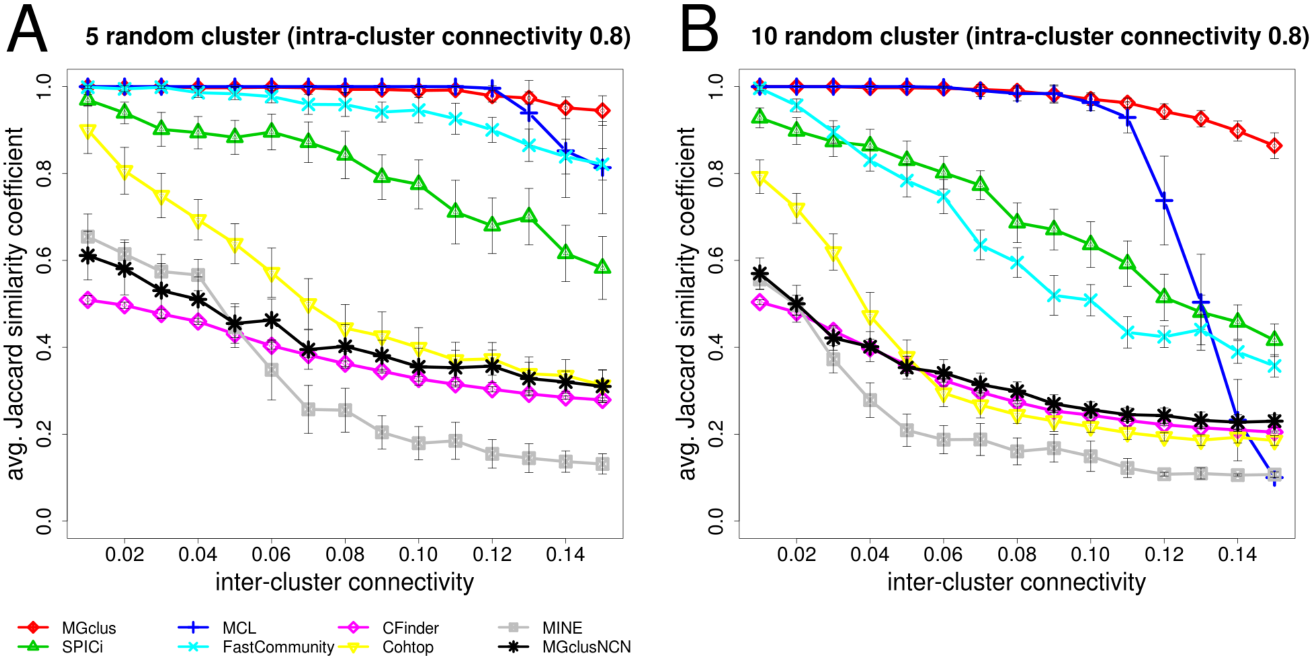

Figure S1 Accuracy benchmark using simulated data. Various clustering methods were benchmarked on random graphs with a) 5 random cluster or b) 10 random cluster of size 10. The intra cluster connectivity was fixed (0.8) and the inter cluster connectivity was varied between 0.01 and 0.15. The shown Jaccard similarity coefficient between predicted and true clusters is the average of 50 runs. Vertical error bars on data points represent the standard deviation for the different methods. We also included a version of *MGclus* that does not use shared neighbors to calculate the clustering score (*MGclusNCN*). Without shared neighbors *MGclus* performed very poorly, thus demonstrating the usefulnesses of incorporating shared neighbor counts in the cluster finding process. Only methods that can be run standalone were included in this benchmark.

Tables:

Small S.cerevisiae PPI network				
	avg. JSC (counting singletons)	avg. JSC (default output)	Coverage (default output)	Time (s)
MGClus	0.42	0.42	1.00	1.8
MCL	0.42	0.42	0.98	0.4
MgclusNCN	0.40	0.40	1.00	1.4
FastCommunity	0.39	0.39	1.00	0.3
SPICI	0.35	0.4	0.47	0.0
Cohtop	0.34	0.34	1.00	2.1
MINE	0.34	0.42	0.16	118.9
CFinder	0.33	0.35	0.19	0.2
MCODE	0.33	0.49	0.09	2.0
NEMO	0.32	0.3	0.44	12.0

Table S1a

Large S.cerevisiae PPI network				
	avg. JSC (counting singletons)	avg. JSC (default output)	Coverage (default output)	Time (s)
MGClus	0.47	0.47	1.00	3.2
MCL	0.46	0.47	0.93	1.7
FastCommunity	0.45	0.45	1.00	1.0
MINE	0.44	0.57	0.40	2114.9
SPICI	0.44	0.49	0.62	0.0
Cohtop	0.43	0.43	1.00	7.0
MgclusNCN	0.40	0.40	1.00	1.4
CFinder	0.37	0.37	0.47	7.4
NEMO	0.37	0.42	0.56	34.0
MCODE	0.37	0.58	0.25	11.0

Table S1b

Human FunCoup PPI network				
	avg. JSC (counting singletons)	avg. JSC (default output)	Coverage (default output)	Time (s)
MGClus	0.085	0.085	1.00	861.1
Cohtop	0.078	0.078	1.00	701.2
FastCommunity	0.056	0.056	1.00	66.4
MCL	0.056	0.056	1.00	89.4
SPICI	0.044	0.055	0.60	1.3
MgclusNCN	0.042	0.042	1.00	110.0
MINE	0.042	0.058	0.64	36666.1
MCODE	0.037	0.079	0.37	27788.4

Table S1c

Table S1a-c: Comparison of different clustering methods on (a) the small *S. cerevisiae* network that was limited to data from yeast two-hybrid experiments, (b) the large *S. cerevisiae* network that contained all interactions, and (c) the human FunCoup network. Shown is the average Jaccard similarity coefficient (JSC) between predicted clusters and known complexes. The comparison of different clustering approaches is complicated by the fact that some methods aim to cluster all nodes in a network (e.g. MGCLUS and MCL), while other methods only report clusters for small parts of the network. In our main benchmark we therefore chose to count unclustered genes as singletons as it makes results between different methods more comparable. We also report the JSC score and the network coverage for the default output as well as the user time.

	inter connectivity 0.02					
intra connectivity	**0.10**	**0.20**	**0.40**	**0.60**	**0.80**	**1.00**
MGclus	0.14	0.21	0.46	**0.90**	**1.00**	**1.00**
SPICi	0.12	0.14	0.26	0.61	0.88	0.88
FastCommunity	**0.14**	**0.23**	**0.62**	0.76	0.78	0.78
CFinder	0.10	0.12	0.25	0.34	0.46	0.50
MGclusNCN	0.12	0.15	0.19	0.25	0.40	0.81
Cohtop	0.11	0.13	0.18	0.47	0.66	0.75
MCL	0.12	0.14	0.25	0.84	**1.00**	**1.00**
MINE	0.14	0.21	0.35	0.40	0.35	0.41
	inter connectivity 0.06					
intra connectivity	**0.10**	**0.20**	**0.40**	**0.60**	**0.80**	**1.00**
MGclus	0.11	**0.15**	**0.29**	**0.69**	**0.99**	**1.00**
SPICi	0.11	0.13	0.19	0.39	0.75	0.82
FastCommunity	**0.13**	0.15	0.22	0.31	0.41	0.52
CFinder	0.10	0.13	0.19	0.23	0.27	0.20
MGclusNCN	0.10	0.11	0.14	0.17	0.24	0.47
Cohtop	0.11	0.12	0.14	0.17	0.20	0.25
MCL	0.10	0.10	0.12	0.22	0.88	**1.00**
MINE	0.11	0.11	0.14	0.16	0.17	0.17
	inter connectivity 0.1					
intra connectivity	**0.10**	**0.20**	**0.40**	**0.60**	**0.80**	**1.00**
MGclus	0.11	**0.13**	**0.20**	**0.49**	**0.93**	**1.00**
SPICi	0.11	0.12	0.16	0.26	0.51	0.72
FastCommunity	0.12	0.13	0.17	0.23	0.29	0.39
CFinder	0.10	0.11	0.15	0.17	0.20	0.17
MGclusNCN	0.10	0.11	0.12	0.15	0.20	0.32
Cohtop	**0.12**	0.12	0.13	0.15	0.17	0.20
MCL	0.10	0.10	0.11	0.16	0.63	**1.00**
MINE	0.10	0.10	0.11	0.12	0.12	0.12
	inter connectivity 0.14					
intra connectivity	**0.10**	**0.20**	**0.40**	**0.60**	**0.80**	**1.00**
MGclus	**0.11**	**0.13**	**0.18**	**0.35**	**0.80**	**1.00**
SPICi	0.11	0.12	0.14	0.22	0.38	0.54
FastCommunity	0.11	0.12	0.14	0.19	0.24	0.30
CFinder	0.09	0.11	0.13	0.15	0.18	0.17
MGclusNCN	0.10	0.10	0.12	0.14	0.18	0.26
Cohtop	0.12	0.12	0.12	0.13	0.14	0.17
MCL	0.10	0.10	0.10	0.08	0.07	0.07
MINE	0.10	0.10	0.10	0.10	0.10	0.10

Table S2: Comparison on random clusters with fixed inter connectivity and increasing intra connectivity. The reported Jaccard similarity coefficient is the average after 30 runs, each with 15 random clusters of size 10. The best method in each column is highlighted in bold.

	intra connectivity 0.2						
inter connectivity	**0.02**	**0.04**	**0.06**	**0.08**	**0.10**	**0.12**	**0.14**
MGclus	0.21	**0.17**	**0.15**	**0.14**	0.13	**0.13**	**0.13**
SPICi	0.14	0.13	0.13	0.13	0.12	0.12	0.12
FastCommunity	**0.23**	0.17	0.15	0.14	**0.13**	0.13	0.12
CFinder	0.12	0.13	0.13	0.12	0.11	0.11	0.11
MGclusNCN	0.15	0.12	0.11	0.11	0.11	0.11	0.10
Cohtop	0.13	0.12	0.12	0.12	0.12	0.12	0.12
MCL	0.14	0.11	0.10	0.10	0.10	0.10	0.10
MINE	0.21	0.15	0.11	0.11	0.10	0.10	0.10
	intra connectivity 0.6						
inter connectivity	**0.02**	**0.04**	**0.06**	**0.08**	**0.10**	**0.12**	**0.14**
MGclus	**0.90**	**0.82**	**0.69**	**0.58**	**0.49**	**0.42**	**0.35**
SPICi	0.61	0.48	0.39	0.33	0.26	0.23	0.22
FastCommunity	0.76	0.45	0.31	0.29	0.23	0.20	0.19
CFinder	0.34	0.28	0.23	0.19	0.17	0.16	0.15
MGclusNCN	0.25	0.20	0.17	0.16	0.15	0.15	0.14
Cohtop	0.47	0.20	0.17	0.16	0.15	0.14	0.13
MCL	0.84	0.39	0.22	0.18	0.16	0.15	0.08
MINE	0.40	0.20	0.16	0.13	0.12	0.10	0.10
	intra connectivity 1.0						
inter connectivity	**0.02**	**0.04**	**0.06**	**0.08**	**0.10**	**0.12**	**0.14**
MGclus	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**
SPICi	0.88	0.86	0.82	0.77	0.72	0.62	0.54
FastCommunity	0.78	0.61	0.52	0.44	0.39	0.32	0.30
CFinder	0.50	0.25	0.20	0.18	0.17	0.17	0.17
MGclusNCN	0.81	0.61	0.47	0.37	0.32	0.28	0.26
Cohtop	0.75	0.45	0.25	0.21	0.20	0.19	0.17
MCL	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**	0.68	0.07
MINE	0.41	0.22	0.17	0.15	0.12	0.11	0.10

Table S3: Comparison on random cluster with fixed intra connectivity and increasing inter connectivity. The reported Jaccard similarity coefficient is the average after 30 runs, each with 15 random clusters of size 10. The best method in each column is highlighted in bold.

	inter connectivity 0.02					
intra connectivity	**0.10**	**0.20**	**0.40**	**0.60**	**0.80**	**1.00**
MGclus	0.14	0.21	0.47	**0.91**	**1.00**	**1.00**
SPICi	0.12	0.14	0.26	0.61	0.87	0.87
FastCommunity	**0.14**	**0.21**	**0.64**	0.76	0.80	0.79
CFinder	0.10	0.12	0.25	0.34	0.46	0.51
MGclusNCN	0.12	0.15	0.19	0.26	0.41	0.83
Cohtop	0.11	0.12	0.20	0.46	0.68	0.74
MCL	0.12	0.14	0.24	0.82	**1.00**	**1.00**
MINE	0.14	0.19	0.36	0.41	0.35	0.40
	inter connectivity 0.06					
intra connectivity	**0.10**	**0.20**	**0.40**	**0.60**	**0.80**	**1.00**
MGclus	0.11	0.15	**0.29**	**0.70**	**0.99**	**1.00**
SPICi	0.11	0.13	0.18	0.41	0.77	0.81
FastCommunity	**0.13**	**0.15**	0.23	0.33	0.41	0.51
CFinder	0.10	0.13	0.19	0.23	0.27	0.20
MGclusNCN	0.10	0.11	0.14	0.17	0.25	0.44
Cohtop	0.11	0.12	0.14	0.17	0.21	0.27
MCL	0.10	0.10	0.12	0.22	0.90	**1.00**
MINE	0.11	0.11	0.13	0.16	0.16	0.18
	inter connectivity 0.1					
intra connectivity	**0.10**	**0.20**	**0.40**	**0.60**	**0.80**	**1.00**
MGclus	0.11	0.13	**0.21**	**0.47**	**0.94**	**1.00**
SPICi	0.11	0.12	0.15	0.27	0.50	0.74
FastCommunity	0.11	**0.13**	0.17	0.24	0.29	0.38
CFinder	0.10	0.11	0.14	0.17	0.20	0.17
MGclusNCN	0.10	0.11	0.12	0.15	0.20	0.33
Cohtop	**0.12**	0.12	0.13	0.15	0.17	0.20
MCL	0.10	0.10	0.11	0.16	0.60	**1.00**
MINE	0.10	0.10	0.11	0.12	0.13	0.12
	inter connectivity 0.14					
intra connectivity	**0.10**	**0.20**	**0.40**	**0.60**	**0.80**	**1.00**
MGclus	0.11	**0.12**	**0.18**	**0.36**	**0.80**	**1.00**
SPICi	0.11	0.12	0.15	0.21	0.38	0.54
FastCommunity	0.11	0.12	0.14	0.18	0.24	0.28
CFinder	0.09	0.11	0.13	0.15	0.18	0.17
MGclusNCN	0.10	0.10	0.12	0.14	0.19	0.25
Cohtop	**0.12**	0.12	0.12	0.14	0.15	0.18
MCL	0.10	0.10	0.11	0.08	0.07	0.07
MINE	0.10	0.10	0.10	0.10	0.10	0.10

Table S4: Comparison on random clusters with fixed inter connectivity and increasing intra connectivity. The reported Jaccard similarity coefficient is the average after 30 runs, each with 30 random clusters of size 10. The best method in each column is highlighted in bold.

	intra connectivity 0.2						
inter connectivity	**0.02**	**0.04**	**0.06**	**0.08**	**0.10**	**0.12**	**0.14**
MGclus	0.21	**0.18**	0.15	**0.14**	0.13	**0.13**	**0.12**
SPICi	0.14	0.13	0.13	0.12	0.12	0.12	0.12
FastCommunity	**0.21**	0.17	**0.15**	0.13	**0.13**	0.12	0.12
CFinder	0.12	0.13	0.13	0.12	0.11	0.11	0.11
MGclusNCN	0.15	0.12	0.11	0.11	0.11	0.11	0.10
Cohtop	0.12	0.12	0.12	0.12	0.12	0.12	0.12
MCL	0.14	0.11	0.10	0.10	0.10	0.10	0.10
MINE	0.19	0.14	0.11	0.11	0.10	0.10	0.10
	intra connectivity 0.6						
inter connectivity	**0.02**	**0.04**	**0.06**	**0.08**	**0.10**	**0.12**	**0.14**
MGclus	**0.91**	**0.84**	**0.70**	**0.59**	**0.47**	**0.41**	**0.36**
SPICi	0.61	0.46	0.41	0.33	0.27	0.23	0.21
FastCommunity	0.76	0.46	0.33	0.28	0.24	0.21	0.18
CFinder	0.34	0.28	0.23	0.20	0.17	0.16	0.15
MGclusNCN	0.26	0.20	0.17	0.16	0.15	0.15	0.14
Cohtop	0.46	0.19	0.17	0.15	0.15	0.14	0.14
MCL	0.82	0.40	0.22	0.17	0.16	0.15	0.08
MINE	0.41	0.19	0.16	0.12	0.12	0.10	0.10
	intra connectivity 1.0						
inter connectivity	**0.02**	**0.04**	**0.06**	**0.08**	**0.10**	**0.12**	**0.14**
MGclus	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**
SPICi	0.87	0.85	0.81	0.74	0.74	0.64	0.54
FastCommunity	0.79	0.62	0.51	0.43	0.38	0.34	0.28
CFinder	0.51	0.25	0.20	0.18	0.17	0.17	0.17
MGclusNCN	0.83	0.65	0.44	0.36	0.33	0.28	0.25
Cohtop	0.74	0.46	0.27	0.21	0.20	0.18	0.18
MCL	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**	**0.71**	0.07
MINE	0.40	0.22	0.18	0.14	0.12	0.10	0.10

Table S5: Comparison on random cluster with fixed intra connectivity and increasing inter connectivity. The reported Jaccard similarity coefficient is the average after 30 runs, each with 30 random clusters of size 10. The best method in each column is highlighted in bold.