

# Supplementary information

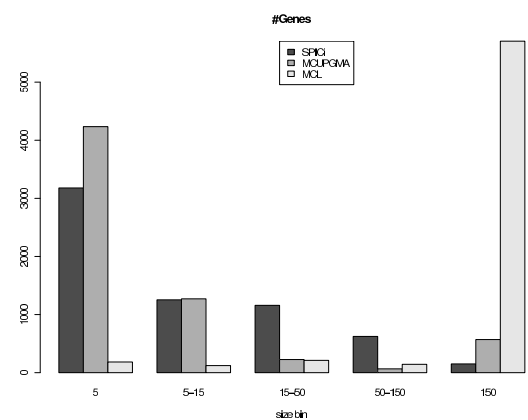
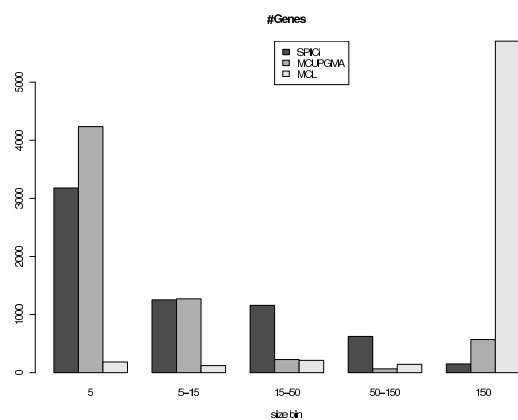
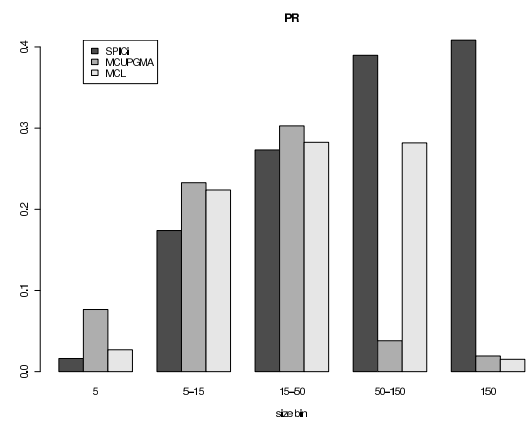
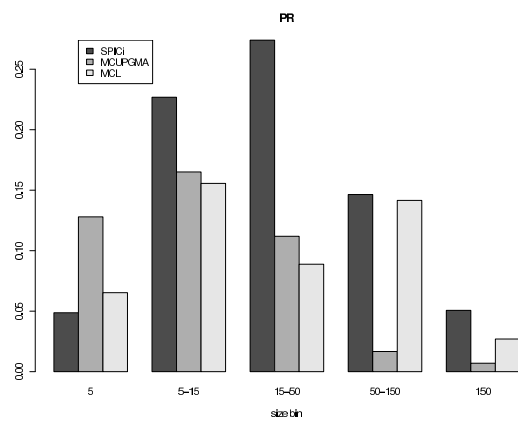
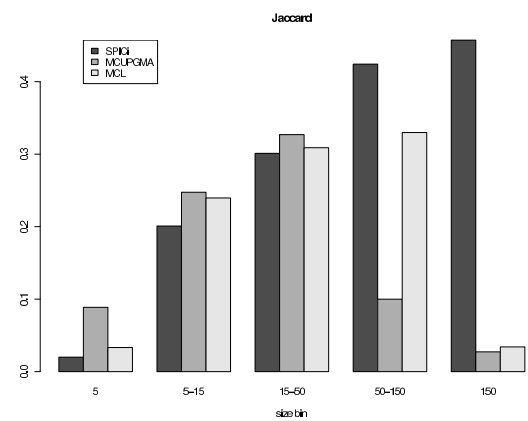
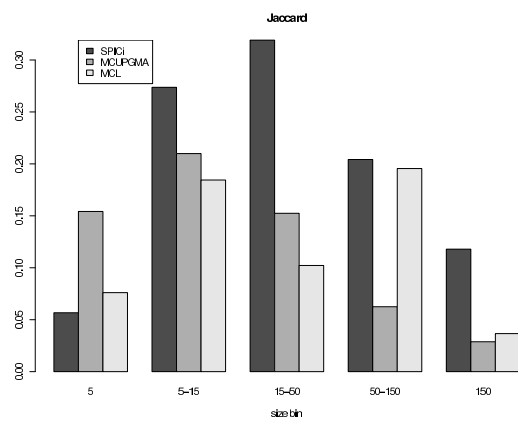
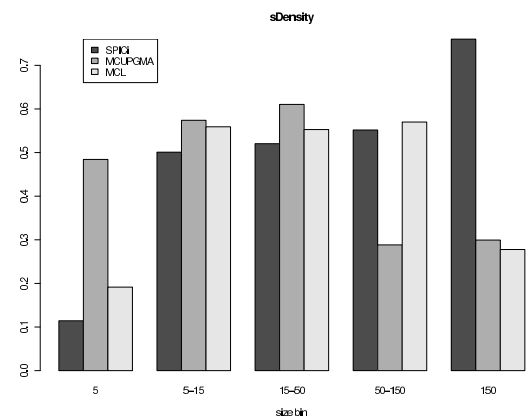
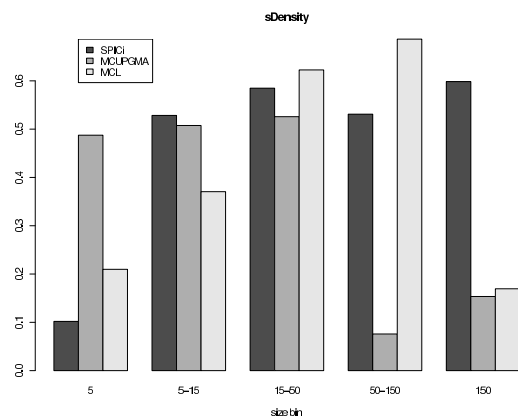
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Network	Algorithm	Biological Process			Cellular Component		
		sDensity	Jaccard	PR	sDensity	Jaccard	PR
Biogrid Yeast	SPICi	0.368	0.214	0.183	0.379	0.167	0.141
	MCUPGMA	0.414	0.200	0.160	0.444	0.147	0.115
	MCL	0.284	0.208	0.156	0.324	0.171	0.125
	Networkblast	0.441	0.207	0.166	0.442	0.210	0.177
	SPC	0.184	0.194	0.182	0.215	0.150	0.129
	MCODE	0.122	0.156	0.138	0.118	0.080	0.067
	DPClus	0.386	0.217	0.185	0.401	0.173	0.149
	RNSC	0.378	0.203	0.158	0.421	0.202	0.168
Biogrid Human	SPICi	0.254	0.183	0.159	0.271	0.097	0.078
	MCUPGMA	0.319	0.179	0.150	0.348	0.096	0.074
	MCL	0.348	0.177	0.141	0.388	0.120	0.091
	Networkblast	0.245	0.180	0.155	0.255	0.111	0.089
	SPC	0.193	0.174	0.139	0.241	0.163	0.132
	MCODE	0.060	0.171	0.165	0.071	0.074	0.068
	DPClus	0.269	0.184	0.160	0.290	0.102	0.082
	RNSC	0.288	0.128	0.093	0.339	0.111	0.076
	CFinder	0.169	0.185	0.157	0.185	0.124	0.098
STRING Yeast	SPICi	0.466	0.264	0.232	0.450	0.220	0.199
	MCUPGMA	0.579	0.235	0.206	0.584	0.187	0.172
	MCL	0.227	0.205	0.194	0.261	0.167	0.143
	Networkblast	0.477	0.224	0.182	0.447	0.191	0.158
	SPC	0.186	0.192	0.181	0.216	0.150	0.132
	MCODE	0.173	0.130	0.100	0.185	0.109	0.082
	RNSC	0.394	0.222	0.172	0.406	0.202	0.163
STRING Human	SPICi	0.316	0.210	0.180	0.331	0.123	0.103
	MCUPGMA	0.338	0.200	0.178	0.344	0.088	0.074
	MCL	0.247	0.197	0.159	0.297	0.163	0.125
	RNSC	0.312	0.172	0.124	0.357	0.115	0.078

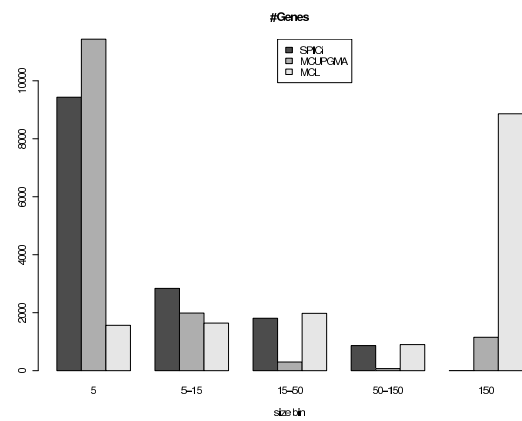
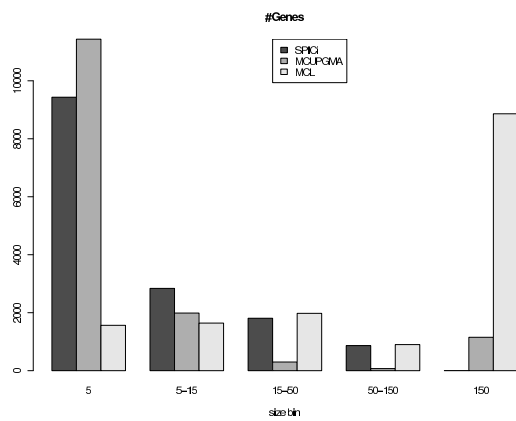
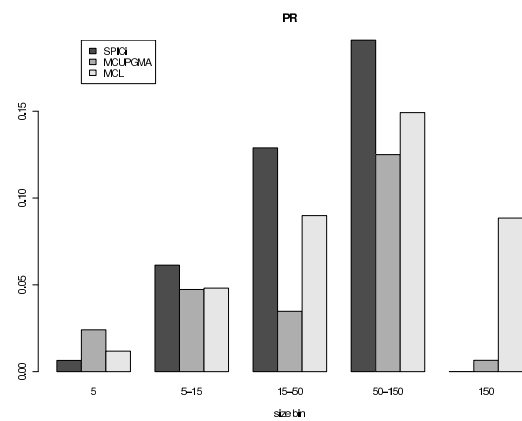
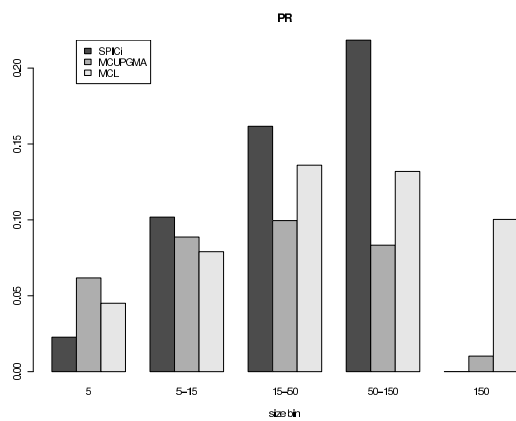
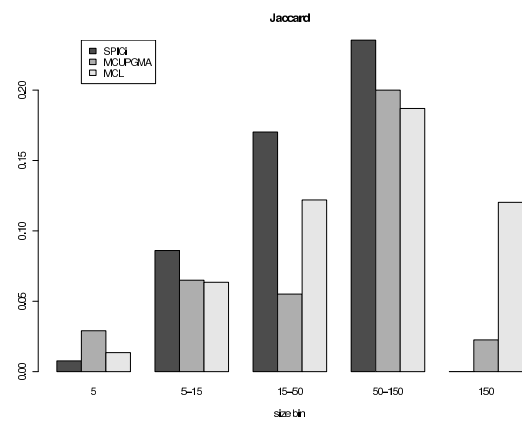
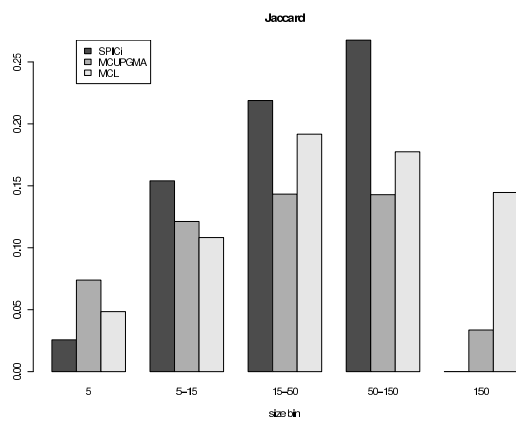
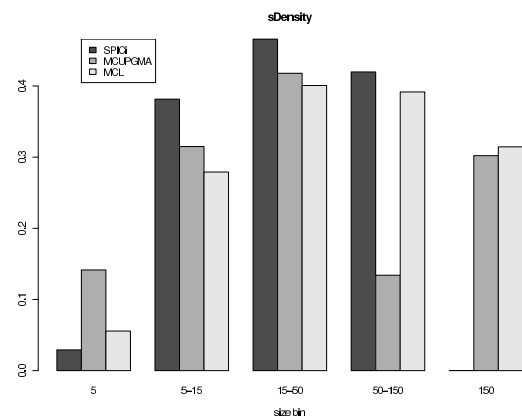
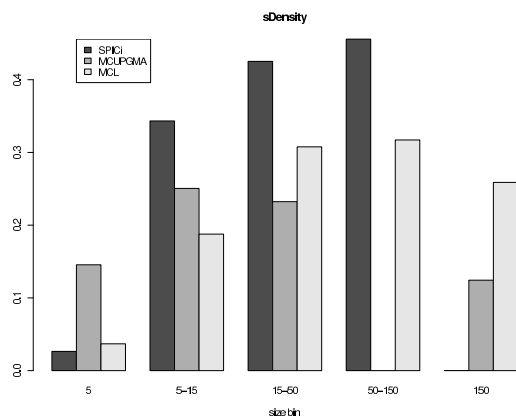
Table 1: GO analysis involving all clustering algorithms. If a method did not produce output within 12 hours on the specified network, then it is not included in the table.

## Quality of clusters as a function of size

We divide the clusters output from *SPICi*, *MCL* and *MCUPGMA* into several size categories, and use the same PR, Jaccard and semantic density measures as in our main text to judge the quality of the clusters in each category. Our categories consist of clusters of size  $\leq 5$ ; from size greater than 5 to at most 15; from size greater than 15 to at most 50; from size greater than 50 to at most 150; and finally of clusters of size larger than 150. For certain algorithm, the whole column is left blank if there is no module in the category. We consider both the String yeast and human networks. We see that on both networks, *MCUPGMA* will perform better in the small size category  $\leq 5$ , but for intermediate-sized modules, *SPICi* generally performs better. This suggests *SPICi* is better at finding intermediate-sized clusters while *MCUPGMA* is better at finding smaller clusters.



**Figure 1(a):** The String Yeast network. Biological process measures are on the left and cellular component measures are on the right. sDensity gives the average weighted semantic density values over clusters within the given size category. Jaccard gives the average weighted Jaccard values over clusters within the given size category. PR gives the average weighted PR values over clusters within the given size category. #Genes gives the number of proteins found in clusters of the given size category.



**Figure 1(b):** The String Human network. Biological process measures are on the left and cellular component measures are on the right. sDensity gives the average weighted semantic density values over clusters within the given size category. Jaccard gives the average weighted Jaccard values over clusters within the given size category. PR gives the average weighted PR values over clusters within the given size category. #Genes gives the number of proteins found in clusters of the given size category. There is no module from SPICi with more than 150 genes.

## Including all interactions is beneficial for clustering algorithms

In weighted functional networks, it is possible to prune the network by throwing out interactions below a certain weight threshold. In this case, the network will be smaller, and thus clustering it will be easier and faster. However, here we show that by using the full network, it is possible to obtain novel functionally enriched clusters that do not significantly overlap clusters in the thresholded network.

We analyze the String human network, using *SPICi*, *MCUPGMA* and *MCL*. We consider the original network, with 18,670 vertices and 1,432,538 interactions, and the thresholded network with all edges below 0.5 eliminated, leaving 15,122 vertices and 265,706 interactions. For the initial network and the pruned network, we cluster them using all three algorithms. For each algorithm, we compare the different clusters in the two networks. For each cluster found in the full network, we determine whether (1) all clusters in the thresholded network overlap at most 20% of it and (2) if at least one of its proteins is not found in any cluster in the thresholded network (singleton proteins are considered unclustered). If both of these conditions are true, then this cluster is classified as unique for the full network. We report unique clusters of size at least 10, and also report the number of such clusters that have at least one enriched functional term, at  $p\text{-value} \leq 0.05$ , as described below. Finally, we report the change in the total number of proteins found in any functionally enriched cluster in the full network vs. the thresholded network.

For each cluster, we search for enriched functions, as judged by the hypergeometric distribution, by starting from the bottom level within the GO ontology and moving up to increasingly more general terms. Since each clustering algorithm  $c$  outputs a different number of clusters  $n_c$  for the same data, and more tests are performed if there are more clusters, we set  $p = .05/n_c$  in order to compare across methods. All three GO ontologies are considered separately.

<b>SPICi</b>	
Unique clusters	36
Unique functionally enriched clusters	24
Change in number of proteins in functionally enriched clusters	+346
<b>MCUPGMA</b>	
Unique clusters	34
Unique functionally enriched clusters	5
Change in number of proteins in functionally enriched clusters	+36
<b>MCL</b>	
Unique clusters	37
Unique functionally enriched clusters	3
Change in number of proteins in functionally enriched clusters	+2527

All three methods find unique clusters in the unthresholded networks. Moreover, many of these clusters are enriched for functional terms. Below are three examples of such clusters.

	nGenes	Best Overlap	GO terms	Enrichment p-value
SPICi	16	0%	aminoacyl-tRNA ligase activity	7.12389e-19
MCUPGMA	18	0%	base-excision repair	8.21791e-22
MCL	562	7.83%	intracellular signaling cascade	1.34912e-19



## Robustness analysis on synthetic networks

In Supplementary Table 2, ten edge deletion and insertion edges are considered (from 0.0 to 0.9 in increments of 0.1). The first row of each table gives the random edge deletion rate, and the first column of each table gives the noisy edge addition rate. In (a), we give the average ratio over 10 networks of the Accuracy for our approach vs. *MCL*. In (b), we give the average ratio over 10 networks of the Separation for our approach vs. *MCL*. In (c), we give the average ratio over 10 networks of the Accuracy for our approach vs. *MCUPGMA*. In (d), we give the average ratio over 10 networks of the Separation for our approach vs. *MCUPGMA*. Numbers greater than 1.0 indicate better performance for our approach.

## Gaussian perturbations of edge weights in functional networks

For each edge in the STRING human and yeast networks, we add Gaussian noise by adjusting each weight by a number sampled from  $N(0, \sigma)$ . The adjusted weights are thresholded to be between 0 and 1. We consider how well *SPICi* can cluster the networks as we vary  $\sigma$  from 0 to 1.0. For each value of  $\sigma$ , five perturbed networks are generated, and *SPICi*'s performance is assessed by the average Jaccard, PR and semantic density measures across these networks (Supplementary Table 3). We find that *SPICi* is relatively robust to this type of perturbation. Even under a significant amount of white noise ( $\sigma = 1$ ), the performance measures are not far from the unperturbed measures. We note that our perturbation approach may remove edges by setting their weights to 0, but does not add edges and that neither of the STRING networks are complete (6,371 nodes and 311,765 edges in the yeast network, and 18,670 nodes and 1,432,538 edges in the human network). Thus very large values of  $\sigma$  result in sampling from the initial STRING networks while increasingly ignoring edge weights.

(a) Accuracy: SPICi vs. MCL

	<b>0.0</b>	<b>0.1</b>	<b>0.2</b>	<b>0.3</b>	<b>0.4</b>	<b>0.5</b>	<b>0.6</b>	<b>0.7</b>	<b>0.8</b>	<b>0.9</b>
<b>0.0</b>	1.068	1.059	1.040	1.026	1.005	0.972	0.864	0.783	0.775	0.910
<b>0.1</b>	1.057	1.046	1.032	1.018	0.998	0.961	0.849	0.779	0.801	0.940
<b>0.2</b>	1.051	1.042	1.034	1.014	0.987	0.945	0.832	0.777	0.830	0.946
<b>0.3</b>	1.041	1.030	1.022	1.002	0.986	0.934	0.829	0.788	0.846	0.952
<b>0.4</b>	1.027	1.023	1.014	0.995	0.973	0.938	0.838	0.792	0.838	0.964
<b>0.5</b>	1.022	1.013	1.013	0.990	0.968	0.937	0.852	0.795	0.863	0.986
<b>0.6</b>	1.004	1.010	1.004	0.988	0.968	0.934	0.836	0.789	0.871	0.984
<b>0.7</b>	1.015	1.006	1.003	0.986	0.972	0.946	0.841	0.803	0.895	0.993
<b>0.8</b>	1.009	1.003	1.004	0.997	0.986	0.969	0.859	0.824	0.875	0.991
<b>0.9</b>	1.002	1.004	0.998	0.998	0.990	0.961	0.873	0.821	0.894	0.998

(b) Separation: SPICi vs. MCL

	<b>0.0</b>	<b>0.1</b>	<b>0.2</b>	<b>0.3</b>	<b>0.4</b>	<b>0.5</b>	<b>0.6</b>	<b>0.7</b>	<b>0.8</b>	<b>0.9</b>
<b>0.0</b>	1.050	1.015	0.960	0.901	0.832	0.758	0.699	0.709	0.755	0.864
<b>0.1</b>	1.022	0.984	0.940	0.887	0.823	0.752	0.708	0.729	0.816	0.934
<b>0.2</b>	1.007	0.974	0.950	0.890	0.828	0.765	0.721	0.770	0.893	0.970
<b>0.3</b>	0.988	0.959	0.929	0.898	0.867	0.803	0.767	0.821	0.922	0.998
<b>0.4</b>	0.956	0.953	0.950	0.933	0.903	0.870	0.824	0.865	0.965	1.043
<b>0.5</b>	0.964	0.978	0.995	0.985	0.969	0.922	0.883	0.888	0.991	1.082
<b>0.6</b>	0.958	1.017	1.029	1.040	1.027	0.973	0.899	0.889	1.005	1.112
<b>0.7</b>	1.051	1.085	1.101	1.098	1.087	1.035	0.911	0.916	1.031	1.125
<b>0.8</b>	1.106	1.143	1.186	1.180	1.157	1.098	0.951	0.933	1.007	1.123
<b>0.9</b>	1.153	1.210	1.225	1.230	1.184	1.080	0.968	0.919	1.014	1.138

(c) Accuracy: SPICi vs. MCUPGMA

	<b>0.0</b>	<b>0.1</b>	<b>0.2</b>	<b>0.3</b>	<b>0.4</b>	<b>0.5</b>	<b>0.6</b>	<b>0.7</b>	<b>0.8</b>	<b>0.9</b>
<b>0.0</b>	1.048	1.291	1.400	1.482	1.523	1.523	1.406	1.249	1.148	1.064
<b>0.1</b>	1.111	1.302	1.422	1.522	1.569	1.580	1.436	1.304	1.184	1.088
<b>0.2</b>	1.065	1.315	1.438	1.562	1.596	1.594	1.445	1.305	1.197	1.101
<b>0.3</b>	1.079	1.324	1.473	1.568	1.639	1.615	1.466	1.314	1.197	1.083
<b>0.4</b>	1.066	1.354	1.489	1.601	1.652	1.658	1.493	1.325	1.183	1.098
<b>0.5</b>	1.078	1.355	1.511	1.629	1.667	1.674	1.522	1.322	1.202	1.103
<b>0.6</b>	1.062	1.396	1.549	1.651	1.698	1.705	1.512	1.307	1.192	1.109
<b>0.7</b>	1.086	1.405	1.565	1.657	1.722	1.721	1.516	1.345	1.199	1.095
<b>0.8</b>	1.099	1.424	1.607	1.708	1.752	1.744	1.496	1.345	1.168	1.087
<b>0.9</b>	1.085	1.465	1.615	1.694	1.741	1.719	1.517	1.327	1.179	1.090

(d) Separation: SPICi vs MCUPGMA

	<b>0.0</b>	<b>0.1</b>	<b>0.2</b>	<b>0.3</b>	<b>0.4</b>	<b>0.5</b>	<b>0.6</b>	<b>0.7</b>	<b>0.8</b>	<b>0.9</b>
<b>0.0</b>	1.078	1.342	1.422	1.440	1.388	1.302	1.193	1.118	1.056	1.016
<b>0.1</b>	1.130	1.373	1.481	1.527	1.464	1.369	1.238	1.166	1.102	1.048
<b>0.2</b>	1.114	1.438	1.543	1.582	1.529	1.403	1.232	1.141	1.091	1.040
<b>0.3</b>	1.165	1.473	1.596	1.616	1.581	1.404	1.242	1.144	1.069	1.025
<b>0.4</b>	1.162	1.511	1.600	1.661	1.599	1.460	1.262	1.152	1.065	1.031
<b>0.5</b>	1.202	1.527	1.659	1.716	1.628	1.467	1.293	1.144	1.061	1.036
<b>0.6</b>	1.172	1.606	1.696	1.719	1.638	1.498	1.278	1.111	1.049	1.026
<b>0.7</b>	1.257	1.612	1.728	1.718	1.658	1.503	1.260	1.149	1.049	1.018
<b>0.8</b>	1.293	1.640	1.784	1.777	1.688	1.545	1.254	1.127	1.016	1.007
<b>0.9</b>	1.243	1.683	1.771	1.774	1.641	1.486	1.289	1.124	1.034	0.998

Table 2: Robustness analysis comparing *SPICi*, *MCL*, *MCUPGMA* in their abilities to recapitulate MIPS complexes from synthetic networks.

(a) String Human

	Biological Process			Cellular Component		
Sigma	sDensity	Jaccard	PR	sDensity	Jaccard	PR
0.0	$0.316 \pm 0.000$	$0.210 \pm 0.000$	$0.180 \pm 0.000$	$0.331 \pm 0.000$	$0.123 \pm 0.000$	$0.103 \pm 0.000$
0.25	$0.309 \pm 0.001$	$0.206 \pm 0.002$	$0.175 \pm 0.002$	$0.324 \pm 0.005$	$0.119 \pm 0.001$	$0.096 \pm 0.001$
0.5	$0.293 \pm 0.002$	$0.198 \pm 0.002$	$0.168 \pm 0.001$	$0.312 \pm 0.002$	$0.112 \pm 0.002$	$0.089 \pm 0.002$
0.75	$0.283 \pm 0.003$	$0.192 \pm 0.001$	$0.161 \pm 0.001$	$0.310 \pm 0.002$	$0.110 \pm 0.002$	$0.086 \pm 0.001$
1.0	$0.281 \pm 0.002$	$0.189 \pm 0.002$	$0.158 \pm 0.002$	$0.308 \pm 0.004$	$0.104 \pm 0.002$	$0.080 \pm 0.002$

(b) String Yeast

	Biological Process			Cellular Component		
Sigma	sDensity	Jaccard	PR	sDensity	Jaccard	PR
0.0	$0.466 \pm 0.000$	$0.264 \pm 0.000$	$0.232 \pm 0.000$	$0.450 \pm 0.000$	$0.220 \pm 0.000$	$0.199 \pm 0.000$
0.25	$0.440 \pm 0.001$	$0.244 \pm 0.002$	$0.211 \pm 0.003$	$0.430 \pm 0.001$	$0.210 \pm 0.003$	$0.187 \pm 0.003$
0.5	$0.414 \pm 0.004$	$0.228 \pm 0.003$	$0.192 \pm 0.004$	$0.413 \pm 0.004$	$0.199 \pm 0.004$	$0.172 \pm 0.004$
0.75	$0.399 \pm 0.002$	$0.214 \pm 0.002$	$0.177 \pm 0.003$	$0.399 \pm 0.003$	$0.184 \pm 0.004$	$0.154 \pm 0.005$
1.0	$0.385 \pm 0.002$	$0.207 \pm 0.002$	$0.168 \pm 0.003$	$0.389 \pm 0.004$	$0.178 \pm 0.005$	$0.146 \pm 0.005$

Table 3: SPICi is robust against Gaussian perturbations to edge weights.