

ANALYSIS OF COOPERATIVE TF TRIADS

Shortest path length in the PIN	CTFTs	Co-functional TF triads		Co-regulatory TF triads		Co-functional $\cap$ co-regulatory TF triads		Random TF triads	
	Mean	Mean	p-value	Mean	p-value	Mean	p-value	Mean	p-value
Method N	2.212	3.000	$7.334 \cdot 10^{-3}$	3.092	$1.523 \cdot 10^{-3}$	-	-	3.159	$2.876 \cdot 10^{-4}$

Table A1.1. Shortest path length between cooperative TF triads (CTFTs) in the PIN. The shortest path length between the members of a CTFT was calculated as the average distance between the three possible pairs of TFs in the triad. The distribution of shortest path lengths between CTFTs predicted by each method was compared to the distributions in the other sets of TF triads by means of a Mann-Whitney test. The *p*-value column is shaded if the shortest path length distribution for a given method is not significantly different to that of the corresponding set (*p*-value < 0.01). The co-functional $\cap$ co-regulatory TF triads column is empty because no groups of three TFs could be made satisfying conditions of being simultaneously co-regulatory and co-functional.

Modularity in the PIN	CTFTs	Co-functional TF triads		Co-regulatory TF triads		Co-functional $\cap$ co-regulatory TF triads		Random TF triads	
	Mean	Mean	p-value	Mean	p-value	Mean	p-value	Mean	p-value
Method N	0.109	0.002	$1.769 \cdot 10^{-4}$	0.000	$3.899 \cdot 10^{-5}$	-	-	0.001	$2.200 \cdot 10^{-16}$

Table A1.2. Modularity of cooperative TF triads in the PIN. Modularity was measured as topological overlap (see *Methods* in the main text). The modularity of the members of a CTFT was calculated as the average modularity of the three possible pairs of TFs in the triad. The distribution of modularity values for the CTFTs predicted by method was compared to distributions in the other sets of TF triads by means of a Mann-Whitney test. The co-functional $\cap$ co-regulatory TF triads column is empty because no groups of three TFs could be made satisfying conditions of being simultaneously co-regulatory and co-functional. Cell shading is as in Table A1.1.

Shortest path length in the regulatory network	CTFTs	Co-functional TF triads		Co-regulatory TF triads		Co-functional $\cap$ co-regulatory TF triads		Random TF triads	
	Mean	Mean	p-value	Mean	p-value	Mean	p-value	Mean	p-value
Method N	2.500	4.667	$8.328 \cdot 10^{-3}$	3.524	$1.253 \cdot 10^{-1}$	-	-	4.293	$7.875 \cdot 10^{-3}$

Table A1.3. Shortest path length between cooperative TF triads in the regulatory network. The shortest path length between the members of a CTFT was calculated as the average distance between the three possible pairs of TFs in the triad. The distribution of shortest path lengths between the CTFTs predicted by each method was compared to distributions in the other sets of TF triads by means of a Mann-Whitney test. The co-functional $\cap$ co-regulatory TF triads column is empty because no groups of three TFs could be made satisfying conditions of being simultaneously co-regulatory and co-functional. Cell shading is as in Table A1.1.

Modularity in the regulatory network (incoming edges)	CTFTs	Co-functional TF triads		Co-regulatory TF triads		Co-functional $\cap$ co-regulatory TF triads		Random TF triads	
	Mean	Mean	p-value	Mean	p-value	Mean	p-value	Mean	p-value
Method N	0.000	0.000	1	0.000	1	-	-	0.003	$6.280 \cdot 10^{-1}$

Table A1.4. In-degree modularity of cooperative TF triads in the regulatory network. The in-degree of a gene denotes the regulatory control performed upon the expression of that gene. Modularity was measured as topological overlap (see *Methods* in the main text). The modularity of the members of a CTFT was calculated as the average modularity of the three possible pairs of TFs in the triad. The distribution of modularity values for the CTFTs predicted by each method was compared to distributions in the other sets of TF triads by means of a Mann-Whitney test. The co-functional $\cap$ co-regulatory TF triads column is empty because no groups of three TFs could be made satisfying conditions of being simultaneously co-regulatory and co-functional. Cell shading is as in Table A1.1.

Modularity in the regulatory network (outgoing edges)	CTFTs	Co-functional TF triads		Co-regulatory TF triads		Co-functional $\cap$ co-regulatory TF triads		Random TF triads	
	Mean	Mean	p-value	Mean	p-value	Mean	p-value	Mean	p-value
Method N	0.311	0.008	$2.200 \cdot 10^{-16}$	0.014	$2.200 \cdot 10^{-16}$	-	-	0.004	$2.200 \cdot 10^{-16}$

Table A1.4. Out-degree modularity of cooperative TF triads in the regulatory network. The out-degree of a gene denotes the regulatory control performed by that gene upon the expression of other genes. Modularity was measured as topological overlap (see *Methods* in the main text). The modularity of the members of a CTFT was calculated as the average modularity of the three possible pairs of TFs in the triad. The distribution of modularity values for the CTFTs predicted by each method was compared to distributions in the other sets of TF triads by means of a Mann-Whitney test. The co-functional $\cap$ co-regulatory TF triads column is empty because no groups of three TFs could be made satisfying conditions of being simultaneously co-regulatory and co-functional. Cell shading is as in Table A1.1.