BRIDGING TOPOLOGICAL AND FUNCTIONAL INFORMATION IN PROTEIN INTERACTION NETWORKS BY SHORT LOOPS PROFILING.

Sun Sook Chung[1,2†], Alessandro Pandini[2†‡], Alessia Annibale[3,4], Anthony C. C. Coolen[3,4], N Shaun B Thomas[1], Franca Fraternali[2,4*]

1 Department of Haematological Medicine, King's College London, UK, 2 Randall Division of Cell and Molecular Biophysics, King's College London, UK, 3 Department of Mathematics, King's College London, UK, 4 Institute for Mathematical and Molecular Biomedicine, King's College London, UK

[†]These two authors contributed equally to this work

Supplementary information

Table S1. Covariance correlation coefficients between the selected topological network properties and the number of loops in the networks of the dataset.

This table reports the covariance value of Pearson correlation coefficients between the number of short loops of length 3-6 and the topological properties of PPINS such as the number of proteins (NP) and interactions (NI), the average (k) and maximum degree (kmax), average betweenness (btwn), the first eigenvalue of the graph adjacent matrix (ev), the average eigenvector centrality (eve_mean), assortativity coefficient (assort), the transitivity ratio (transitivity) and the average degree-degree correlation (kk_corr). Values were calculated using R.

[‡] Current address : Department of Computer Science and Synthetic Biology Theme, Brunel University London, UK

	NP	NI	k_mean	k_max	kk_corr	ev	evc_mean	btwn	assort	transitivity
Loop3	0.139863	0.483473	0.690803	0.265776	0.554298	0.903656	0.129541	0.097707	0.616809	0.65777
Loop4	0.066541	0.462378	0.744659	0.439423	0.730637	0.893113	0.163428	0.016694	0.438406	0.496856
Loop5	0.03285	0.381672	0.645121	0.295179	0.571586	0.868958	0.115673	0.004536	0.552221	0.589696
Loop6	-0.00046	0.322492	0.622218	0.18914	0.464543	0.819226	0.14594	-0.03596	0.621109	0.65373

Table S2. The number of loops conserved after Markov Chain Graphic Dynamics (MCGD)

The number of short loops of lengths 3 and 4 of in the H. Sapiens V (BP-MS) network was compared after in 10 replicas of MCGD simulation constrained by the degree distribution and the degree-degree correlation for 10 replicas. As shown in Figure 1a-b, the number of short loops of lengths 3 and 4 decrease about to half of short loops the number in the original network after MCGD. There are common loops among the remaining loops of 10 replicas all of which exist in the original network. We called them resilient loops and reported them shown in Figure 3.

Loop length	Original # of loops	Average # of loops after graph dynamics in 10 replicas	The # of common conserved loops (ratio from the original #)
Loop 3	47270	24478.1	8342 (13.46%)
Loop 4	1628074	902051.7	219217 (17.65%)

Table S3. Comparison of network properties in the resilient loop set with the 1st cluster obtained by MCODE and by Cluster One

The set of resilient loops of lengths of 3 and 4 obtained from 10 replicas of MCGD and their merged set were compared with the 1st cluster obtained by MCODE and Cluster One. The following network properties were calculated for each set: number of nodes, number of edges, average number of neighbours, shortest paths, clustering coefficient, the number of connected components, network diameter, network radius, network centralization, characteristic path length, network density, network heterogeneity.

	Resilient loop3	**Resilient loop4**	**Resilient loops of length 3 or 4**	**MCODE 1st cluster**	**ClusterOne 1st cluster**
Number of nodes	**58**	**60**	**60**	**62**	**87**
Number of edges	**1161**	**861**	**1165**	**1650**	**2251**
Avg. number of neighbors	**40.03**	**28.7**	**38.83**	**53.23**	**51.75**

Shortest paths	**3306 (100%)**	**3540 (100%)**	**3540 (100%)**	**3782 (100%)**	**7482 (100%)**
Clustering coefficient	**0.85**	**0.82**	**0.82**	**0.91**	**0.79**
Connected components	**1**	**1**	**1**	**1**	**1**
Network diameter	**3**	**3**	**3**	**2**	**3**
Network radius	**2**	**2**	**2**	**1**	**2**
Network centralization	**0.22**	**0.36**	**0.23**	**0.13**	**0.36**
Characteristic path length	**1.31**	**1.63**	**1.37**	**1.13**	**1.40**
Network density	**0.70**	**0.49**	**0.66**	**0.87**	**0.60**
Network heterogeneity	**0.33**	**0.54**	**0.37**	**0.14**	**0.38**

Table S4. Comparison of distribution of network properties in the resilient loop set with the 1st cluster obtained by MCODE and by Cluster One

Local properties on the merged resilient loops and those of other clusters were plotted in Figure S2. The difference of their distribution was measured by Welch t-test calculated with R and annotated on the plots (Figure S2). Network Analyzer function in Cytoscape was used to obtain the network properties[60].

Resilient loops vs.	**MCODE**	**Cluster One**
Avg.ShortestPathLength	**6.65E-08**	**1.37E-1**
ClosenessCentrality	**1.36E-10**	**3.41E-2**
ClusteringCoefficient	**4.89E-4**	**1.38E-2**
BetweennessCentrality	**3.59E-4**	**1.18E-4**
Topological Coefficient	**1.45E-20**	**2.93E-09**
NeighborhoodConnectivity	**6.90E-26**	**1.13E-33**
Degree	**1.40E-09**	**8.40E-3**

Table S5. Comparison of composition of proteins in the resilient loop set with the 1st cluster obtained by MCODE and by Cluster One

Overview composition of proteins in resilient loops and other clusters are reported.

	Resilient loops of length 3 or 4	MCODE	Cluster One
Number of ribosomal proteins	45 (75%)	57 (91.94%)	77 (88.51%)
Other proteins	Table S4	elongation factors	elongation factors, heat shock proteins, ATP related proteins, nucleolin

Table S6. Description of proteins in resilient loops shown in Figure 3

In total 60 proteins were found in resilient loops (see Figure 3), conserved after MCGD and described in the main section and Table S2. All common ribosomal proteins were also detected after clustering with MCODE and Cluster One (white box). Some of the proteins were detected by one of the clustering methods (blue box) and 10 proteins are only identified in resilient loops (yellow box).

UniprotID	Method	Gene names	Protein names
DHX9_HUMAN	Resilient loops Only	DHX9 DDX9 LKP NDH2	ATP-dependent RNA helicase A (RHA) (EC 3.6.4.13) (DEAH box protein 9) (Leukophysin) (LKP) (Nuclear DNA helicase II) (NDH II)
HNRPM_HUMAN	Resilient loops Only	HNRNPM HNRPM NAGR1	Heterogeneous nuclear ribonucleoprotein M (hnRNP M)
HNRPR_HUMAN	Resilient loops Only	HNRNPR HNRPR	Heterogeneous nuclear ribonucleoprotein R (hnRNP R)
HNRPU_HUMAN	Resilient loops Only	HNRNPU HNRPU SAFA U21.1	Heterogeneous nuclear ribonucleoprotein U (hnRNP U) (Scaffold attachment factor A) (SAF-A) (p120) (pp120)
ILF2_HUMAN	Resilient loops Only	ILF2 NF45 PRO3063	Interleukin enhancer-binding factor 2 (Nuclear factor of activated T-cells 45 kDa)
NH2L1_HUMAN	Resilient loops Only	NHP2L1	NHP2-like protein 1 (High mobility group-like nuclear protein 2 homolog 1) (OTK27) (SNU13 homolog) (hSNU13) (U4/U6.U5 tri-snRNP 15.5 kDa protein) [Cleaved into: NHP2-like protein 1, N-terminally processed]
NICA_HUMAN	Resilient loops Only	NCSTN KIAA0253 UNQ1874/PRO4317	Nicastrin
PSB1_HUMAN	Resilient loops Only	PSMB1 PSC5	Proteasome subunit beta type-1 (EC 3.4.25.1) (Macropain subunit C5) (Multicatalytic endopeptidase complex subunit C5) (Proteasome component C5)

			(Proteasome gamma chain)
SAP18_HUMAN	Resilient loops Only	SAP18 GIG38	Histone deacetylase complex subunit SAP18 (18 kDa Sin3-associated polypeptide) (2HOR0202) (Cell growth-inhibiting gene 38 protein) (Sin3-associated polypeptide p18)
SF3A1_HUMAN	Resilient loops Only	SF3A1 SAP114	Splicing factor 3A subunit 1
U2AF1_HUMAN	Resilient loops Only	U2AF1 U2AF35 U2AFBP FP793	Splicing factor U2AF 35 kDa subunit (U2 auxiliary factor 35 kDa subunit) (U2 small nuclear RNA auxiliary factor 1) (U2 snRNP auxiliary factor small subunit)
U2AF2_HUMAN	Resilient loops Only	U2AF2 U2AF65	Splicing factor U2AF 65 kDa subunit (U2 auxiliary factor 65 kDa subunit) (hU2AF(65)) (hU2AF65) (U2 snRNP auxiliary factor large subunit)
EF1A1_HUMAN	Resilient loops & MCODE	EEF1A1 EEF1A EF1A LENG7	Elongation factor 1-alpha 1 (EF-1-alpha-1) (Elongation factor Tu) (EF-Tu) (Eukaryotic elongation factor 1 A-1) (eEF1A-1) (Leukocyte receptor cluster member 7)
EFTU_HUMAN	Resilient loops & Cluster One	TUFM	Elongation factor Tu, mitochondrial (EF-Tu) (P43)
ILF3_HUMAN	Resilient loops & MCODE	ILF3 DRBF MPHOSPH4 NF90	Interleukin enhancer-binding factor 3 (Double-stranded RNA-binding protein 76) (DRBP76) (M-phase phosphoprotein 4) (MPP4) (Nuclear factor associated with dsRNA) (NFAR) (Nuclear factor of activated T-cells 90 kDa) (NF-AT-90) (Translational control protein 80) (TCP80)
RL10A_HUMAN	all	RPL10A NEDD6	60S ribosomal protein L10a (CSA-19) (Neural precursor cell expressed developmentally down-regulated protein 6) (NEDD-6)
RL10L_HUMAN	all	RPL10L	60S ribosomal protein L10-like
RL11_HUMAN	all	RPL11	60S ribosomal protein L11 (CLL-associated antigen KW-12)
RL12_HUMAN	all	RPL12	60S ribosomal protein L12
RL14_HUMAN	all	RPL14	60S ribosomal protein L14 (CAG-ISL 7)
RL17_HUMAN	all	RPL17	60S ribosomal protein L17 (60S ribosomal protein L23) (PD-1)
RL18A_HUMAN	all	RPL18A	60S ribosomal protein L18a
RL18_HUMAN	all	RPL18	60S ribosomal protein L18
RL19_HUMAN	all	RPL19	60S ribosomal protein L19
RL21_HUMAN	all	RPL21	60S ribosomal protein L21
RL23A_HUMAN	all	RPL23A	60S ribosomal protein L23a
RL24_HUMAN	all	RPL24	60S ribosomal protein L24 (60S ribosomal protein L30)
RL30_HUMAN	all	RPL30	60S ribosomal protein L30
RL31_HUMAN	all	RPL31	60S ribosomal protein L31
RL37A_HUMAN	all	RPL37A	60S ribosomal protein L37a
RL4_HUMAN	all	RPL4 RPL1	60S ribosomal protein L4 (60S ribosomal protein L1)
RL5_HUMAN	all	RPL5 MSTP030	60S ribosomal protein L5
RL6_HUMAN	all	RPL6 TXREB1	60S ribosomal protein L6 (Neoplasm-related protein C140) (Tax-responsive enhancer element-binding

			protein 107) (TaxREB107)
RL7A_HUMAN	all	RPL7A SURF-3 SURF3	60S ribosomal protein L7a (PLA-X polypeptide) (Surfeit locus protein 3)
RL7_HUMAN	all	RPL7	60S ribosomal protein L7
RL8_HUMAN	all	RPL8	60S ribosomal protein L8
RL9_HUMAN	all	RPL9 OK/SW-cl.103; RPL9P7; RPL9P8; RPL9P9	60S ribosomal protein L9
RLA0L_HUMAN	all	RPLP0P6	60S acidic ribosomal protein P0-like
RLA0_HUMAN	all	RPLP0	60S acidic ribosomal protein P0 (60S ribosomal protein L10E)
RS11_HUMAN	all	RPS11	40S ribosomal protein S11
RS13_HUMAN	all	RPS13	40S ribosomal protein S13
RS14_HUMAN	all	RPS14 PRO2640	40S ribosomal protein S14
RS15A_HUMAN	all	RPS15A OK/SW-cl.82	40S ribosomal protein S15a
RS16_HUMAN	all	RPS16	40S ribosomal protein S16
RS19_HUMAN	all	RPS19	40S ribosomal protein S19
RS21_HUMAN	all	RPS21	40S ribosomal protein S21
RS23_HUMAN	all	RPS23	40S ribosomal protein S23
RS24_HUMAN	all	RPS24	40S ribosomal protein S24
RS25_HUMAN	all	RPS25	40S ribosomal protein S25
RS26_HUMAN	all	RPS26	40S ribosomal protein S26
RS28_HUMAN	all	RPS28	40S ribosomal protein S28
RS2_HUMAN	all	RPS2 RPS4	40S ribosomal protein S2 (40S ribosomal protein S4) (Protein LLRep3)
RS3A_HUMAN	all	RPS3A FTE1 MFTL	40S ribosomal protein S3a (v-fos transformation effector protein) (Fte-1)
RS3_HUMAN	all	RPS3 OK/SW-cl.26	40S ribosomal protein S3
RS4X_HUMAN	all	RPS4X CCG2 RPS4 SCAR	40S ribosomal protein S4, X isoform (SCR10) (Single copy abundant mRNA protein)
RS5_HUMAN	all	RPS5	40S ribosomal protein S5 [Cleaved into: 40S ribosomal protein S5, N-terminally processed]
RS6_HUMAN	all	RPS6 OK/SW-cl.2	40S ribosomal protein S6 (Phosphoprotein NP33)
RS7_HUMAN	all	RPS7	40S ribosomal protein S7
RS8_HUMAN	all	RPS8 OK/SW-cl.83	40S ribosomal protein S8
RSSA_HUMAN	all	RPSA LAMBR LAMR1	40S ribosomal protein SA (37 kDa laminin receptor precursor) (37LRP) (37/67 kDa laminin receptor) (LRP/LR) (67 kDa laminin receptor) (67LR) (Colon carcinoma laminin-binding protein) (Laminin receptor 1) (LamR) (Laminin-binding protein precursor p40) (LBP/p40) (Multidrug resistance-associated protein MGr1-Ag) (NEM/1CHD4)

Table S7. Enrichment of Gene Ontology (GO) terms in short loops

The plots from (Figure 6a and 6b) report the relative frequency (in %) of GO terms in the network and loops of length 3, 4 and 5: (a) H. Sapiens V (BP-MS) and (b) H. Sapiens V (BP-MS) without the largest ribosomal complex. The values for each GO term are coloured according to their trend: higher frequencies in the loops than in the network (Trend 1 in red and Trend 4 in purple); higher frequency in the network (Trend 2 in blue and Trend 5 in orange) and lower frequencies in the loops with a consistent value independent by the loop length (Trend 3 in green). The tables list specific terms found in each Trends : (a) Trend 1, (b) Trend 2, (c) Trend 3, (d) Trend 4 and (e) Trend 5.

(a) Trend 1

GOID	Network	Loop3	Loop4	Loop5	Term
GO:0000184	2.74	42.9	44.4	40.85	nuclear-transcribed mRNA catabolic process, nonsense-mediated decay
GO:0006415	2.78	42.92	44.42	40.86	translational termination
GO:0043624	3.04	43.38	45.04	41.59	cellular protein complex disassembly
GO:0072599	3.08	42.92	44.42	40.87	establishment of protein localization to endoplasmic reticulum
GO:0006614	3.08	42.92	44.42	40.87	SRP-dependent cotranslational protein targeting to membrane
GO:0006414	3.12	43.37	45.03	41.58	translational elongation
GO:0043241	3.12	43.38	45.04	41.59	protein complex disassembly
GO:0006613	3.12	43.38	45.05	41.6	cotranslational protein targeting to membrane
GO:0045047	3.12	43.38	45.05	41.6	protein targeting to ER
GO:0070972	3.16	42.92	44.42	40.87	protein localization to endoplasmic reticulum
GO:0090150	3.46	43.01	44.53	40.99	establishment of protein localization to membrane
GO:0006612	3.61	43.38	45.06	41.61	protein targeting to membrane
GO:0072657	3.77	43.01	44.53	40.99	protein localization to membrane
GO:0032984	3.77	43.52	45.06	41.6	macromolecular complex disassembly
GO:0072594	3.8	43.01	44.53	40.99	establishment of protein localization to organelle
GO:0019083	3.84	42.97	44.41	40.85	viral transcription
GO:0019080	3.96	43.43	45.03	41.58	viral gene expression
GO:0006413	3.96	43.88	45.16	41.63	translational initiation
GO:0000956	4.3	43.45	45.05	41.6	nuclear-transcribed mRNA catabolic process
GO:0006402	4.45	43.45	45.05	41.6	mRNA catabolic process
GO:0019058	4.79	45.3	47.66	44.66	viral life cycle
GO:0006401	4.83	43.45	45.05	41.6	RNA catabolic process
GO:0022411	5.1	43.52	45.06	41.6	cellular component disassembly
GO:0061024	5.9	43.1	44.56	41.02	membrane organization

GO:0033365	6.12	43.62	45.35	41.95	protein localization to organelle
GO:1901361	6.85	44.79	47.06	43.96	organic cyclic compound catabolic process
GO:0006605	6.92	44.01	45.85	42.54	protein targeting
GO:0046700	7.07	44.8	47.06	43.96	heterocycle catabolic process
GO:0044270	7.53	45.27	47.7	44.72	cellular nitrogen compound catabolic process
GO:0070727	7.76	43.09	44.57	41.03	cellular macromolecule localization
GO:0034655	8.29	45.36	47.71	44.72	nucleobase-containing compound catabolic process
GO:0044265	8.67	54.75	52.47	45.96	cellular macromolecule catabolic process
GO:0019439	8.75	45.37	47.71	44.72	aromatic compound catabolic process
GO:0006412	9.01	52.24	56.25	54.79	translation
GO:0006886	9.32	44.09	45.89	42.57	intracellular protein transport
GO:0016482	9.62	44.13	45.97	42.67	cytoplasmic transport
GO:1901362	10.08	44.07	45.98	42.68	organic cyclic compound biosynthetic process
GO:0071822	10.31	43.44	45	41.54	protein complex subunit organization
GO:0034613	10.54	43.74	45.4	42	cellular protein localization
GO:0016032	11.11	56.6	55	48.95	viral process
GO:0051649	11.6	43.77	45.4	41.99	establishment of localization in cell
GO:0044764	11.72	55.31	53.23	46.84	multi-organism cellular process
GO:0009057	12.1	55.03	52.54	46	macromolecule catabolic process
GO:1901575	12.1	55.97	54.27	48.07	organic substance catabolic process
GO:0071702	12.21	43.45	44.83	41.32	organic substance transport
GO:0044419	12.21	55.36	53.23	46.85	interspecies interaction between organisms
GO:0045184	12.25	43.92	45.43	42.02	establishment of protein localization
GO:0044403	12.36	57.68	56.49	50.71	symbiosis, encompassing mutualism through parasitism
GO:0044271	12.55	45.01	47.27	44.2	cellular nitrogen compound biosynthetic process
GO:0046907	12.63	44.35	46.04	42.73	intracellular transport
GO:0016071	13.24	60.19	57.81	51.69	mRNA metabolic process
GO:0015031	13.35	43.91	45.43	42.03	protein transport
GO:0051641	14	44.38	46.22	42.96	cellular localization
GO:0051704	14.34	55.57	53.52	47.18	multi-organism process
GO:0044248	14.42	56.75	55.2	49.14	cellular catabolic process
GO:0043933	14.45	45.1	46.55	43.24	macromolecular complex subunit organization
GO:0032774	15.6	46.12	47.88	44.81	RNA biosynthetic process
GO:0034654	16.39	45.66	47.81	44.81	nucleobase-containing compound biosynthetic process
GO:0044765	17.46	44.22	45.61	42.21	single-organism transport
GO:0008104	18.49	44.52	46.08	42.77	protein localization
GO:0009056	19.32	56.95	55.23	49.15	catabolic process
GO:0019438	19.36	46.31	47.92	44.83	aromatic compound biosynthetic process
GO:0033036	19.44	44.41	45.81	42.44	macromolecule localization

GO:1901576	19.44	47.75	49.96	47.24	organic substance biosynthetic process
GO:0051234	20.27	44.82	46.33	43.05	establishment of localization
GO:0018130	20.39	46.41	47.94	44.84	heterocycle biosynthetic process
GO:0044267	22.06	58.9	56.47	50.4	cellular protein metabolic process
GO:0034645	23.24	52.27	55.62	53.98	cellular macromolecule biosynthetic process
GO:0044249	24.27	52.14	55.88	54.36	cellular biosynthetic process
GO:0051179	25.83	45.12	46.55	43.3	localization
GO:0006810	26.7	46.35	48.22	45.24	transport
GO:0090304	26.85	63.5	62.2	56.99	nucleic acid metabolic process
GO:0016070	28.95	65.5	63.01	57.48	RNA metabolic process
GO:0071840	29.02	51.6	54.55	52.65	cellular component organization or biogenesis
GO:0019538	29.44	64.29	63.32	58.53	protein metabolic process
GO:0009059	31.19	59.24	64.15	64.36	macromolecule biosynthetic process
GO:1901360	32.26	64.36	63.47	58.53	organic cyclic compound metabolic process
GO:0046483	32.6	65.05	64.26	59.46	heterocycle metabolic process
GO:0010467	35.83	74.8	74.58	71.4	gene expression
GO:0016043	36.4	47.24	47.71	44.39	cellular component organization
GO:0009058	37.28	59.72	64.71	65.04	biosynthetic process
GO:0034641	38.04	68.14	66.99	62.36	cellular nitrogen compound metabolic process
GO:0044260	41.54	70.11	69.12	65.07	cellular macromolecule metabolic process
GO:0006139	45.91	75.82	75.57	72.29	nucleobase-containing compound metabolic process
GO:0006725	46.18	75.28	75.13	71.91	cellular aromatic compound metabolic process
GO:0043170	47.93	72.84	71.46	67.5	macromolecule metabolic process
GO:0006807	47.97	75.88	75.73	72.54	nitrogen compound metabolic process
GO:0071704	53.14	69.99	68.32	63.88	organic substance metabolic process
GO:0044238	53.67	73.26	72.66	69.19	primary metabolic process
GO:0044237	55.65	73.88	72.84	69.27	cellular metabolic process

(b) Trend 2

GOID	Network	Loop3	Loop4	Loop5	Term
GO:0009653	10.46	0.07	0	0	anatomical structure morphogenesis
GO:0006259	10.46	0.25	0.01	0	DNA metabolic process
GO:0006366	10.99	0.96	0.12	0.01	transcription from RNA polymerase II promoter
GO:0070887	11.18	0.08	0	0	cellular response to chemical stimulus
GO:0065008	11.22	0.18	0.01	0	regulation of biological quality
GO:0007166	11.56	0.19	0.01	0	cell surface receptor signaling pathway
GO:0048731	12.74	0.38	0.07	0.01	system development
GO:0006396	12.82	5.87	2.16	0.74	RNA processing
GO:0030154	13.2	0.09	0	0	cell differentiation
GO:0019219	13.28	0.34	0.02	0	regulation of nucleobase-containing compound metabolic process

GO:0006355	13.58	0.84	0.12	0.01	regulation of transcription, DNA-templated
GO:0010033	13.81	0.13	0.01	0	response to organic substance
GO:0022607	14.57	0.89	0.13	0.02	cellular component assembly
GO:0010556	15.1	0.83	0.12	0.02	regulation of macromolecule biosynthetic process
GO:0044085	15.1	3.27	1.02	0.3	cellular component biogenesis
GO:0006796	16.09	0.32	0.03	0	phosphate-containing compound metabolic process
GO:0042221	16.58	0.19	0.01	0	response to chemical
GO:0044767	16.62	0.16	0.01	0	single-organism developmental process
GO:0006793	16.74	0.33	0.04	0	phosphorus metabolic process
GO:0048856	17	0.46	0.07	0.01	anatomical structure development
GO:0010468	17.84	1.38	0.2	0.03	regulation of gene expression
GO:0009889	18.87	1.56	0.24	0.03	regulation of biosynthetic process
GO:0006351	19.89	1.73	0.26	0.03	transcription, DNA-templated
GO:0007275	20.81	0.51	0.07	0.01	multicellular organismal development
GO:0032502	23.2	0.54	0.08	0.01	developmental process
GO:0006996	24.08	1.34	0.16	0.02	organelle organization
GO:0044707	24.31	0.69	0.09	0.01	single-multicellular organism process
GO:0032501	26.89	0.8	0.1	0.01	multicellular organismal process

(c) Trend 3

GOID	Network	Loop3	Loop4	Loop5	Term
GO:0006521	1.52	11.01	7.09	4	regulation of cellular amino acid metabolic process
GO:0051436	1.56	10.22	6.41	3.52	negative regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle
GO:0072413	1.56	11.01	7.09	4	signal transduction involved in mitotic cell cycle checkpoint
GO:0072422	1.56	11.01	7.09	4	signal transduction involved in DNA damage checkpoint
GO:0072401	1.56	11.01	7.09	4	signal transduction involved in DNA integrity checkpoint
GO:0006977	1.56	11.01	7.09	4	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest
GO:0031571	1.56	11.01	7.09	4	mitotic G1 DNA damage checkpoint
GO:0072395	1.56	11.01	7.09	4	signal transduction involved in cell cycle checkpoint
GO:0072431	1.56	11.01	7.09	4	signal transduction involved in mitotic G1 DNA damage checkpoint
GO:0051444	1.6	10.22	6.41	3.52	negative regulation of ubiquitin-protein transferase activity
GO:0051352	1.6	10.22	6.41	3.52	negative regulation of ligase activity
GO:2000134	1.6	11.01	7.09	4	negative regulation of G1/S transition of mitotic cell cycle

GO:0051437	1.6	11.01	7.09	4	positive regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle
GO:0071158	1.6	11.01	7.09	4	positive regulation of cell cycle arrest
GO:0051439	1.64	11.01	7.09	4	regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle
GO:0033238	1.64	11.01	7.09	4	regulation of cellular amine metabolic process
GO:0044783	1.64	11.01	7.09	4	G1 DNA damage checkpoint
GO:0051443	1.67	11.01	7.09	4	positive regulation of ubiquitin-protein transferase activity
GO:0044773	1.71	11.01	7.09	4	mitotic DNA damage checkpoint
GO:2000045	1.71	11.01	7.09	4	regulation of G1/S transition of mitotic cell cycle
GO:0002479	1.71	11.01	7.09	4	antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent
GO:0051438	1.71	11.01	7.09	4	regulation of ubiquitin-protein transferase activity
GO:0042590	1.71	11.01	7.09	4	antigen processing and presentation of exogenous peptide antigen via MHC class I
GO:0044774	1.75	11.01	7.09	4	mitotic DNA integrity checkpoint
GO:0051340	1.79	11.01	7.09	4	regulation of ligase activity
GO:0071156	1.79	11.01	7.09	4	regulation of cell cycle arrest
GO:0051351	1.79	11.01	7.09	4	positive regulation of ligase activity
GO:0042180	1.9	11.01	7.09	4	cellular ketone metabolic process
GO:0010565	1.9	11.01	7.09	4	regulation of cellular ketone metabolic process
GO:0044106	1.9	11.01	7.09	4	cellular amine metabolic process
GO:0090068	1.98	11.01	7.09	4	positive regulation of cell cycle process
GO:0009308	1.98	11.01	7.09	4	amine metabolic process
GO:0031145	1.98	11.05	7.1	4	anaphase-promoting complex-dependent proteasomal ubiquitin-dependent protein catabolic process
GO:1901991	2.02	11.01	7.09	4	negative regulation of mitotic cell cycle phase transition
GO:0031398	2.02	11.05	7.1	4	positive regulation of protein ubiquitination
GO:0051248	2.05	10.22	6.41	3.52	negative regulation of protein metabolic process
GO:0030330	2.05	11.01	7.09	4	DNA damage response, signal transduction by p53 class mediator
GO:0042770	2.05	11.01	7.09	4	signal transduction in response to DNA damage
GO:0031397	2.09	10.26	6.42	3.52	negative regulation of protein ubiquitination
GO:0002474	2.09	11.03	7.11	4.01	antigen processing and presentation of peptide antigen via MHC class I
GO:0072331	2.17	11.01	7.09	4	signal transduction by p53 class mediator
GO:1901990	2.4	11.01	7.09	4	regulation of mitotic cell cycle phase transition
GO:0000077	2.47	11.01	7.09	4	DNA damage checkpoint
GO:0031400	2.55	10.26	6.42	3.52	negative regulation of protein modification process

GO:0031570	2.55	11.01	7.09	4	DNA integrity checkpoint
GO:0031396	2.59	11.05	7.1	4	regulation of protein ubiquitination
GO:0007050	2.62	11.01	7.09	4	cell cycle arrest
GO:0007093	2.62	11.16	7.11	4	mitotic cell cycle checkpoint
GO:1901988	2.7	11.01	7.09	4	negative regulation of cell cycle phase transition
GO:0032269	2.93	10.26	6.42	3.52	negative regulation of cellular protein metabolic process
GO:0043161	3	11.1	7.14	4.03	proteasome-mediated ubiquitin-dependent protein catabolic process
GO:0000209	3.04	11.21	7.12	4.01	protein polyubiquitination
GO:0002478	3.04	11.07	7.12	4.02	antigen processing and presentation of exogenous peptide antigen
GO:1901987	3.08	11.01	7.09	4	regulation of cell cycle phase transition
GO:0043086	3.12	10.26	6.42	3.52	negative regulation of catalytic activity
GO:0051247	3.12	11.02	7.09	4	positive regulation of protein metabolic process
GO:0048002	3.12	11.07	7.12	4.02	antigen processing and presentation of peptide antigen
GO:0019884	3.12	11.07	7.12	4.02	antigen processing and presentation of exogenous antigen
GO:0051329	3.27	10.27	6.41	3.52	mitotic interphase
GO:0051325	3.27	10.27	6.41	3.52	interphase
GO:0045786	3.27	11.01	7.09	4	negative regulation of cell cycle
GO:0019882	3.39	11.07	7.12	4.02	antigen processing and presentation
GO:0060548	3.5	11.01	7.09	4	negative regulation of cell death
GO:0000082	3.61	10.28	6.42	3.53	G1/S transition of mitotic cell cycle
GO:0022403	3.69	10.28	6.41	3.52	cell cycle phase
GO:0044092	3.73	10.26	6.42	3.52	negative regulation of molecular function
GO:0000075	3.77	11.16	7.11	4	cell cycle checkpoint
GO:0010498	3.8	11.26	7.19	4.06	proteasomal protein catabolic process
GO:0043066	3.96	11.01	7.09	4	negative regulation of apoptotic process
GO:0010948	4.07	11.05	7.1	4	negative regulation of cell cycle process
GO:0031401	4.22	11.06	7.1	4.01	positive regulation of protein modification process
GO:0044257	4.26	11.18	7.18	4.06	cellular protein catabolic process
GO:0007346	4.3	11.16	7.11	4	regulation of mitotic cell cycle
GO:0043069	4.37	11.02	7.09	4	negative regulation of programmed cell death
GO:0032270	4.53	11.05	7.1	4	positive regulation of cellular protein metabolic process
GO:0016567	4.56	11.24	7.13	4.01	protein ubiquitination
GO:0043632	4.68	11.19	7.18	4.06	modification-dependent macromolecule catabolic process
GO:0032446	4.72	11.25	7.13	4.01	protein modification by small protein conjugation
GO:0070647	4.79	11.15	7.11	4.01	protein modification by small protein conjugation or removal

GO:0006511	4.83	11.24	7.16	4.04	ubiquitin-dependent protein catabolic process
GO:0043085	4.91	11.06	7.1	4	positive regulation of catalytic activity
GO:0006520	5.02	11.43	7.17	4.02	cellular amino acid metabolic process
GO:0051246	5.17	11.38	7.16	4.01	regulation of protein metabolic process
GO:0010564	5.48	11.05	7.1	4	regulation of cell cycle process
GO:0044093	5.63	11.06	7.1	4	positive regulation of molecular function
GO:0031399	5.67	11.07	7.11	4.01	regulation of protein modification process
GO:0030163	5.67	11.21	7.19	4.07	protein catabolic process
GO:0019941	5.71	11.35	7.21	4.07	modification-dependent protein catabolic process
GO:0031324	5.74	10.29	6.42	3.52	negative regulation of cellular metabolic process
GO:0051603	5.82	11.35	7.21	4.07	proteolysis involved in cellular protein catabolic process
GO:0050790	5.86	11.02	7.1	4	regulation of catalytic activity
GO:0044772	5.97	10.47	6.46	3.54	mitotic cell cycle phase transition
GO:0051171	6.28	11.05	7.1	4.01	regulation of nitrogen compound metabolic process
GO:0044770	6.5	10.47	6.46	3.54	cell cycle phase transition
GO:0043436	6.54	11.19	7.12	4.01	oxoacid metabolic process
GO:0019752	6.62	11.34	7.15	4.01	carboxylic acid metabolic process
GO:0065009	6.73	11.03	7.1	4.01	regulation of molecular function
GO:0043067	6.92	11.04	7.1	4	regulation of programmed cell death
GO:0042981	7.19	11.04	7.1	4	regulation of apoptotic process
GO:0006082	7.65	11.46	7.18	4.02	organic acid metabolic process
GO:0006508	7.68	11.35	7.21	4.07	proteolysis
GO:0031325	7.84	11.06	7.1	4.01	positive regulation of cellular metabolic process
GO:0032268	7.91	11.64	7.28	4.08	regulation of cellular protein metabolic process
GO:0080090	7.95	11.05	7.11	4.01	regulation of primary metabolic process
GO:0051726	8.06	11.19	7.12	4.01	regulation of cell cycle
GO:0010941	8.1	11.05	7.1	4	regulation of cell death
GO:0010605	8.44	10.46	6.44	3.53	negative regulation of macromolecule metabolic process
GO:1901564	9.17	11.14	7.12	4.01	organonitrogen compound metabolic process
GO:0006974	9.21	11.19	7.14	4.03	cellular response to DNA damage stimulus
GO:0009892	10.31	10.53	6.45	3.53	negative regulation of metabolic process
GO:0010604	11.11	11.33	7.13	4.01	positive regulation of macromolecule metabolic process
GO:0035556	11.22	11.05	7.1	4.01	intracellular signal transduction
GO:0006915	11.37	11.1	7.12	4.02	apoptotic process
GO:0012501	11.45	11.09	7.12	4.02	programmed cell death
GO:0048522	11.49	11.12	7.1	4	positive regulation of cellular process
GO:0060255	11.49	11.49	7.18	4.02	regulation of macromolecule metabolic process
GO:0000278	11.72	11.41	7.18	4.04	mitotic cell cycle

GO:0022402	12.06	11.41	7.17	4.03	cell cycle process
GO:0048523	12.21	11.14	7.11	4.01	negative regulation of cellular process
GO:0016265	12.59	11.09	7.12	4.02	death
GO:0033554	12.86	11.22	7.16	4.04	cellular response to stress
GO:0008219	13.01	11.1	7.12	4.02	cell death
GO:0043412	13.2	11.51	7.19	4.04	macromolecule modification
GO:0009893	13.43	11.5	7.15	4.01	positive regulation of metabolic process
GO:0036211	13.43	11.52	7.19	4.04	protein modification process
GO:0002376	13.62	11.35	7.15	4.03	immune system process
GO:0048519	13.96	11.15	7.11	4.01	negative regulation of biological process
GO:0048518	14.19	11.25	7.12	4.01	positive regulation of biological process
GO:0007049	16.7	11.49	7.18	4.04	cell cycle
GO:0044281	16.77	11.51	7.17	4.02	small molecule metabolic process
GO:0006464	17.15	11.66	7.22	4.05	cellular protein modification process
GO:0044700	18.79	11.37	7.17	4.05	single organism signaling
GO:0031323	19.09	12.07	7.33	4.1	regulation of cellular metabolic process
GO:0044710	19.13	11.58	7.19	4.03	single-organism metabolic process
GO:0023052	21.83	11.51	7.19	4.05	signaling
GO:0007165	22.37	11.44	7.15	4.02	signal transduction
GO:0051716	22.56	11.6	7.21	4.06	cellular response to stimulus
GO:0006950	23.47	11.57	7.2	4.06	response to stress
GO:0019222	24.76	12.77	7.47	4.12	regulation of metabolic process
GO:0007154	25.48	11.57	7.2	4.05	cell communication
GO:0050794	29.9	12.7	7.38	4.06	regulation of cellular process
GO:0050896	33.7	12.16	7.33	4.11	response to stimulus
GO:0050789	35.18	13.52	7.66	4.16	regulation of biological process
GO:0065007	35.34	13.74	7.72	4.17	biological regulation

(d) Trend 4

GOID	Network	Loop3	Loop4	Loop5	Term
GO:0051436	1.56	34.72	47	54.74	negative regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle
GO:0051329	3.27	34.89	47.01	54.74	mitotic interphase
GO:0051325	3.27	34.89	47.01	54.74	interphase
GO:0022403	3.69	34.9	47.01	54.74	cell cycle phase
GO:0051444	1.6	34.73	47.01	54.76	negative regulation of ubiquitin-protein transferase activity
GO:0051352	1.6	34.73	47.01	54.76	negative regulation of ligase activity
GO:0051248	2.05	34.73	47.01	54.76	negative regulation of protein metabolic process
GO:0031397	2.09	34.84	47.02	54.76	negative regulation of protein ubiquitination
GO:0031400	2.55	34.84	47.02	54.76	negative regulation of protein modification process

GO:0032269	2.93	34.84	47.02	54.76	negative regulation of cellular protein metabolic process
GO:0043086	3.12	34.84	47.02	54.76	negative regulation of catalytic activity
GO:0044092	3.73	34.84	47.02	54.76	negative regulation of molecular function
GO:0031324	5.74	34.91	47.06	54.81	negative regulation of cellular metabolic process
GO:0000082	3.61	34.93	47.1	54.87	G1/S transition of mitotic cell cycle
GO:0010605	8.44	35.44	47.23	54.9	negative regulation of macromolecule metabolic process
GO:0009892	10.31	35.56	47.24	54.9	negative regulation of metabolic process
GO:0044772	5.97	35.55	47.33	55.03	mitotic cell cycle phase transition
GO:0044770	6.5	35.55	47.33	55.03	cell cycle phase transition
GO:0006521	1.52	37.4	51.98	62.24	regulation of cellular amino acid metabolic process
GO:0072413	1.56	37.4	51.98	62.24	signal transduction involved in mitotic cell cycle checkpoint
GO:0072422	1.56	37.4	51.98	62.24	signal transduction involved in DNA damage checkpoint
GO:0072401	1.56	37.4	51.98	62.24	signal transduction involved in DNA integrity checkpoint
GO:0006977	1.56	37.4	51.98	62.24	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest
GO:0031571	1.56	37.4	51.98	62.24	mitotic G1 DNA damage checkpoint
GO:0072395	1.56	37.4	51.98	62.24	signal transduction involved in cell cycle checkpoint
GO:0072431	1.56	37.4	51.98	62.24	signal transduction involved in mitotic G1 DNA damage checkpoint
GO:2000134	1.6	37.4	51.98	62.24	negative regulation of G1/S transition of mitotic cell cycle
GO:0051437	1.6	37.4	51.98	62.24	positive regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle
GO:0071158	1.6	37.4	51.98	62.24	positive regulation of cell cycle arrest
GO:0033238	1.64	37.4	51.98	62.24	regulation of cellular amine metabolic process
GO:0044783	1.64	37.4	51.98	62.24	G1 DNA damage checkpoint
GO:0044773	1.71	37.4	51.98	62.24	mitotic DNA damage checkpoint
GO:2000045	1.71	37.4	51.98	62.24	regulation of G1/S transition of mitotic cell cycle
GO:0002479	1.71	37.4	51.98	62.24	antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent
GO:0042590	1.71	37.4	51.98	62.24	antigen processing and presentation of exogenous peptide antigen via MHC class I
GO:0044774	1.75	37.4	51.98	62.24	mitotic DNA integrity checkpoint
GO:0071156	1.79	37.4	51.98	62.24	regulation of cell cycle arrest
GO:0042180	1.9	37.4	51.98	62.24	cellular ketone metabolic process
GO:0010565	1.9	37.4	51.98	62.24	regulation of cellular ketone metabolic process
GO:0044106	1.9	37.4	51.98	62.24	cellular amine metabolic process
GO:0009308	1.98	37.4	51.98	62.24	amine metabolic process

GO:0030330	2.05	37.4	51.98	62.24	DNA damage response, signal transduction by p53 class mediator
GO:0042770	2.05	37.4	51.98	62.24	signal transduction in response to DNA damage
GO:0072331	2.17	37.4	51.98	62.24	signal transduction by p53 class mediator
GO:0000077	2.47	37.4	51.98	62.24	DNA damage checkpoint
GO:0031570	2.55	37.4	51.98	62.24	DNA integrity checkpoint
GO:0007050	2.62	37.4	51.98	62.24	cell cycle arrest
GO:0060548	3.5	37.41	51.98	62.24	negative regulation of cell death
GO:0043066	3.96	37.41	51.98	62.24	negative regulation of apoptotic process
GO:0043069	4.37	37.41	51.98	62.24	negative regulation of programmed cell death
GO:0051439	1.64	37.41	52	62.26	regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle
GO:0051443	1.67	37.41	52	62.26	positive regulation of ubiquitin-protein transferase activity
GO:0051438	1.71	37.41	52	62.26	regulation of ubiquitin-protein transferase activity
GO:0051340	1.79	37.41	52	62.26	regulation of ligase activity
GO:0051351	1.79	37.41	52	62.26	positive regulation of ligase activity
GO:0090068	1.98	37.41	52	62.26	positive regulation of cell cycle process
GO:0031145	1.98	37.52	52.01	62.26	anaphase-promoting complex-dependent proteasomal ubiquitin-dependent protein catabolic process
GO:1901991	2.02	37.41	52	62.26	negative regulation of mitotic cell cycle phase transition
GO:0031398	2.02	37.52	52.01	62.26	positive regulation of protein ubiquitination
GO:1901990	2.4	37.41	52	62.26	regulation of mitotic cell cycle phase transition
GO:0031396	2.59	37.52	52.01	62.26	regulation of protein ubiquitination
GO:1901988	2.7	37.41	52	62.26	negative regulation of cell cycle phase transition
GO:1901987	3.08	37.41	52	62.26	regulation of cell cycle phase transition
GO:0051247	3.12	37.41	52	62.26	positive regulation of protein metabolic process
GO:0045786	3.27	37.41	52	62.26	negative regulation of cell cycle
GO:0010948	4.07	37.53	52.01	62.26	negative regulation of cell cycle process
GO:0010564	5.48	37.53	52.01	62.26	regulation of cell cycle process
GO:0032270	4.53	37.54	52.02	62.28	positive regulation of cellular protein metabolic process
GO:0044093	5.63	37.57	52.03	62.28	positive regulation of molecular function
GO:0050790	5.86	37.43	52.01	62.28	regulation of catalytic activity
GO:0043067	6.92	37.45	52.01	62.28	regulation of programmed cell death
GO:0042981	7.19	37.45	52.01	62.28	regulation of apoptotic process
GO:0010941	8.1	37.46	52.01	62.28	regulation of cell death
GO:0048522	11.49	37.54	52.02	62.28	positive regulation of cellular process
GO:0007093	2.62	37.91	52.13	62.29	mitotic cell cycle checkpoint
GO:0000075	3.77	37.91	52.13	62.29	cell cycle checkpoint
GO:0007346	4.3	37.91	52.13	62.29	regulation of mitotic cell cycle

GO:0043085	4.91	37.55	52.04	62.3	positive regulation of catalytic activity
GO:0051171	6.28	37.46	52.04	62.33	regulation of nitrogen compound metabolic process
GO:0043436	6.54	38	52.17	62.33	oxoacid metabolic process
GO:0048518	14.19	37.85	52.09	62.33	positive regulation of biological process
GO:0031401	4.22	37.56	52.06	62.34	positive regulation of protein modification process
GO:0065009	6.73	37.44	52.05	62.34	regulation of molecular function
GO:0031325	7.84	37.57	52.06	62.34	positive regulation of cellular metabolic process
GO:0000209	3.04	38.07	52.21	62.35	protein polyubiquitination
GO:0035556	11.22	37.54	52.06	62.35	intracellular signal transduction
GO:0016032	11.11	38.04	52.14	62.36	viral process
GO:0044403	12.36	38.23	52.17	62.37	symbiosis, encompassing mutualism through parasitism
GO:0044764	11.72	38.1	52.15	62.37	multi-organism cellular process
GO:0044419	12.21	38.23	52.17	62.37	interspecies interaction between organisms
GO:0002474	2.09	37.47	52.08	62.39	antigen processing and presentation of peptide antigen via MHC class I
GO:0019752	6.62	38.51	52.38	62.39	carboxylic acid metabolic process
GO:0070647	4.79	37.88	52.15	62.4	protein modification by small protein conjugation or removal
GO:1901564	9.17	37.84	52.16	62.4	organonitrogen compound metabolic process
GO:0010604	11.11	38.47	52.28	62.4	positive regulation of macromolecule metabolic process
GO:0048523	12.21	37.73	52.11	62.4	negative regulation of cellular process
GO:0048519	13.96	37.75	52.11	62.4	negative regulation of biological process
GO:0031399	5.67	37.6	52.11	62.41	regulation of protein modification process
GO:0080090	7.95	37.52	52.09	62.41	regulation of primary metabolic process
GO:0051726	8.06	38	52.22	62.42	regulation of cell cycle
GO:0009893	13.43	39.03	52.39	62.42	positive regulation of metabolic process
GO:0032446	4.72	38.21	52.28	62.43	protein modification by small protein conjugation
GO:0051704	14.34	38.27	52.2	62.43	multi-organism process
GO:0016567	4.56	38.19	52.3	62.45	protein ubiquitination
GO:0051246	5.17	38.63	52.48	62.45	regulation of protein metabolic process
GO:0006520	5.02	38.83	52.58	62.47	cellular amino acid metabolic process
GO:0006082	7.65	38.92	52.6	62.49	organic acid metabolic process
GO:0002478	3.04	37.6	52.17	62.52	antigen processing and presentation of exogenous peptide antigen
GO:0019884	3.12	37.6	52.17	62.52	antigen processing and presentation of exogenous antigen
GO:0006915	11.37	37.59	52.17	62.53	apoptotic process
GO:0012501	11.45	37.6	52.17	62.53	programmed cell death
GO:0016265	12.59	37.61	52.17	62.53	death
GO:0008219	13.01	37.63	52.17	62.53	cell death

GO:0048002	3.12	37.61	52.19	62.54	antigen processing and presentation of peptide antigen
GO:0019882	3.39	37.61	52.19	62.54	antigen processing and presentation
GO:0060255	11.49	38.82	52.56	62.55	regulation of macromolecule metabolic process
GO:0007165	22.37	38.82	52.4	62.57	signal transduction
GO:0044281	16.77	39.09	52.57	62.59	small molecule metabolic process
GO:0044710	19.13	39.32	52.66	62.68	single-organism metabolic process
GO:0050794	29.9	41.06	53.08	62.7	regulation of cellular process
GO:0002376	13.62	38.4	52.42	62.72	immune system process
GO:0043161	3	37.69	52.31	62.73	proteasome-mediated ubiquitin-dependent protein catabolic process
GO:0006974	9.21	38.02	52.36	62.75	cellular response to DNA damage stimulus
GO:0022402	12.06	38.77	52.53	62.76	cell cycle process
GO:0044265	8.67	37.91	52.37	62.8	cellular macromolecule catabolic process
GO:0006511	4.83	38.16	52.48	62.81	ubiquitin-dependent protein catabolic process
GO:0043412	13.2	39.08	52.72	62.86	macromolecule modification
GO:0036211	13.43	39.12	52.72	62.86	protein modification process
GO:1901575	12.1	37.85	52.42	62.89	organic substance catabolic process
GO:0033554	12.86	38.11	52.46	62.9	cellular response to stress
GO:0000278	11.72	38.74	52.61	62.91	mitotic cell cycle
GO:0007049	16.7	39.04	52.65	62.92	cell cycle
GO:0044700	18.79	38.61	52.57	62.93	single organism signaling
GO:0006464	17.15	39.6	52.91	62.98	cellular protein modification process
GO:0023052	21.83	39.06	52.73	63.01	signaling
GO:0007154	25.48	39.25	52.77	63.02	cell communication
GO:0051716	22.56	39.34	52.82	63.13	cellular response to stimulus
GO:0010498	3.8	38.24	52.72	63.19	proteasomal protein catabolic process
GO:0044257	4.26	37.98	52.64	63.2	cellular protein catabolic process
GO:0006950	23.47	39.25	52.8	63.2	response to stress
GO:0065007	35.34	42.2	53.65	63.21	biological regulation
GO:0043632	4.68	38.01	52.66	63.23	modification-dependent macromolecule catabolic process
GO:0030163	5.67	38.08	52.71	63.29	protein catabolic process
GO:0019941	5.71	38.56	52.86	63.32	modification-dependent protein catabolic process
GO:0051603	5.82	38.56	52.86	63.32	proteolysis involved in cellular protein catabolic process
GO:0006508	7.68	38.56	52.86	63.32	proteolysis
GO:0009057	12.1	38.85	52.88	63.33	macromolecule catabolic process
GO:0044248	14.42	38.32	52.77	63.36	cellular catabolic process
GO:0009056	19.32	39	52.96	63.44	catabolic process
GO:0032268	7.91	39.54	53.37	63.54	regulation of cellular protein metabolic process
GO:0050789	35.18	42.26	53.93	63.66	regulation of biological process

GO:0031323	19.09	40.44	53.6	63.69	regulation of cellular metabolic process
GO:0019222	24.76	41.8	54.06	63.84	regulation of metabolic process
GO:0050896	33.7	40.94	53.58	63.88	response to stimulus
GO:0044267	22.06	43.07	54.49	64.02	cellular protein metabolic process
GO:0019538	29.44	45.8	55.87	64.88	protein metabolic process
GO:0016071	13.24	45.06	57.2	66.05	mRNA metabolic process
GO:0090304	26.85	46.04	57.08	66.13	nucleic acid metabolic process
GO:1901360	32.26	46.15	57.18	66.23	organic cyclic compound metabolic process
GO:0046483	32.6	46.71	57.61	66.54	heterocycle metabolic process
GO:0016070	28.95	52.15	60.75	68.03	RNA metabolic process
GO:0044260	41.54	53.63	60.66	68.21	cellular macromolecule metabolic process
GO:0034641	38.04	52.14	61.31	69.04	cellular nitrogen compound metabolic process
GO:0071704	53.14	55.46	61.98	69.11	organic substance metabolic process
GO:0044238	53.67	57.38	63.61	70.46	primary metabolic process
GO:0044237	55.65	59.37	64.59	70.94	cellular metabolic process
GO:0043170	47.93	59.09	64.95	71.51	macromolecule metabolic process
GO:0010467	35.83	59.34	65.65	71.54	gene expression
GO:0006725	46.18	60.07	67.28	73.73	cellular aromatic compound metabolic process
GO:0006807	47.97	60.99	68.2	74.54	nitrogen compound metabolic process
GO:0006139	45.91	61.26	68.8	75.23	nucleobase-containing compound metabolic process

(e) Trend 5

GOID	Network	Loop3	Loop4	Loop5	Term
GO:0009653	10.46	0.21	0.02	0	anatomical structure morphogenesis
GO:0006259	10.46	0.83	0.08	0.01	DNA metabolic process
GO:0006366	10.99	3.25	0.9	0.21	transcription from RNA polymerase II promoter
GO:0070887	11.18	0.27	0.03	0	cellular response to chemical stimulus
GO:0065008	11.22	0.43	0.04	0	regulation of biological quality
GO:0007166	11.56	0.63	0.09	0.01	cell surface receptor signaling pathway
GO:0048731	12.74	1.27	0.49	0.15	system development
GO:0006396	12.82	11.37	8.46	5.88	RNA processing
GO:0030154	13.2	0.28	0.03	0	cell differentiation
GO:0019219	13.28	0.91	0.11	0.01	regulation of nucleobase-containing compound metabolic process
GO:0006355	13.58	2.82	0.84	0.21	regulation of transcription, DNA-templated
GO:0010033	13.81	0.41	0.04	0	response to organic substance
GO:0022607	14.57	2.87	0.93	0.27	cellular component assembly
GO:0010556	15.1	2.57	0.81	0.24	regulation of macromolecule biosynthetic process
GO:0044085	15.1	2.59	0.84	0.25	cellular component biogenesis
GO:0006796	16.09	1.06	0.25	0.06	phosphate-containing compound metabolic

					process
GO:0042221	16.58	0.6	0.08	0.01	response to chemical
GO:0044767	16.62	0.5	0.07	0.01	single-organism developmental process
GO:0006793	16.74	1.1	0.26	0.06	phosphorus metabolic process
GO:0048856	17	1.51	0.52	0.15	anatomical structure development
GO:0010468	17.84	3.83	1.14	0.31	regulation of gene expression
GO:0009889	18.87	5.02	1.7	0.5	regulation of biosynthetic process
GO:0006351	19.89	5.7	1.85	0.52	transcription, DNA-templated
GO:0007275	20.81	1.66	0.53	0.16	multicellular organismal development
GO:0032502	23.2	1.66	0.53	0.16	developmental process
GO:0006996	24.08	4.37	1.17	0.29	organelle organization
GO:0044707	24.31	2.26	0.66	0.18	single-multicellular organism process
GO:0032501	26.89	2.54	0.73	0.19	multicellular organismal process
GO:1901362	10.08	0.23	0.03	0	organic cyclic compound biosynthetic process
GO:0044271	12.55	0.26	0.03	0	cellular nitrogen compound biosynthetic process
GO:0034613	10.54	0.34	0.05	0	cellular protein localization
GO:0071822	10.31	0.35	0.05	0	protein complex subunit organization
GO:0071702	12.21	0.75	0.1	0.01	organic substance transport
GO:0015031	13.35	0.82	0.12	0.01	protein transport
GO:0051641	14	0.49	0.08	0.01	cellular localization
GO:0051649	11.6	0.46	0.08	0.01	establishment of localization in cell
GO:0046907	12.63	0.9	0.14	0.02	intracellular transport
GO:0045184	12.25	0.87	0.14	0.02	establishment of protein localization
GO:0044765	17.46	1.46	0.24	0.03	single-organism transport
GO:0034654	16.39	1.22	0.21	0.03	nucleobase-containing compound biosynthetic process
GO:0008104	18.49	1.28	0.22	0.03	protein localization
GO:0051234	20.27	1.75	0.28	0.03	establishment of localization
GO:0033036	19.44	1.58	0.28	0.04	macromolecule localization
GO:0051179	25.83	2.16	0.39	0.05	localization
GO:0006810	26.7	2.58	0.47	0.06	transport
GO:0032774	15.6	2.82	0.79	0.2	RNA biosynthetic process
GO:0019438	19.36	3.43	0.99	0.25	aromatic compound biosynthetic process
GO:0043933	14.45	2.45	0.82	0.25	macromolecular complex subunit organization
GO:0018130	20.39	3.74	1.1	0.28	heterocycle biosynthetic process
GO:1901576	19.44	3.49	1.12	0.33	organic substance biosynthetic process
GO:0044249	24.27	4.69	1.43	0.41	cellular biosynthetic process
GO:0071840	29.02	5.28	1.66	0.47	cellular component organization or biogenesis
GO:0034645	23.24	5.93	1.88	0.55	cellular macromolecule biosynthetic process
GO:0016043	36.4	7.24	2.21	0.6	cellular component organization
GO:0009059	31.19	10.93	3.92	1.26	macromolecule biosynthetic process
GO:0009058	37.28	11.37	4.09	1.32	biosynthetic process

Table S8. Description of proteins in short loops related to “Cell Cycle” in Figure 7

There are 167 proteins in short loops of length 3 and 4 having functional consensus with respect to “Cell Cycle” GO term. These proteins and their loop intetactions compose complexes or clusters wired to KEGG pathway of "cell cycle".

Cluster	Gene Name	UniprotID	Protein Description
Anaphase	ANAPC1	APC1_HUMAN	Anaphase-promoting complex subunit 1 (APC1) (Cyclosome subunit 1) (Mitotic checkpoint regulator) (Testis-specific gene 24 protein)
	ANAPC10	APC10_HUMAN	Anaphase-promoting complex subunit 10 (APC10) (Cyclosome subunit 10)
	ANAPC13	APC13_HUMAN	Anaphase-promoting complex subunit 13 (APC13) (Cyclosome subunit 13)
	ANAPC2	ANC2_HUMAN	Anaphase-promoting complex subunit 2 (APC2) (Cyclosome subunit 2)
	ANAPC4	APC4_HUMAN	Anaphase-promoting complex subunit 4 (APC4) (Cyclosome subunit 4)
	ANAPC5	APC5_HUMAN	Anaphase-promoting complex subunit 5 (APC5) (Cyclosome subunit 5)
	ANAPC7	APC7_HUMAN	Anaphase-promoting complex subunit 7 (APC7) (Cyclosome subunit 7)
	CDC16	CDC16_HUMAN	Cell division cycle protein 16 homolog (Anaphase-promoting complex subunit 6) (APC6) (CDC16 homolog) (CDC16Hs) (Cyclosome subunit 6)
	CDC23	CDC23_HUMAN	Cell division cycle protein 23 homolog (Anaphase-promoting complex subunit 8) (APC8) (Cyclosome subunit 8)
	CDC26	CDC26_HUMAN	Anaphase-promoting complex subunit CDC26 (Anaphase-promoting complex subunit 12) (APC12) (Cell division cycle protein 26 homolog)
	CDC27	CDC27_HUMAN	Cell division cycle protein 27 homolog (Anaphase-promoting complex subunit 3) (APC3) (CDC27 homolog) (CDC27Hs) (H-NUC)
Cell division	NDC80	NDC80_HUMAN	Kinetochore protein NDC80 homolog (Highly expressed in cancer protein) (Kinetochore protein Hec1) (HsHec1) (Kinetochore-associated protein 2) (Retinoblastoma-associated protein HEC)
	NUF2	NUF2_HUMAN	Kinetochore protein Nuf2 (hNuf2) (hNuf2R) (hsNuf2) (Cell division cycle-associated protein 1)
	SPC24	SPC24_HUMAN	Kinetochore protein Spc24 (hSpc24)
	SPC25	SPC25_HUMAN	Kinetochore protein Spc25 (hSpc25)
Chromosome/Nucleopore complex	NCAPD2	CND1_HUMAN	Condensin complex subunit 1 (Chromosome condensation-related SMC-associated protein 1) (Chromosome-associated protein D2) (hCAP-D2) (Non-SMC condensin I complex subunit D2) (XCAP-D2 homolog)
	NCAPG	CND3_HUMAN	Condensin complex subunit 3 (Chromosome-associated protein G) (Condensin subunit CAP-G) (hCAP-G) (Melanoma antigen NY-MEL-3) (Non-SMC condensin I complex subunit G) (XCAP-G homolog)
	NCAPH	CND2_HUMAN	Condensin complex subunit 2 (Barren homolog protein 1) (Chromosome-associated protein H) (hCAP-H) (Non-SMC condensin I complex subunit H) (XCAP-H homolog)

	NUP107	NU107_HUMAN	Nuclear pore complex protein Nup107 (107 kDa nucleoporin) (Nucleoporin Nup107)
	NUP153	NU153_HUMAN	Nuclear pore complex protein Nup153 (153 kDa nucleoporin) (Nucleoporin Nup153)
	PNPT1	PNPT1_HUMAN	Polyribonucleotide nucleotidyltransferase 1, mitochondrial (EC 2.7.7.8) (3'-5' RNA exonuclease OLD35) (PNPase old-35) (Polynucleotide phosphorylase 1) (PNPase 1) (Polynucleotide phosphorylase-like protein)
	SMC1A	SMC1A_HUMAN	Structural maintenance of chromosomes protein 1A (SMC protein 1A) (SMC-1-alpha) (SMC-1A) (Sb1.8)
	SMC2	SMC2_HUMAN	Structural maintenance of chromosomes protein 2 (SMC protein 2) (SMC-2) (Chromosome-associated protein E) (hCAP-E) (XCAP-E homolog)
	SMC3	SMC3_HUMAN	Structural maintenance of chromosomes protein 3 (SMC protein 3) (SMC-3) (Basement membrane-associated chondroitin proteoglycan) (Bamacan) (Chondroitin sulfate proteoglycan 6) (Chromosome-associated polypeptide) (hCAP)
	SMC4	SMC4_HUMAN	Structural maintenance of chromosomes protein 4 (SMC protein 4) (SMC-4) (Chromosome-associated polypeptide C) (hCAP-C) (XCAP-C homolog)
DNA Polymerase	POLA1	DPOLA_HUMAN	DNA polymerase alpha catalytic subunit (EC 2.7.7.7) (DNA polymerase alpha catalytic subunit p180)
	POLA2	DPOA2_HUMAN	DNA polymerase alpha subunit B (DNA polymerase alpha 70 kDa subunit)
	PRIM1	PRI1_HUMAN	DNA primase small subunit (EC 2.7.7.-) (DNA primase 49 kDa subunit) (p49)
	PRIM2	PRI2_HUMAN	DNA primase large subunit (EC 2.7.7.-) (DNA primase 58 kDa subunit) (p58)
Dynactin	DCTN1	DCTN1_HUMAN	Dynactin subunit 1 (150 kDa dynein-associated polypeptide) (DAP-150) (DP-150) (p135) (p150-glued)
	DCTN2	DCTN2_HUMAN	Dynactin subunit 2 (50 kDa dynein-associated polypeptide) (Dynactin complex 50 kDa subunit) (DCTN-50) (p50 dynamitin)
	DCTN3	DCTN3_HUMAN	Dynactin subunit 3 (Dynactin complex subunit 22 kDa subunit) (p22)
	DYNC1H1	DYHC1_HUMAN	Cytoplasmic dynein 1 heavy chain 1 (Cytoplasmic dynein heavy chain 1) (Dynein heavy chain, cytosolic)
	DYNLT3	DYLT3_HUMAN	Dynein light chain Tctex-type 3 (Protein 91/23) (T-complex-associated testis-expressed 1-like)
Gi1 Alpha	GNAI1	GNAI1_HUMAN	Guanine nucleotide-binding protein G(i) subunit alpha-1 (Adenylate cyclase-inhibiting G alpha protein)
	GNAI2	GNAI2_HUMAN	Guanine nucleotide-binding protein G(i) subunit alpha-2 (Adenylate cyclase-inhibiting G alpha protein)
	GNAI3	GNAI3_HUMAN	Guanine nucleotide-binding protein G(k) subunit alpha (G(i) alpha-3)
MCM	MCM2	MCM2_HUMAN	DNA replication licensing factor MCM2 (EC 3.6.4.12) (Minichromosome maintenance protein 2 homolog) (Nuclear protein BM28)
	MCM3	MCM3_HUMAN	DNA replication licensing factor MCM3 (EC 3.6.4.12) (DNA polymerase alpha holoenzyme-associated protein P1) (P1-MCM3) (RLF subunit beta) (p102)
	MCM4	MCM4_HUMAN	DNA replication licensing factor MCM4 (EC 3.6.4.12) (CDC21 homolog) (P1-CDC21)
	MCM5	MCM5_HUMAN	DNA replication licensing factor MCM5 (EC 3.6.4.12) (CDC46

			homolog) (P1-CDC46)
	MCM6	MCM6_HUMAN	DNA replication licensing factor MCM6 (EC 3.6.4.12) (p105MCM)
	MCM7	MCM7_HUMAN	DNA replication licensing factor MCM7 (EC 3.6.4.12) (CDC47 homolog) (P1.1-MCM3)
MRN/X	MRE11A	MRE11_HUMAN	Double-strand break repair protein MRE11A (Meiotic recombination 11 homolog 1) (MRE11 homolog 1) (Meiotic recombination 11 homolog A) (MRE11 homolog A)
	NBN	NBN_HUMAN	Nibrin (Cell cycle regulatory protein p95) (Nijmegen breakage syndrome protein 1)
	RAD50	RAD50_HUMAN	DNA repair protein RAD50 (hRAD50) (EC 3.6.-.-)
	TERF2	TERF2_HUMAN	Telomeric repeat-binding factor 2 (TTAGGG repeat-binding factor 2) (Telomeric DNA-binding protein)
MutS Homolog	MSH2	MSH2_HUMAN	DNA mismatch repair protein Msh2 (hMSH2) (MutS protein homolog 2)
	MSH3	MSH3_HUMAN	DNA mismatch repair protein Msh3 (hMSH3) (Divergent upstream protein) (DUP) (Mismatch repair protein 1) (MRP1)
	MSH6	MSH6_HUMAN	DNA mismatch repair protein Msh6 (hMSH6) (G/T mismatch-binding protein) (GTBP) (GTMBP) (MutS-alpha 160 kDa subunit) (p160)
ORC	ORC2	ORC2_HUMAN	Origin recognition complex subunit 2
	ORC3	ORC3_HUMAN	Origin recognition complex subunit 3 (Origin recognition complex subunit Latheo)
	ORC5	ORC5_HUMAN	Origin recognition complex subunit 5
Proteosome	PSMA1	PSA1_HUMAN	Proteasome subunit alpha type-1 (EC 3.4.25.1) (30 kDa prosomal protein) (PROS-30) (Macropain subunit C2) (Multicatalytic endopeptidase complex subunit C2) (Proteasome component C2) (Proteasome nu chain)
	PSMA2	PSA2_HUMAN	Proteasome subunit alpha type-2 (EC 3.4.25.1) (Macropain subunit C3) (Multicatalytic endopeptidase complex subunit C3) (Proteasome component C3)
	PSMA3	PSA3_HUMAN	Proteasome subunit alpha type-3 (EC 3.4.25.1) (Macropain subunit C8) (Multicatalytic endopeptidase complex subunit C8) (Proteasome component C8)
	PSMA4	PSA4_HUMAN	Proteasome subunit alpha type-4 (EC 3.4.25.1) (Macropain subunit C9) (Multicatalytic endopeptidase complex subunit C9) (Proteasome component C9) (Proteasome subunit L)
	PSMA5	PSA5_HUMAN	Proteasome subunit alpha type-5 (EC 3.4.25.1) (Macropain zeta chain) (Multicatalytic endopeptidase complex zeta chain) (Proteasome zeta chain)
	PSMA6	PSA6_HUMAN	Proteasome subunit alpha type-6 (EC 3.4.25.1) (27 kDa prosomal protein) (PROS-27) (p27K) (Macropain iota chain) (Multicatalytic endopeptidase complex iota chain) (Proteasome iota chain)
	PSMA7	PSA7_HUMAN	Proteasome subunit alpha type-7 (EC 3.4.25.1) (Proteasome subunit RC6-1) (Proteasome subunit XAPC7)
	PSMA8	PSA7L_HUMAN	Proteasome subunit alpha type-7-like (EC 3.4.25.1)
	PSMB1	PSB1_HUMAN	Proteasome subunit beta type-1 (EC 3.4.25.1) (Macropain subunit C5) (Multicatalytic endopeptidase complex subunit C5) (Proteasome component C5) (Proteasome gamma chain)
	PSMB10	PSB10_HUMAN	Proteasome subunit beta type-10 (EC 3.4.25.1) (Low molecular mass protein 10) (Macropain subunit MECl-1) (Multicatalytic endopeptidase complex subunit MECl-1) (Proteasome MECl-1)

			(Proteasome subunit beta-2i)
	PSMB2	PSB2_HUMAN	Proteasome subunit beta type-2 (EC 3.4.25.1) (Macropain subunit C7-I) (Multicatalytic endopeptidase complex subunit C7-I) (Proteasome component C7-I)
	PSMB3	PSB3_HUMAN	Proteasome subunit beta type-3 (EC 3.4.25.1) (Proteasome chain 13) (Proteasome component C10-II) (Proteasome theta chain)
	PSMB4	PSB4_HUMAN	Proteasome subunit beta type-4 (EC 3.4.25.1) (26 kDa prosomal protein) (HsBPROS26) (PROS-26) (Macropain beta chain) (Multicatalytic endopeptidase complex beta chain) (Proteasome beta chain) (Proteasome chain 3) (HsN3)
	PSMB5	PSB5_HUMAN	Proteasome subunit beta type-5 (EC 3.4.25.1) (Macropain epsilon chain) (Multicatalytic endopeptidase complex epsilon chain) (Proteasome chain 6) (Proteasome epsilon chain) (Proteasome subunit MB1) (Proteasome subunit X)
	PSMB6	PSB6_HUMAN	Proteasome subunit beta type-6 (EC 3.4.25.1) (Macropain delta chain) (Multicatalytic endopeptidase complex delta chain) (Proteasome delta chain) (Proteasome subunit Y)
	PSMB7	PSB7_HUMAN	Proteasome subunit beta type-7 (EC 3.4.25.1) (Macropain chain Z) (Multicatalytic endopeptidase complex chain Z) (Proteasome subunit Z)
	PSMB8	PSB8_HUMAN	Proteasome subunit beta type-8 (EC 3.4.25.1) (Low molecular mass protein 7) (Macropain subunit C13) (Multicatalytic endopeptidase complex subunit C13) (Proteasome component C13) (Proteasome subunit beta-5i) (Really interesting new gene 10 protein)
	PSMC1	PRS4_HUMAN	26S protease regulatory subunit 4 (P26s4) (26S proteasome AAA-ATPase subunit RPT2) (Proteasome 26S subunit ATPase 1)
	PSMC2	PRS7_HUMAN	26S protease regulatory subunit 7 (26S proteasome AAA-ATPase subunit RPT1) (Proteasome 26S subunit ATPase 2) (Protein MSS1)
	PSMC3	PRS6A_HUMAN	26S protease regulatory subunit 6A (26S proteasome AAA-ATPase subunit RPT5) (Proteasome 26S subunit ATPase 3) (Proteasome subunit P50) (Tat-binding protein 1) (TBP-1)
	PSMC4	PRS6B_HUMAN	26S protease regulatory subunit 6B (26S proteasome AAA-ATPase subunit RPT3) (MB67-interacting protein) (MIP224) (Proteasome 26S subunit ATPase 4) (Tat-binding protein 7) (TBP-7)
	PSMC5	PRS8_HUMAN	26S protease regulatory subunit 8 (26S proteasome AAA-ATPase subunit RPT6) (Proteasome 26S subunit ATPase 5) (Proteasome subunit p45) (Thyroid hormone receptor-interacting protein 1) (TRIP1) (p45/SUG)
	PSMC6	PRS10_HUMAN	26S protease regulatory subunit 10B (26S proteasome AAA-ATPase subunit RPT4) (Proteasome 26S subunit ATPase 6) (Proteasome subunit p42)
	PSMD1	PSMD1_HUMAN	26S proteasome non-ATPase regulatory subunit 1 (26S proteasome regulatory subunit RPN2) (26S proteasome regulatory subunit S1) (26S proteasome subunit p112)
	PSMD10	PSD10_HUMAN	26S proteasome non-ATPase regulatory subunit 10 (26S proteasome regulatory subunit p28) (Gankyrin) (p28(GANK))
	PSMD11	PSD11_HUMAN	26S proteasome non-ATPase regulatory subunit 11 (26S proteasome regulatory subunit RPN6) (26S proteasome regulatory subunit S9) (26S proteasome regulatory subunit p44.5)
	PSMD12	PSD12_HUMAN	26S proteasome non-ATPase regulatory subunit 12 (26S

			proteasome regulatory subunit RPN5) (26S proteasome regulatory subunit p55)
	PSMD13	PSD13_HUMAN	26S proteasome non-ATPase regulatory subunit 13 (26S proteasome regulatory subunit RPN9) (26S proteasome regulatory subunit S11) (26S proteasome regulatory subunit p40.5)
	PSMD14	PSDE_HUMAN	26S proteasome non-ATPase regulatory subunit 14 (EC 3.4.19.-) (26S proteasome regulatory subunit RPN11) (26S proteasome-associated PAD1 homolog 1)
	PSMD2	PSMD2_HUMAN	26S proteasome non-ATPase regulatory subunit 2 (26S proteasome regulatory subunit RPN1) (26S proteasome regulatory subunit S2) (26S proteasome subunit p97) (Protein 55.11) (Tumor necrosis factor type 1 receptor-associated protein 2)
	PSMD3	PSMD3_HUMAN	26S proteasome non-ATPase regulatory subunit 3 (26S proteasome regulatory subunit RPN3) (26S proteasome regulatory subunit S3) (Proteasome subunit p58)
	PSMD4	PSMD4_HUMAN	26S proteasome non-ATPase regulatory subunit 4 (26S proteasome regulatory subunit RPN10) (26S proteasome regulatory subunit S5A) (Antisecretory factor 1) (AF) (ASF) (Multiubiquitin chain-binding protein)
	PSMD5	PSMD5_HUMAN	26S proteasome non-ATPase regulatory subunit 5 (26S protease subunit S5 basic) (26S proteasome subunit S5B)
	PSMD6	PSMD6_HUMAN	26S proteasome non-ATPase regulatory subunit 6 (26S proteasome regulatory subunit RPN7) (26S proteasome regulatory subunit S10) (Breast cancer-associated protein SGA-113M) (Phosphonoformate immuno-associated protein 4) (Proteasome regulatory particle subunit p44S10) (p42A)
	PSMD7	PSD7_HUMAN	26S proteasome non-ATPase regulatory subunit 13 (26S proteasome regulatory subunit RPN9) (26S proteasome regulatory subunit S11) (26S proteasome regulatory subunit p40.5)
	PSMD8	PSMD8_HUMAN	26S proteasome non-ATPase regulatory subunit 8 (26S proteasome regulatory subunit RPN12) (26S proteasome regulatory subunit S14) (p31)
	PSME1	PSME1_HUMAN	Proteasome activator complex subunit 1 (11S regulator complex subunit alpha) (REG-alpha) (Activator of multicatalytic protease subunit 1) (Interferon gamma up-regulated I-5111 protein) (IGUP I-5111) (Proteasome activator 28 subunit alpha) (PA28a) (PA28alpha)
	PSME2	PSME2_HUMAN	Proteasome activator complex subunit 2 (11S regulator complex subunit beta) (REG-beta) (Activator of multicatalytic protease subunit 2) (Proteasome activator 28 subunit beta) (PA28b) (PA28beta)
	PSME3	PSME3_HUMAN	Proteasome activator complex subunit 3 (11S regulator complex subunit gamma) (REG-gamma) (Activator of multicatalytic protease subunit 3) (Ki nuclear autoantigen) (Proteasome activator 28 subunit gamma) (PA28g) (PA28gamma)
RAS	RAN	RAN_HUMAN	GTP-binding nuclear protein Ran (Androgen receptor-associated protein 24) (GTPase Ran) (Ras-like protein TC4) (Ras-related nuclear protein)
	RANBP1	RANG_HUMAN	Ran-specific GTPase-activating protein (Ran-binding protein 1) (RanBP1)
	RCC1	RCC1_HUMAN	Regulator of chromosome condensation (Cell cycle regulatory

			protein) (Chromosome condensation protein 1)
Replication Factor	RFC1	RFC1_HUMAN	Replication factor C subunit 1 (Activator 1 140 kDa subunit) (A1 140 kDa subunit) (Activator 1 large subunit) (Activator 1 subunit 1) (DNA-binding protein PO-GA) (Replication factor C 140 kDa subunit) (RF-C 140 kDa subunit) (RFC140) (Replication factor C large subunit)
	RFC2	RFC2_HUMAN	Replication factor C subunit 2 (Activator 1 40 kDa subunit) (A1 40 kDa subunit) (Activator 1 subunit 2) (Replication factor C 40 kDa subunit) (RF-C 40 kDa subunit) (RFC40)
	RFC3	RFC3_HUMAN	Replication factor C subunit 3 (Activator 1 38 kDa subunit) (A1 38 kDa subunit) (Activator 1 subunit 3) (Replication factor C 38 kDa subunit) (RF-C 38 kDa subunit) (RFC38)
	RFC4	RFC4_HUMAN	Replication factor C subunit 4 (Activator 1 37 kDa subunit) (A1 37 kDa subunit) (Activator 1 subunit 4) (Replication factor C 37 kDa subunit) (RF-C 37 kDa subunit) (RFC37)
	RFC5	RFC5_HUMAN	Replication factor C subunit 5 (Activator 1 36 kDa subunit) (A1 36 kDa subunit) (Activator 1 subunit 5) (Replication factor C 36 kDa subunit) (RF-C 36 kDa subunit) (RFC36)
Septin	SEPT11	SEP11_HUMAN	Septin-11
	SEPT2	SEPT2_HUMAN	Septin-2 (Neural precursor cell expressed developmentally down-regulated protein 5) (NEDD-5)
	SEPT7	SEPT7_HUMAN	Septin-7 (CDC10 protein homolog)
	SEPT9	SEPT9_HUMAN	Septin-9 (MLL septin-like fusion protein MSF-A) (MLL septin-like fusion protein) (Ovarian/Breast septin) (Ov/Br septin) (Septin D1)
Serine/threonine-protein phosphatase	PPP1CA	PP1A_HUMAN	Serine/threonine-protein phosphatase PP1-alpha catalytic subunit (PP-1A) (EC 3.1.3.16)
	PPP2CA	PP2AA_HUMAN	Serine/threonine-protein phosphatase 2A catalytic subunit alpha isoform (PP2A-alpha) (EC 3.1.3.16) (Replication protein C) (RP-C)
	PPP2R1A	2AAA_HUMAN	Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform (Medium tumor antigen-associated 61 kDa protein) (PP2A subunit A isoform PR65-alpha) (PP2A subunit A isoform R1-alpha)
	PPP2R2A	2ABA_HUMAN	Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B alpha isoform (PP2A subunit B isoform B55-alpha) (PP2A subunit B isoform PR55-alpha) (PP2A subunit B isoform R2-alpha) (PP2A subunit B isoform alpha)
TFIID	TAF1	TAF1_HUMAN	Transcription initiation factor TFIID subunit 1 (EC 2.7.11.1) (Cell cycle gene 1 protein) (TBP-associated factor 250 kDa) (p250) (Transcription initiation factor TFIID 250 kDa subunit) (TAF(II)250) (TAFII-250) (TAFII250)
	TAF2	TAF2_HUMAN	Transcription initiation factor TFIID subunit 2 (150 kDa cofactor of initiator function) (RNA polymerase II TBP-associated factor subunit B) (TBP-associated factor 150 kDa) (Transcription initiation factor TFIID 150 kDa subunit) (TAF(II)150) (TAFII-150) (TAFII150)
	TAF6	TAF6_HUMAN	Transcription initiation factor TFIID subunit 6 (RNA polymerase II TBP-associated factor subunit E) (Transcription initiation factor TFIID 70 kDa subunit) (TAF(II)70) (TAFII-70) (TAFII70) (Transcription initiation factor TFIID 80 kDa subunit) (TAF(II)80) (TAFII-80) (TAFII80)
Tubulin	TUBA1A	TBA1A_HUMAN	Tubulin alpha-1A chain (Alpha-tubulin 3) (Tubulin B-alpha-1) (Tubulin alpha-3 chain)

	TUBA4A	TBA4A_HUMAN	Tubulin alpha-4A chain (Alpha-tubulin 1) (Testis-specific alpha-tubulin) (Tubulin H2-alpha) (Tubulin alpha-1 chain)
	TUBB	TBB5_HUMAN	Tubulin beta chain (Tubulin beta-5 chain)
	TUBB3	TBB3_HUMAN	Tubulin beta-3 chain (Tubulin beta-4 chain) (Tubulin beta-III)
	TUBB4B	TBB2C_HUMAN	Tubulin alpha-4A chain (Alpha-tubulin 1) (Testis-specific alpha-tubulin) (Tubulin H2-alpha) (Tubulin alpha-1 chain)
Ubiquitin-conjugating Enzyme	UBE2B	UBE2B_HUMAN	Ubiquitin-conjugating enzyme E2 B (EC 6.3.2.19) (RAD6 homolog B) (HR6B) (hHR6B) (Ubiquitin carrier protein B) (Ubiquitin-conjugating enzyme E2-17 kDa) (Ubiquitin-protein ligase B)
	UBE2C	UBE2C_HUMAN	Ubiquitin-conjugating enzyme E2 C (EC 6.3.2.19) (UbcH10) (Ubiquitin carrier protein C) (Ubiquitin-protein ligase C)
	UBE2D1	UB2D1_HUMAN	Ubiquitin-conjugating enzyme E2 D1 (EC 6.3.2.19) (Stimulator of Fe transport) (SFT) (UBC4/5 homolog) (UbcH5) (Ubiquitin carrier protein D1) (Ubiquitin-conjugating enzyme E2(17)KB 1) (Ubiquitin-conjugating enzyme E2-17 kDa 1) (Ubiquitin-protein ligase D1)
	ACTR1A	ACTZ_HUMAN	Alpha-centractin (Centractin) (ARP1) (Actin-RPV) (Centrosome-associated actin homolog)
	CCNH	CCNH_HUMAN	Cyclin-H (MO15-associated protein) (p34) (p37)
	CDC5L	CDC5L_HUMAN	Cell division cycle 5-like protein (Cdc5-like protein) (Pombe cdc5-related protein)
	CDK7	CDK7_HUMAN	Cyclin-dependent kinase 7 (EC 2.7.11.22) (EC 2.7.11.23) (39 kDa protein kinase) (p39 Mo15) (CDK-activating kinase 1) (Cell division protein kinase 7) (Serine/threonine-protein kinase 1) (TFIIH basal transcription factor complex kinase subunit)
	CHD3	CHD3_HUMAN	Chromodomain-helicase-DNA-binding protein 3 (CHD-3) (EC 3.6.4.12) (ATP-dependent helicase CHD3) (Mi-2 autoantigen 240 kDa protein) (Mi2-alpha) (Zinc finger helicase) (hZFH)
	CSNK2A1	CSK21_HUMAN	Casein kinase II subunit alpha (CK II alpha) (EC 2.7.11.1)
	ECD	SGT1_HUMAN	Protein SGT1 (hSGT1) (Protein ecdysoneless homolog) (Suppressor of GCR2)
	ERCC2	ERCC2_HUMAN	TFIIH basal transcription factor complex helicase XPD subunit (EC 3.6.4.12) (Basic transcription factor 2 80 kDa subunit) (BTF2 p80) (CXPD) (DNA excision repair protein ERCC-2) (DNA repair protein complementing XP-D cells) (TFIIH basal transcription factor complex 80 kDa subunit) (TFIIH 80 kDa subunit) (TFIIH p80) (Xeroderma pigmentosum group D-complementing protein)
	ERCC3	ERCC3_HUMAN	TFIIH basal transcription factor complex helicase XPB subunit (EC 3.6.4.12) (Basic transcription factor 2 89 kDa subunit) (BTF2 p89) (DNA excision repair protein ERCC-3) (DNA repair protein complementing XP-B cells) (TFIIH basal transcription factor complex 89 kDa subunit) (TFIIH 89 kDa subunit) (TFIIH p89) (Xeroderma pigmentosum group B-complementing protein)
	FLNA	FLNA_HUMAN	Filamin-A (FLN-A) (Actin-binding protein 280) (ABP-280) (Alpha-filamin) (Endothelial actin-binding protein) (Filamin-1) (Non-muscle filamin)
	GTF2H1	TF2H1_HUMAN	General transcription factor IIH subunit 1 (Basic transcription factor 2 62 kDa subunit) (BTF2 p62) (General transcription factor IIH polypeptide 1) (TFIIH basal transcription factor complex p62 subunit)
	HCFC1	HCFC1_HUMAN	Host cell factor 1 (HCF) (HCF-1) (C1 factor) (CFF) (VCAF) (VP16

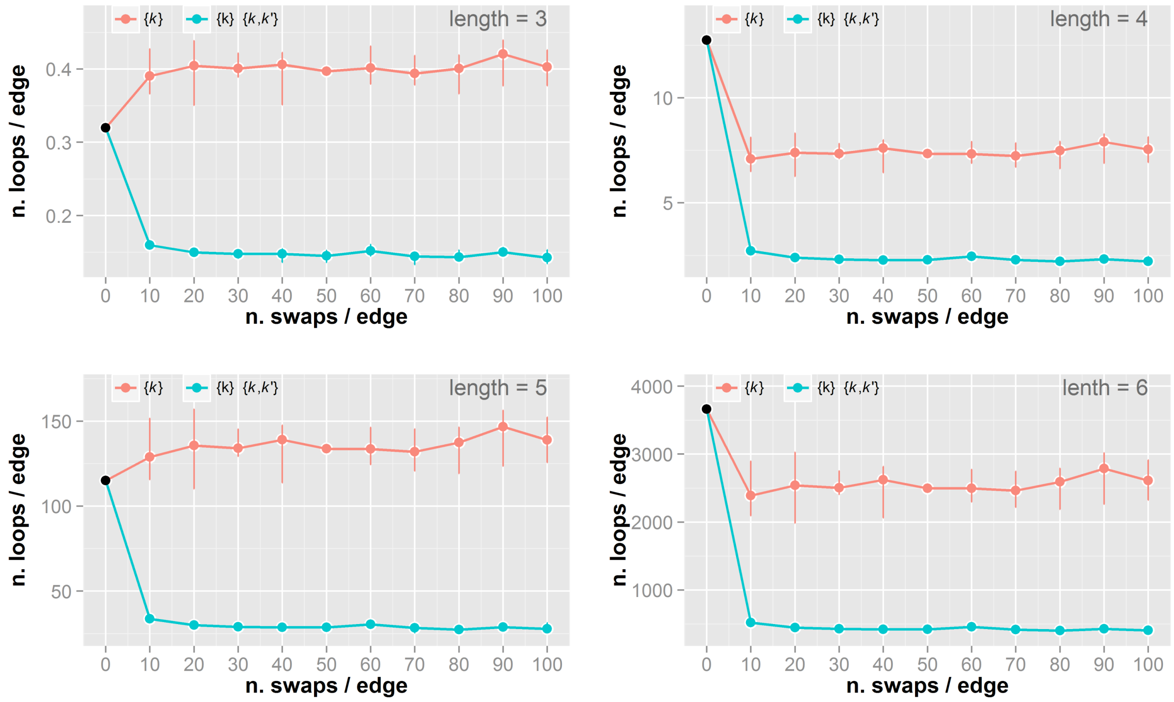
			accessory protein) [Cleaved into: HCF N-terminal chain 1; HCF N-terminal chain 2; HCF N-terminal chain 3; HCF N-terminal chain 4; HCF N-terminal chain 5; HCF N-terminal chain 6; HCF C-terminal chain 1; HCF C-terminal chain 2; HCF C-terminal chain 3; HCF C-terminal chain 4; HCF C-terminal chain 5; HCF C-terminal chain 6]
	HDAC1	HDAC1_HUMAN	Histone deacetylase 1 (HD1) (EC 3.5.1.98)
	HDAC2	HDAC2_HUMAN	Histone deacetylase 2 (HD2) (EC 3.5.1.98)
	HSPA8	HSP7C_HUMAN	Heat shock cognate 71 kDa protein (Heat shock 70 kDa protein 8) (Lipopolysaccharide-associated protein 1) (LAP-1) (LPS-associated protein 1)
	ILF3	ILF3_HUMAN	Interleukin enhancer-binding factor 3 (Double-stranded RNA-binding protein 76) (DRBP76) (M-phase phosphoprotein 4) (MPP4) (Nuclear factor associated with dsRNA) (NFAR) (Nuclear factor of activated T-cells 90 kDa) (NF-AT-90) (Translational control protein 80) (TCP80)
	MNAT1	MAT1_HUMAN	CDK-activating kinase assembly factor MAT1 (CDK7/cyclin-H assembly factor) (Cyclin-G1-interacting protein) (Menage a trois) (RING finger protein 66) (RING finger protein MAT1) (p35) (p36)
	MYBBP1A	MBB1A_HUMAN	Myb-binding protein 1A
	MYH10	MYH10_HUMAN	Myosin-10 (Cellular myosin heavy chain, type B) (Myosin heavy chain 10) (Myosin heavy chain, non-muscle IIb) (Non-muscle myosin heavy chain B) (NMMHC-B) (Non-muscle myosin heavy chain IIb) (NMMHC II-b) (NMMHC-IIB)
	MYH9	MYH9_HUMAN	Myosin-9 (Cellular myosin heavy chain, type A) (Myosin heavy chain 9) (Myosin heavy chain, non-muscle IIa) (Non-muscle myosin heavy chain A) (NMMHC-A) (Non-muscle myosin heavy chain IIa) (NMMHC II-a) (NMMHC-IIA)
	PCNA	PCNA_HUMAN	Proliferating cell nuclear antigen (PCNA) (Cyclin)
	POLD1	DPOD1_HUMAN	DNA polymerase delta catalytic subunit (EC 2.7.7.7) (DNA polymerase subunit delta p125)
	PPM1G	PPM1G_HUMAN	Protein phosphatase 1G (EC 3.1.3.16) (Protein phosphatase 1C) (Protein phosphatase 2C isoform gamma) (PP2C-gamma) (Protein phosphatase magnesium-dependent 1 gamma)
	PPP1CB	PP1B_HUMAN	Serine/threonine-protein phosphatase PP1-beta catalytic subunit (PP-1B) (PPP1CD) (EC 3.1.3.16) (EC 3.1.3.53)
	RAB11A	RB11A_HUMAN	Ras-related protein Rab-11A (Rab-11) (YL8)
	RAD21	RAD21_HUMAN	Double-strand-break repair protein rad21 homolog (hHR21) (Nuclear matrix protein 1) (NXP-1) (SCC1 homolog)
	RALA	RALA_HUMAN	Ras-related protein Ral-A
	RANBP2	RBP2_HUMAN	E3 SUMO-protein ligase RanBP2 (EC 6.3.2.-) (358 kDa nucleoporin) (Nuclear pore complex protein Nup358) (Nucleoporin Nup358) (Ran-binding protein 2) (RanBP2) (p270)
	RBBP4	RBBP4_HUMAN	Histone-binding protein RBBP4 (Chromatin assembly factor 1 subunit C) (CAF-1 subunit C) (Chromatin assembly factor I p48 subunit) (CAF-I 48 kDa subunit) (CAF-I p48) (Nucleosome-remodeling factor subunit RBAP48) (Retinoblastoma-binding protein 4) (RBBP-4) (Retinoblastoma-binding protein p48)
	RPA1	RFA1_HUMAN	Replication protein A 70 kDa DNA-binding subunit (RP-A p70) (Replication factor A protein 1) (RF-A protein 1) (Single-stranded DNA-binding protein) [Cleaved into: Replication protein A 70 kDa DNA-binding subunit, N-terminally processed]

	RPA2	RFA2_HUMAN	Replication protein A 32 kDa subunit (RP-A p32) (Replication factor A protein 2) (RF-A protein 2) (Replication protein A 34 kDa subunit) (RP-A p34)
	RPA3	RFA3_HUMAN	Replication protein A 14 kDa subunit (RP-A p14) (Replication factor A protein 3) (RF-A protein 3)
	RPS15A	RS15A_HUMAN	40S ribosomal protein S15a
	RRS1	RRS1_HUMAN	Ribosome biogenesis regulatory protein homolog
	RUVBL1	RUVB1_HUMAN	RuvB-like 1 (EC 3.6.4.12) (49 kDa TATA box-binding protein-interacting protein) (49 kDa TBP-interacting protein) (54 kDa erythrocyte cytosolic protein) (ECP-54) (INO80 complex subunit H) (Nuclear matrix protein 238) (NMP 238) (Pontin 52) (TIP49a) (TIP60-associated protein 54-alpha) (TAP54-alpha)
	SART1	SNUT1_HUMAN	U4/U6.U5 tri-snRNP-associated protein 1 (SNU66 homolog) (hSnu66) (Squamous cell carcinoma antigen recognized by T-cells 1) (SART-1) (hSART-1) (U4/U6.U5 tri-snRNP-associated 110 kDa protein) (allergen Hom s 1)
	SMARCA4	SMCA4_HUMAN	Transcription activator BRG1 (EC 3.6.4.-) (ATP-dependent helicase SMARCA4) (BRG1-associated factor 190A) (BAF190A) (Mitotic growth and transcription activator) (Protein BRG-1) (Protein brahma homolog 1) (SNF2-beta) (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4)
	SMARCB1	SNF5_HUMAN	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (BRG1-associated factor 47) (BAF47) (Integrase interactor 1 protein) (SNF5 homolog) (hSNF5)
	SON	SON_HUMAN	Protein SON (Bax antagonist selected in saccharomyces 1) (BASS1) (Negative regulatory element-binding protein) (NRE-binding protein) (Protein DBP-5) (SON3)
	SRSF5	SRSF5_HUMAN	Serine/arginine-rich splicing factor 5 (Delayed-early protein HRS) (Pre-mRNA-splicing factor SRP40) (Splicing factor, arginine/serine-rich 5)
	SSSCA1	SSA27_HUMAN	Sjoegren syndrome/scleroderma autoantigen 1 (Autoantigen p27)
	SUGT1	SUGT1_HUMAN	Suppressor of G2 allele of SKP1 homolog (Protein 40-6-3) (Sgt1)
	TOP2B	TOP2B_HUMAN	DNA topoisomerase 2-beta (EC 5.99.1.3) (DNA topoisomerase II, beta isozyme)
	TYMS	TYSY_HUMAN	Thymidylate synthase (TS) (TSase) (EC 2.1.1.45)
	USP39	SNUT2_HUMAN	U4/U6.U5 tri-snRNP-associated protein 2 (Inactive ubiquitin-specific peptidase 39) (SAD1 homolog) (U4/U6.U5 tri-snRNP-associated 65 kDa protein) (65K)
	USP9X	USP9X_HUMAN	Probable ubiquitin carboxyl-terminal hydrolase FAF-X (EC 3.4.19.12) (Deubiquitinating enzyme FAF-X) (Fat facets in mammals) (hFAM) (Fat facets protein-related, X-linked) (Ubiquitin thioesterase FAF-X) (Ubiquitin-specific protease 9, X chromosome) (Ubiquitin-specific-processing protease FAF-X)
	VPS4B	VPS4B_HUMAN	Vacuolar protein sorting-associated protein 4B (EC 3.6.4.6) (Cell migration-inducing gene 1 protein) (Suppressor of K(+) transport growth defect 1) (Protein SKD1)
	XPO1	XPO1_HUMAN	Exportin-1 (Exp1) (Chromosome region maintenance 1 protein homolog)

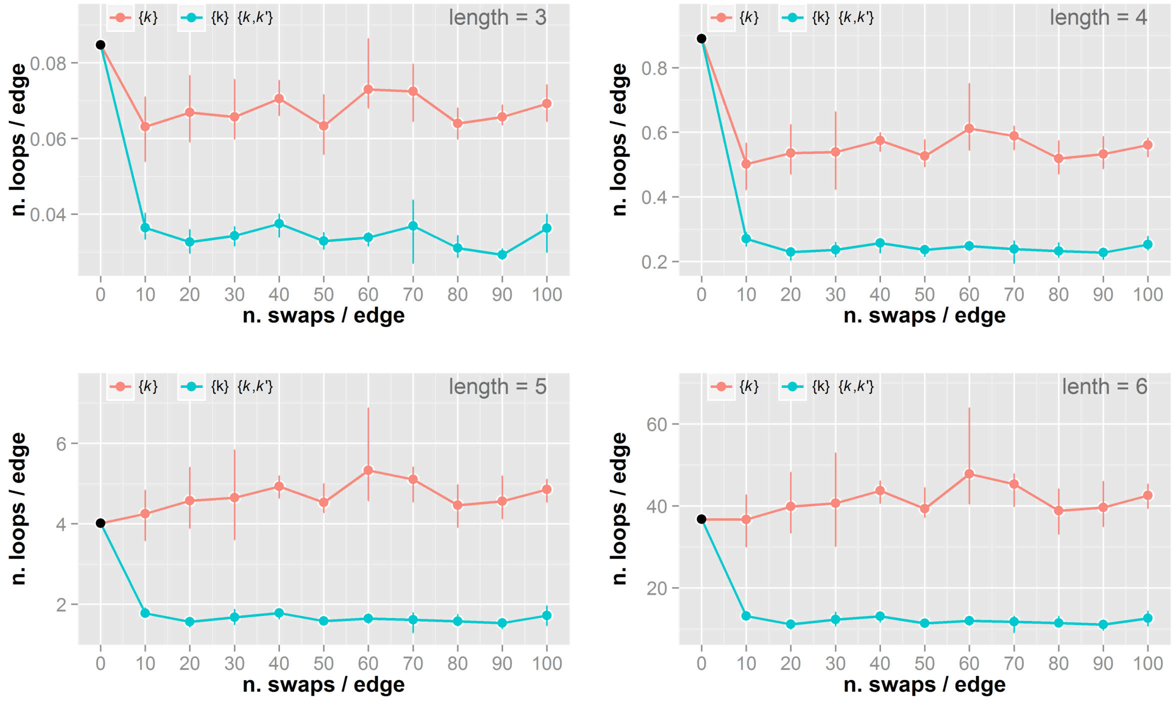
Figure S1. Number of loops of length 3-6 in the all PPINs of the datasets during randomisation.

The change in number of loops per edge during Markov Chain Graph Dynamics (MCGD) is reported for loops of length 3 (a), 4 (b), 5 (c) and 6 (d) in the H. Sapiens V (BP-MS) network. Simulations were performed under two set of constraints: 1) degree distribution {k} (in red in the plots) and 2) degree distribution {k} and degree-degree correlation {k,k'} (in light blue).

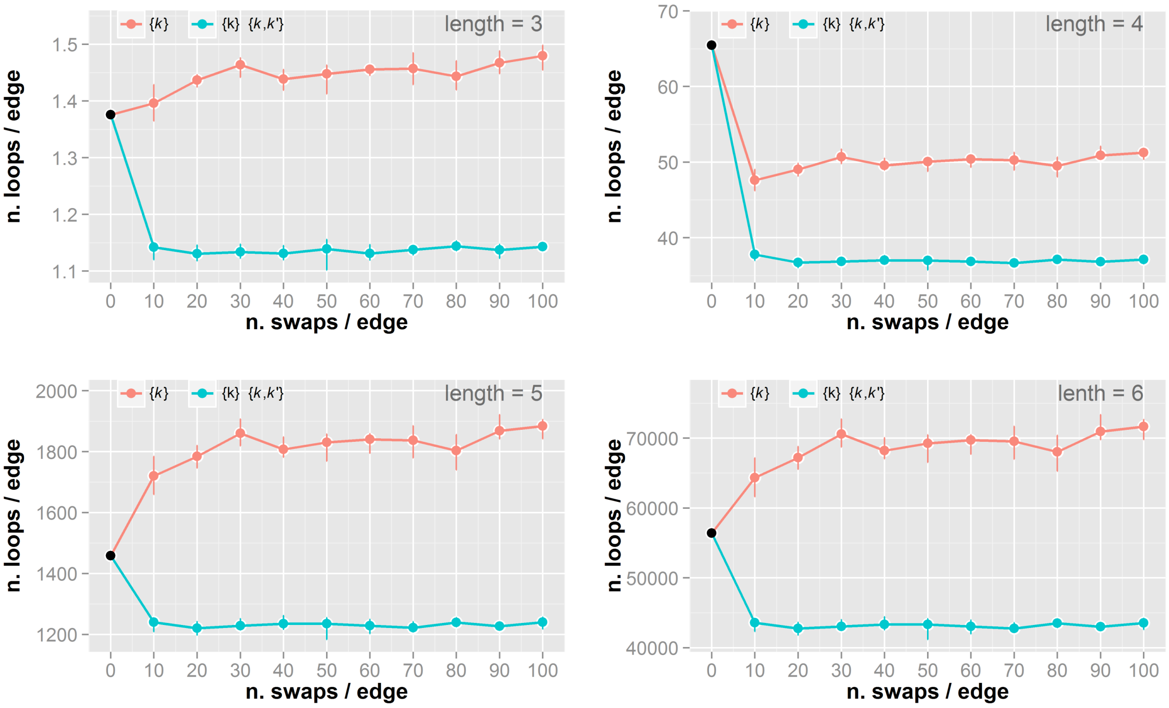
C.elegans I



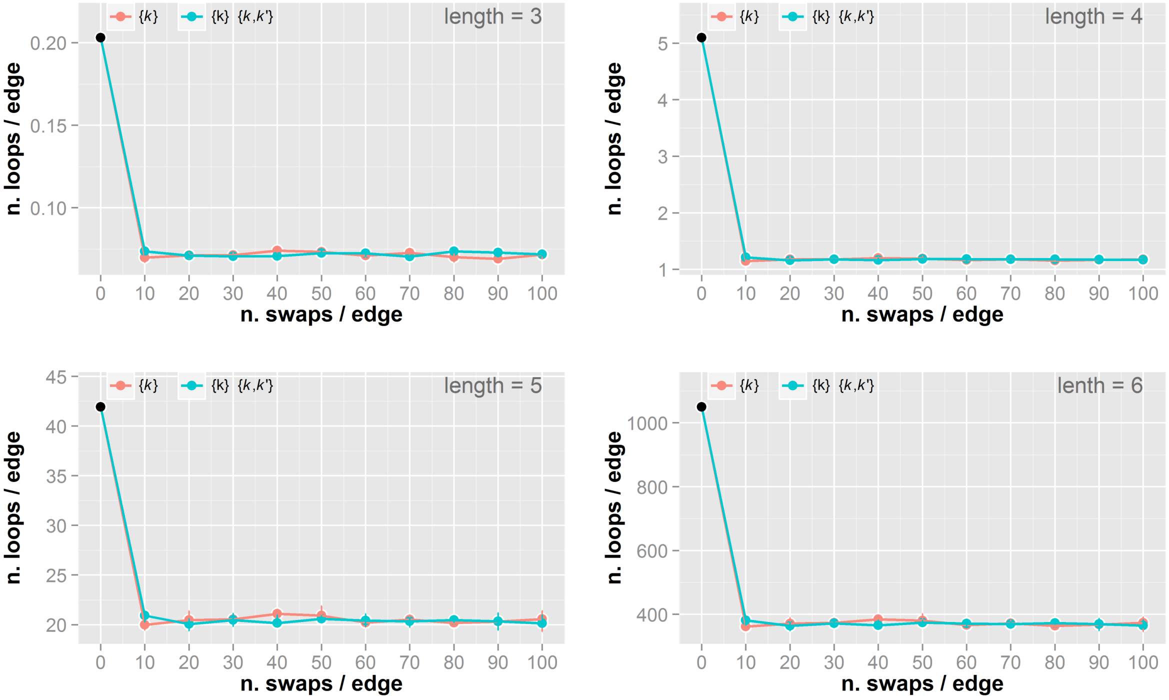
C.elegans II



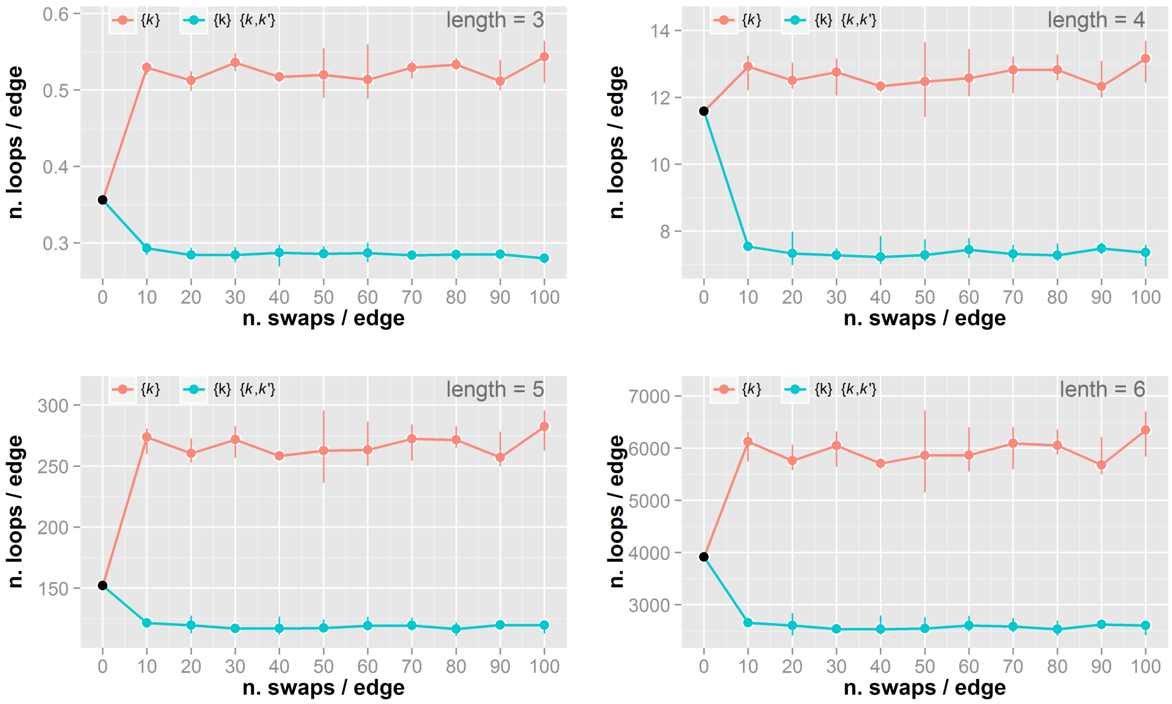
C.jejuni



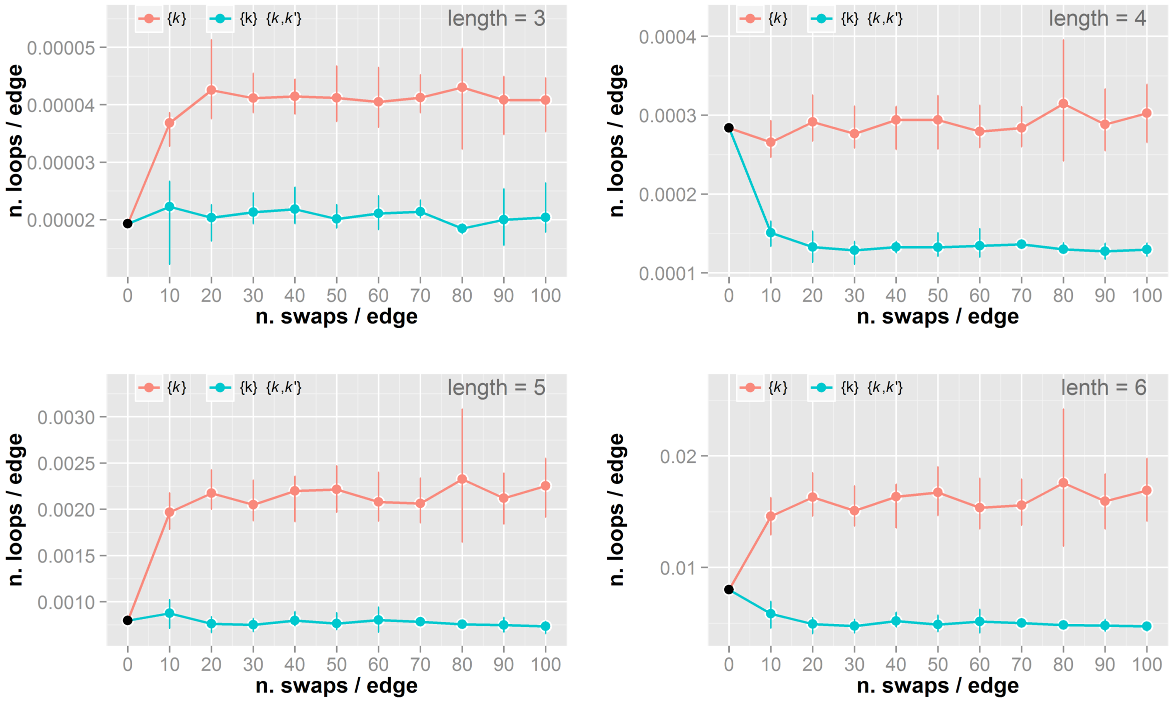
D.melanogaster



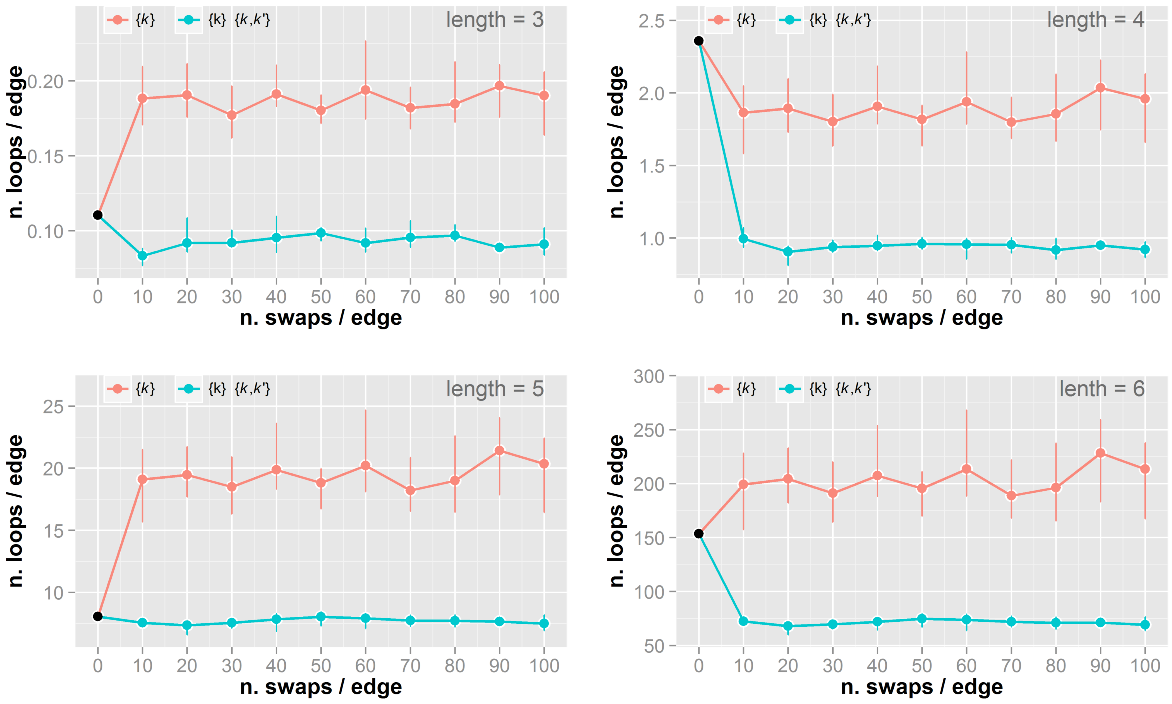
E.coli



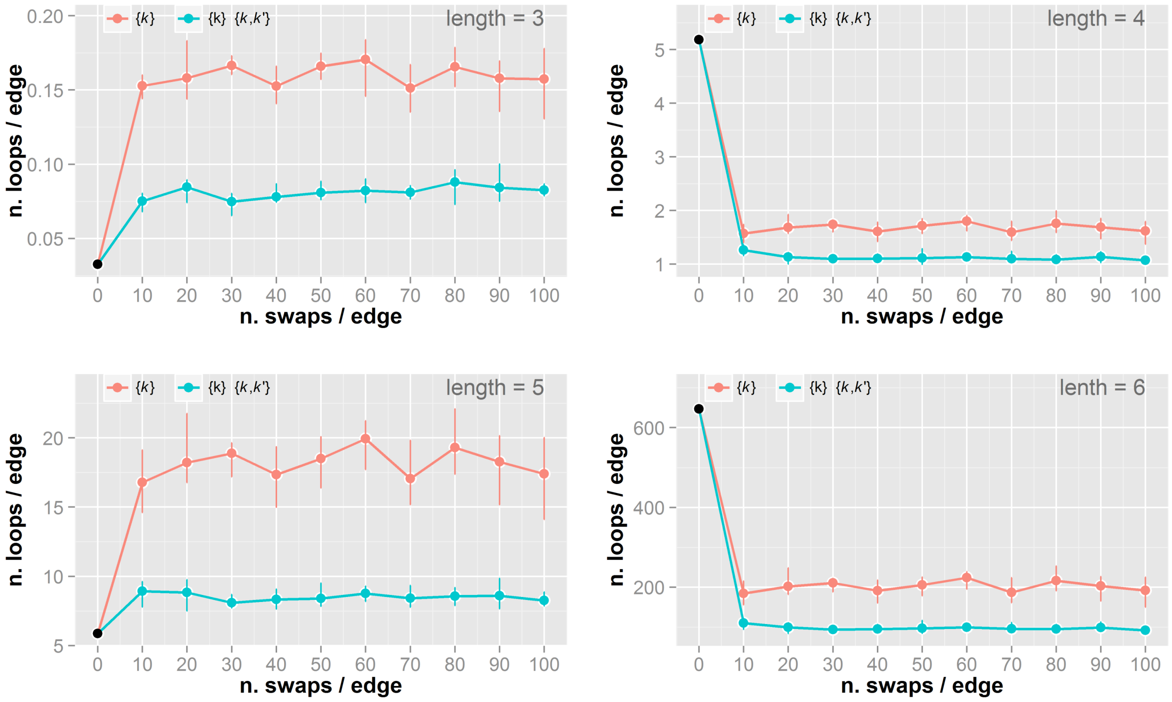
H.pylori



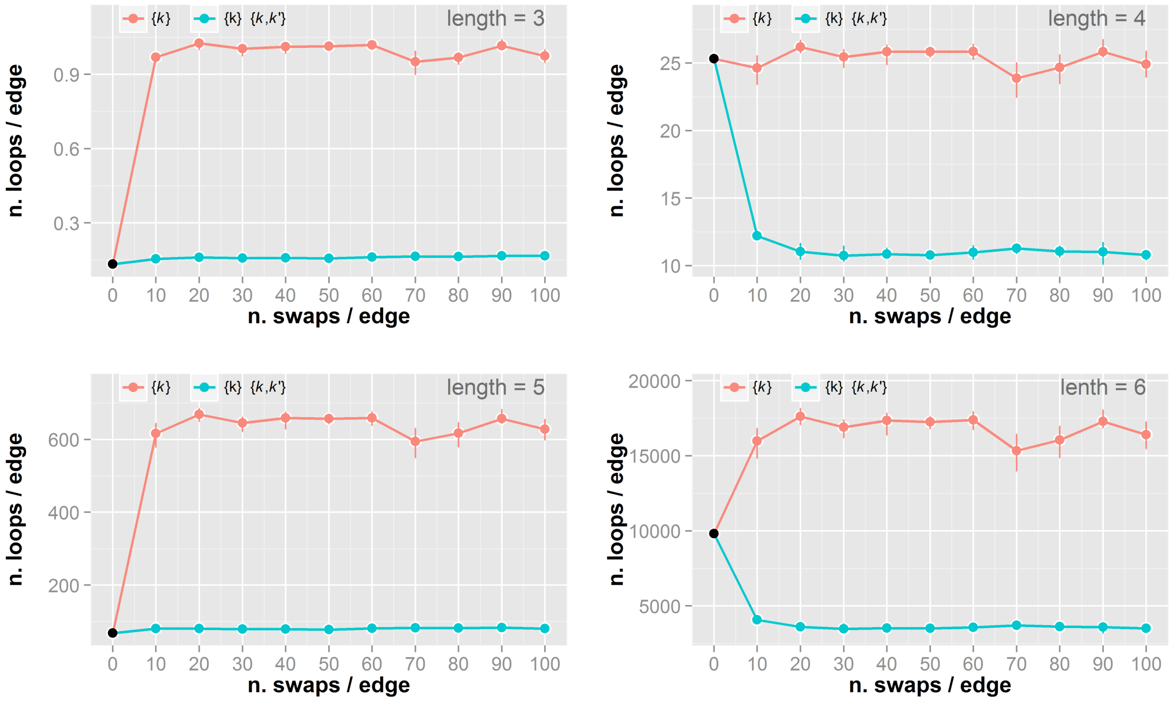
H.sapiens I



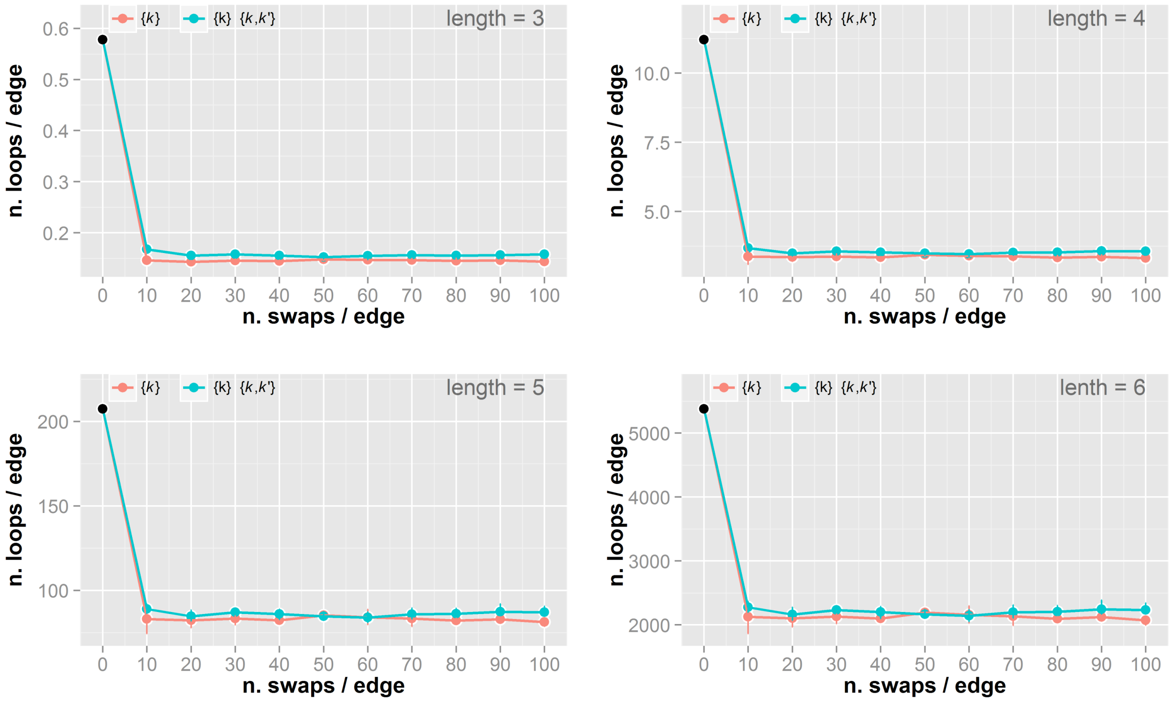
H.sapiens II



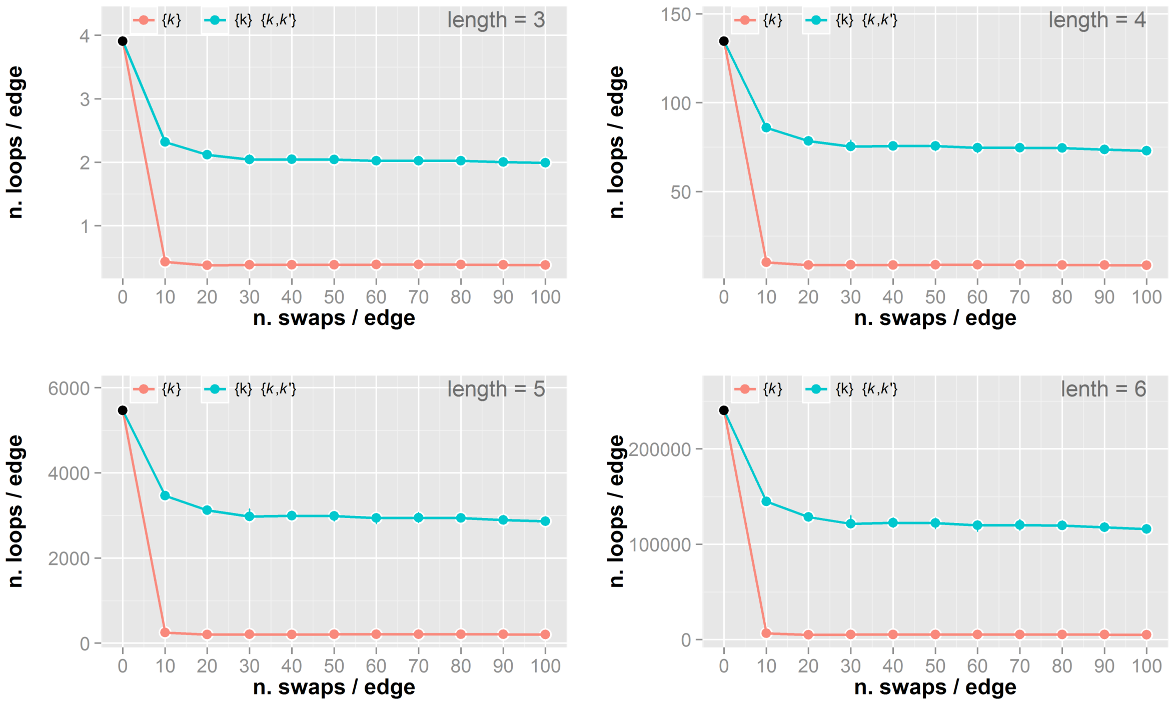
H.sapiens III



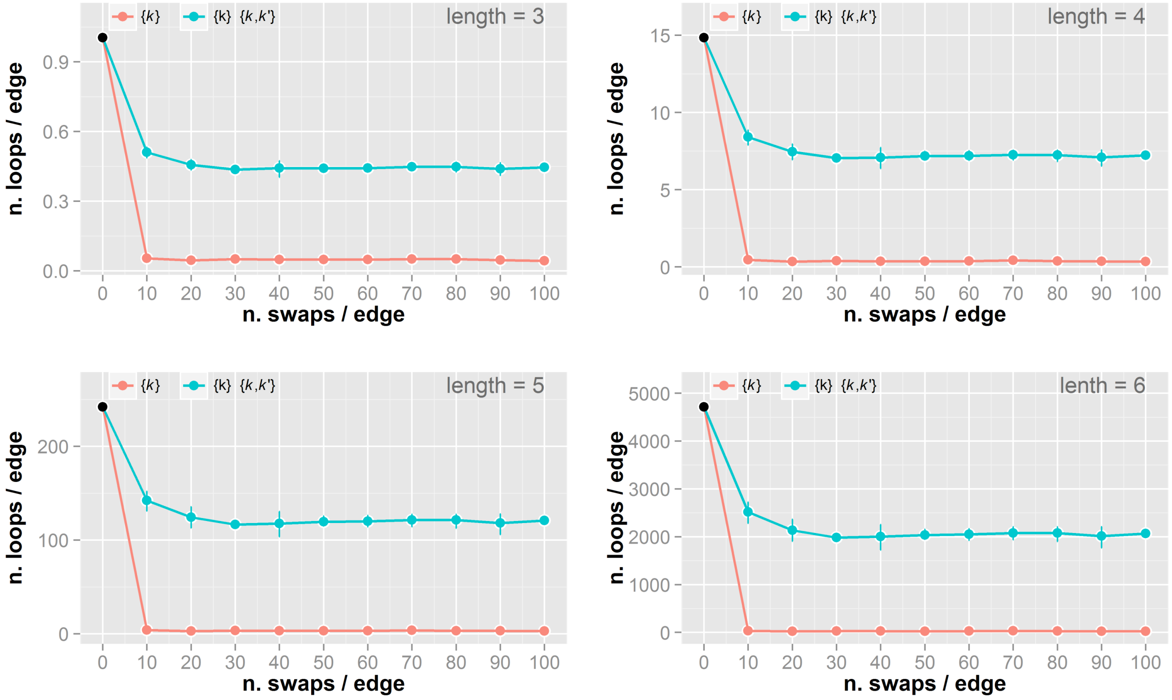
H.sapiens IV

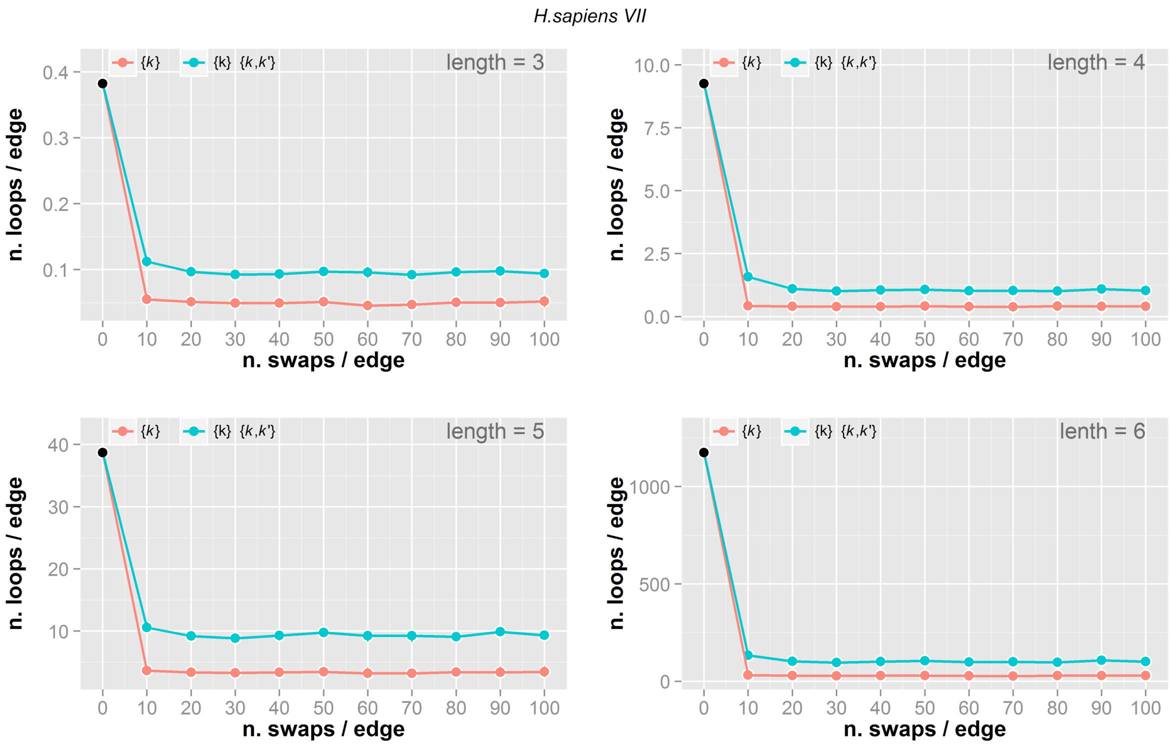


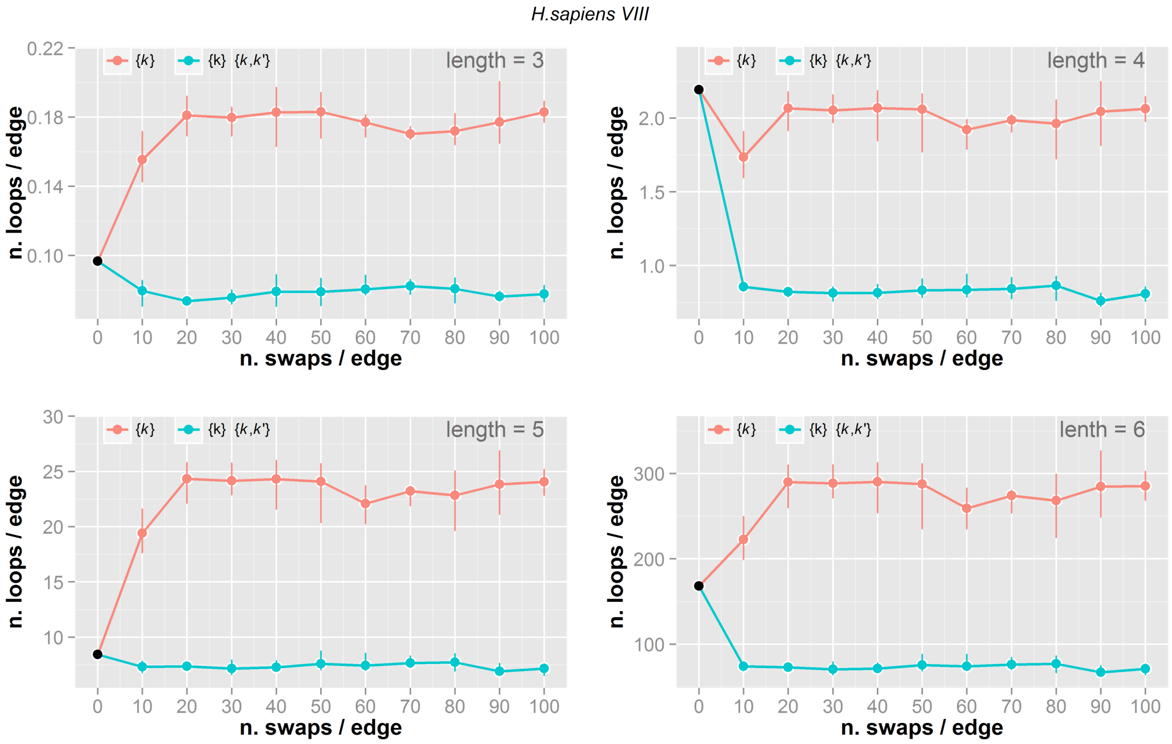
H.sapiens V



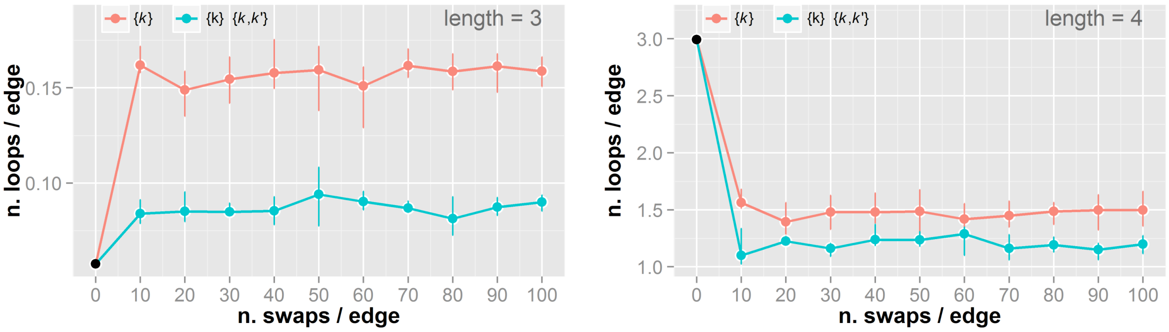
H.sapiens VI



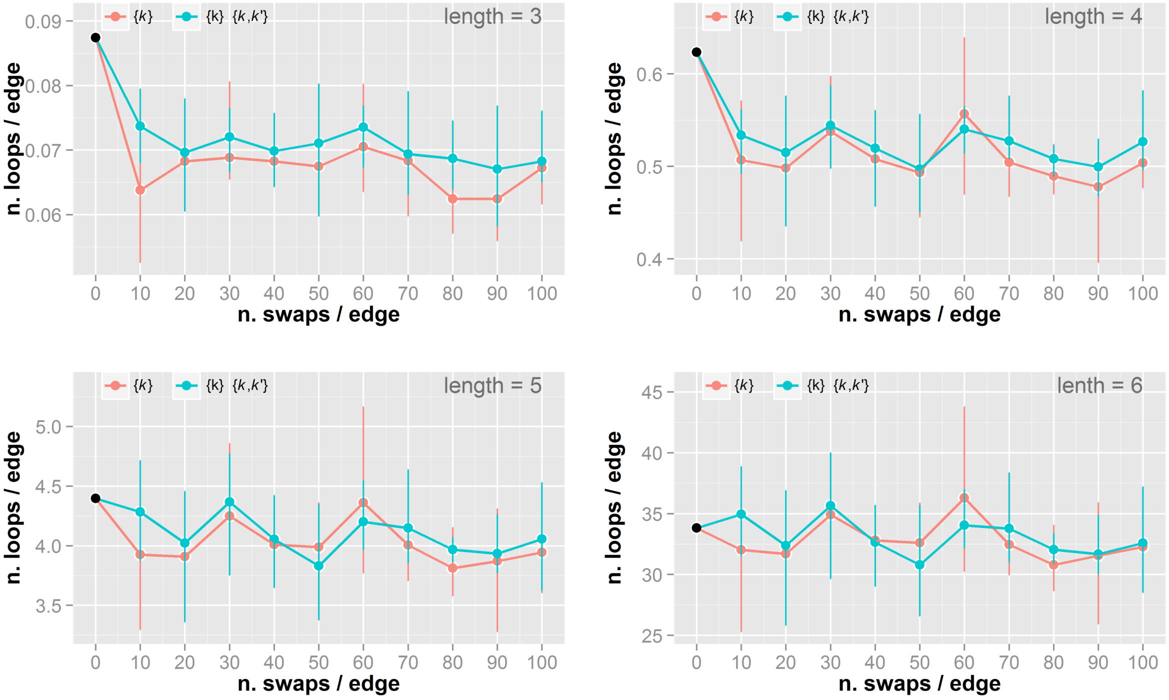

H.sapiens VII
{k}
{k} {k,k'}
length = 3
n. loops / edge
0.4
0.3
0.2
0.1
n. swaps / edge
0
10
20
30
40
50
60
70
80
90
100
length = 4
10.0
7.5
5.0
2.5
0.0
length = 5
40
30
20
10
lenth = 6
1000
500
0


H.sapiens VIII
{k}
{k} {k,k'}
length = 3
n. loops / edge
0.22
0.18
0.14
0.10
n. swaps / edge
0
10
20
30
40
50
60
70
80
90
100
length = 4
2.0
1.5
1.0
length = 5
30
25
20
15
10
lenth = 6
300
200
100

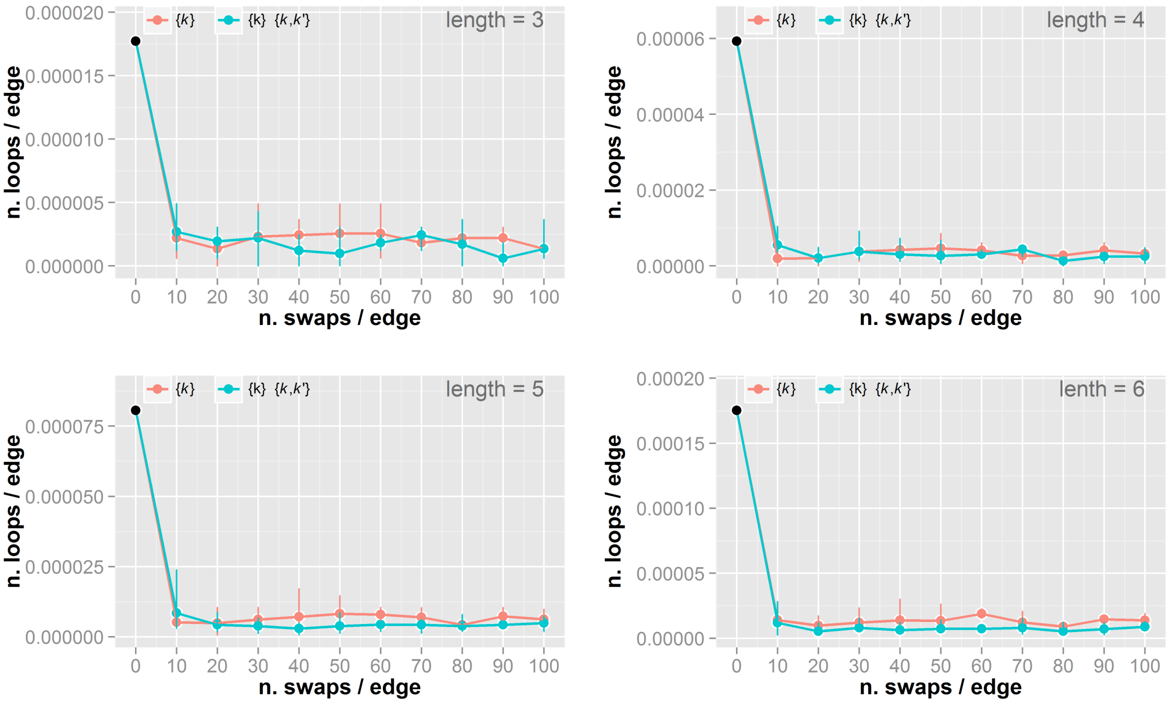
M.loti



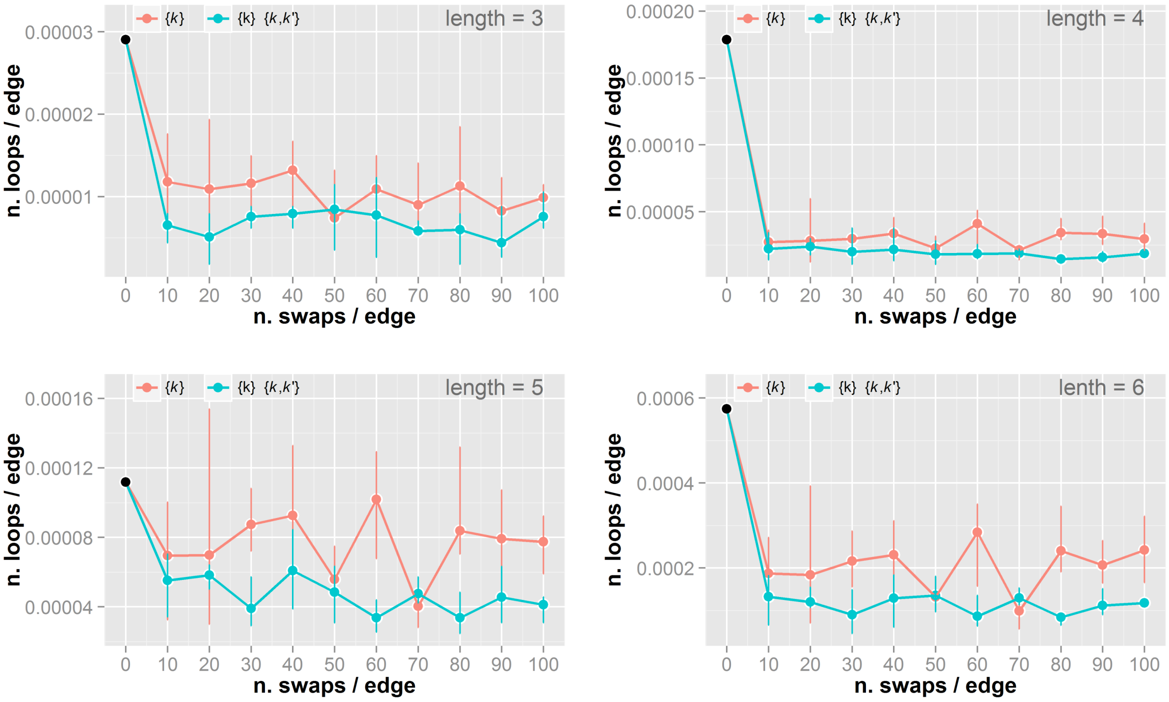
P.falciparum



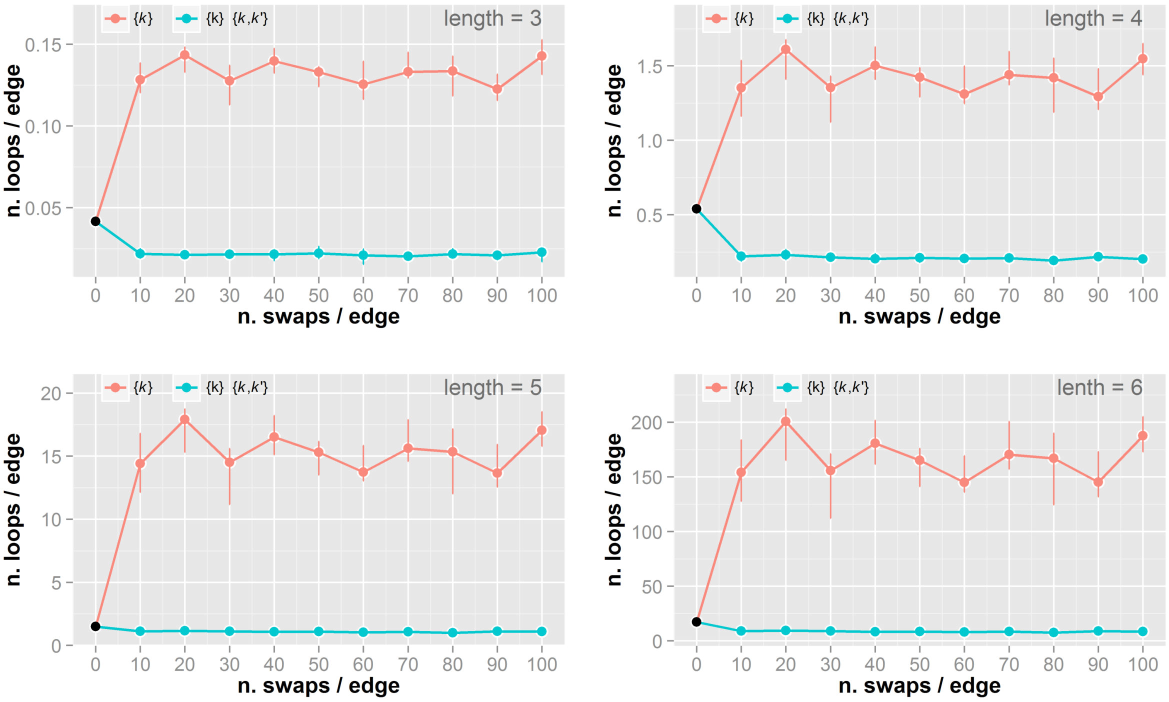
S.cerevisiae I



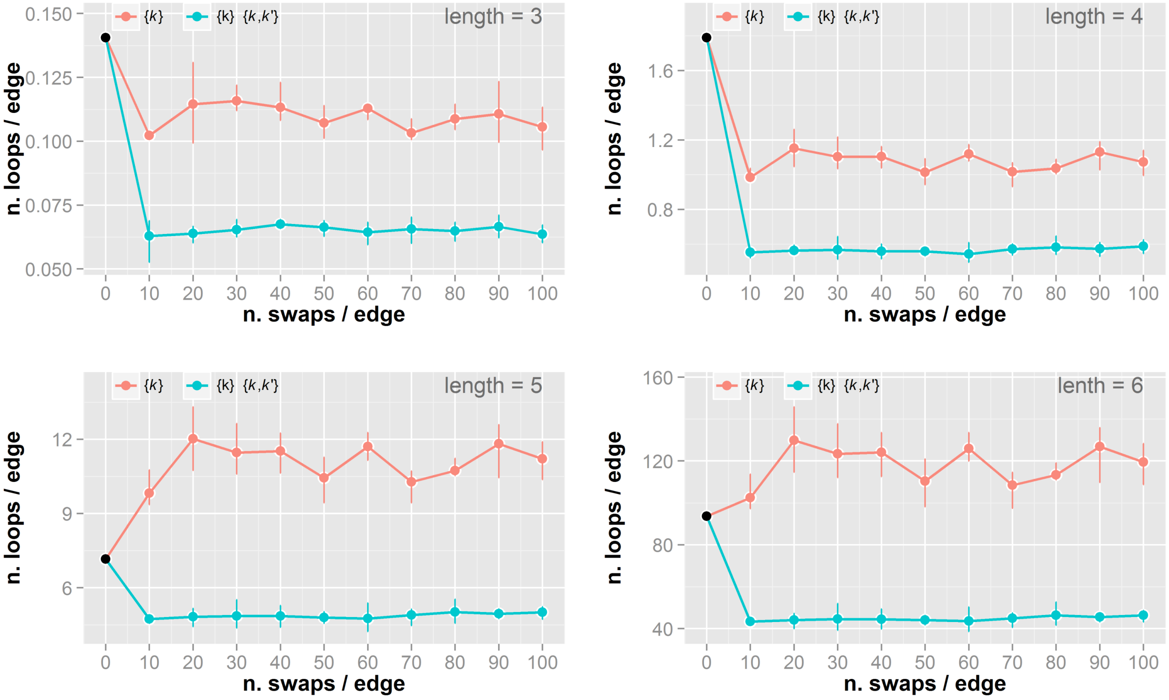
S.cerevisiae II



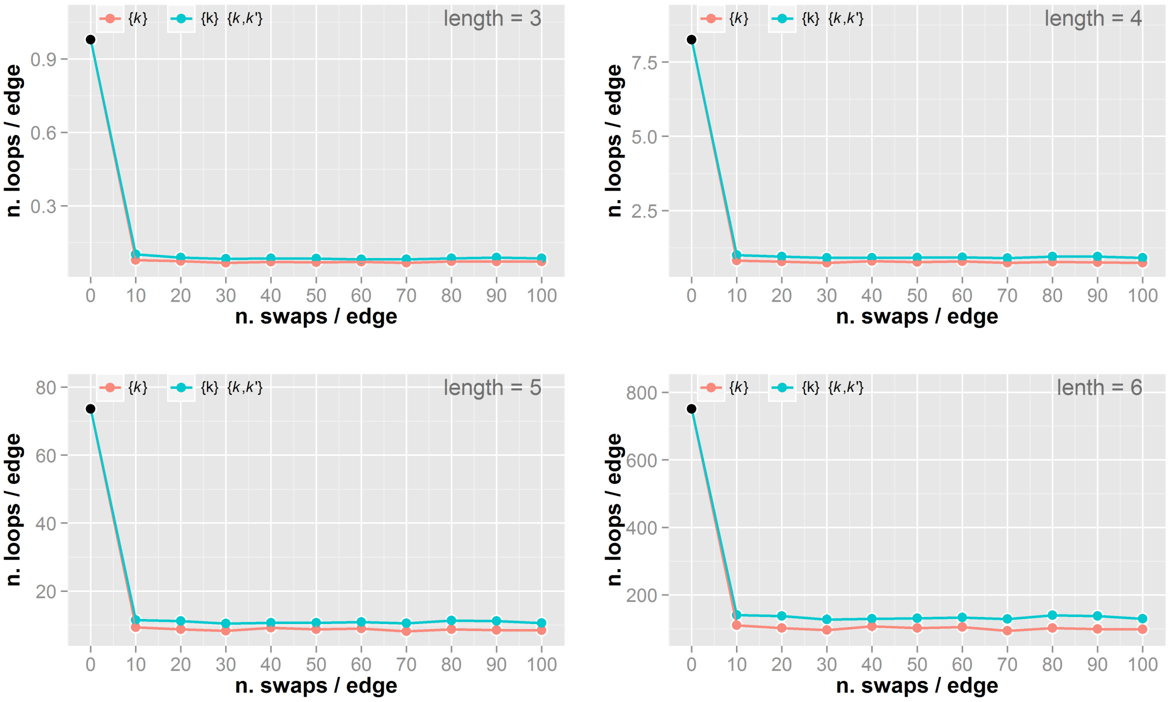
S.cerevisiae III



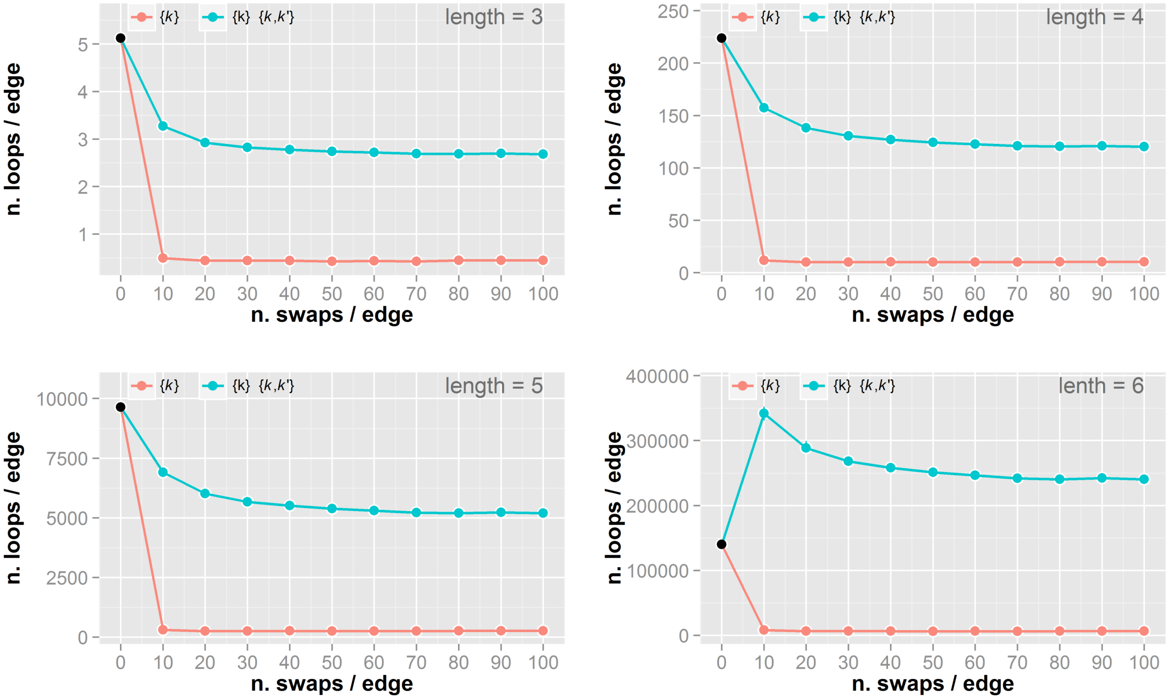
S.cerevisiae IV



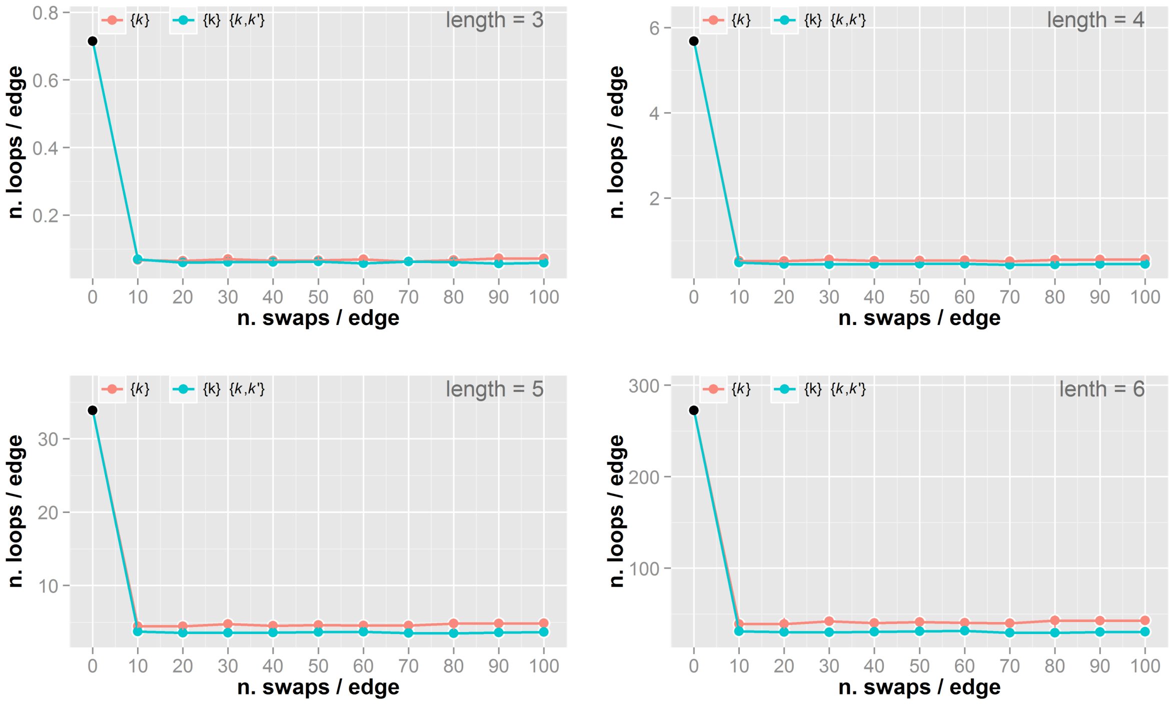
S.cerevisiae IX



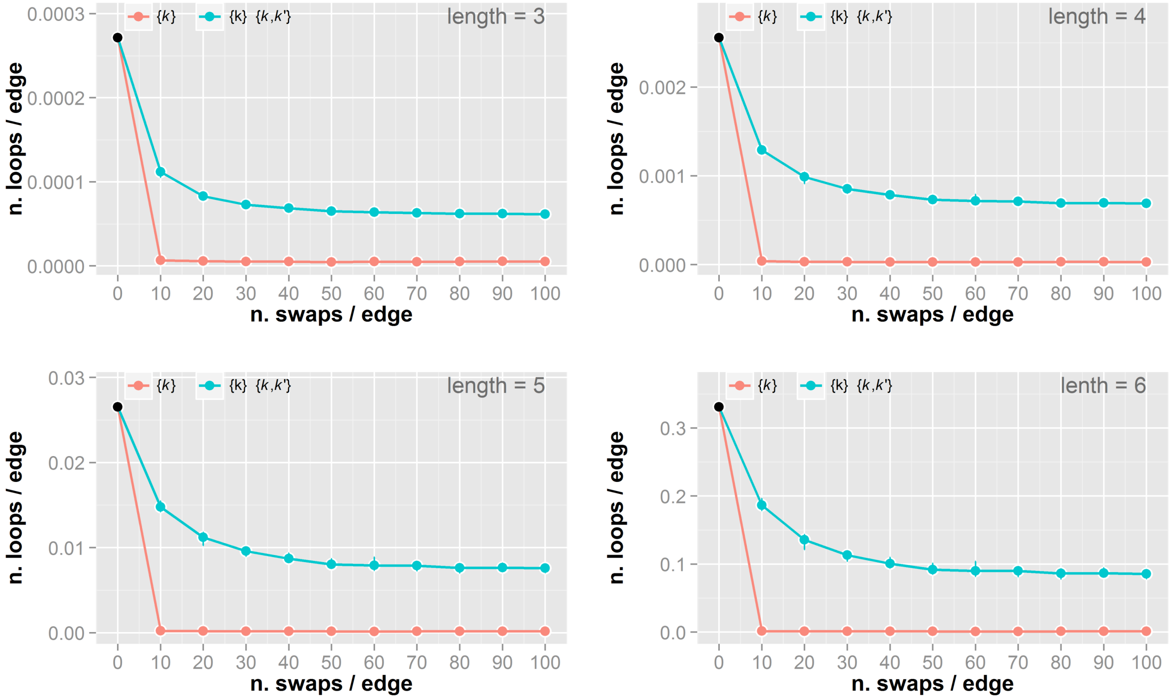
S.cerevisiae V



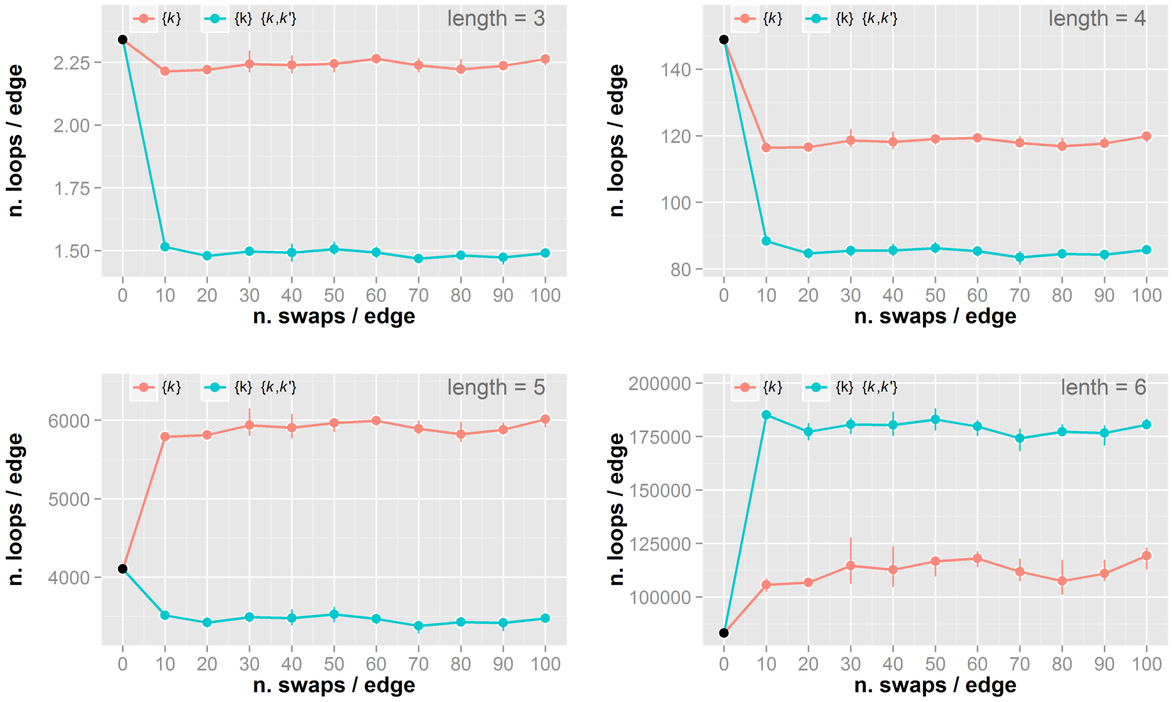
S.cerevisiae VI



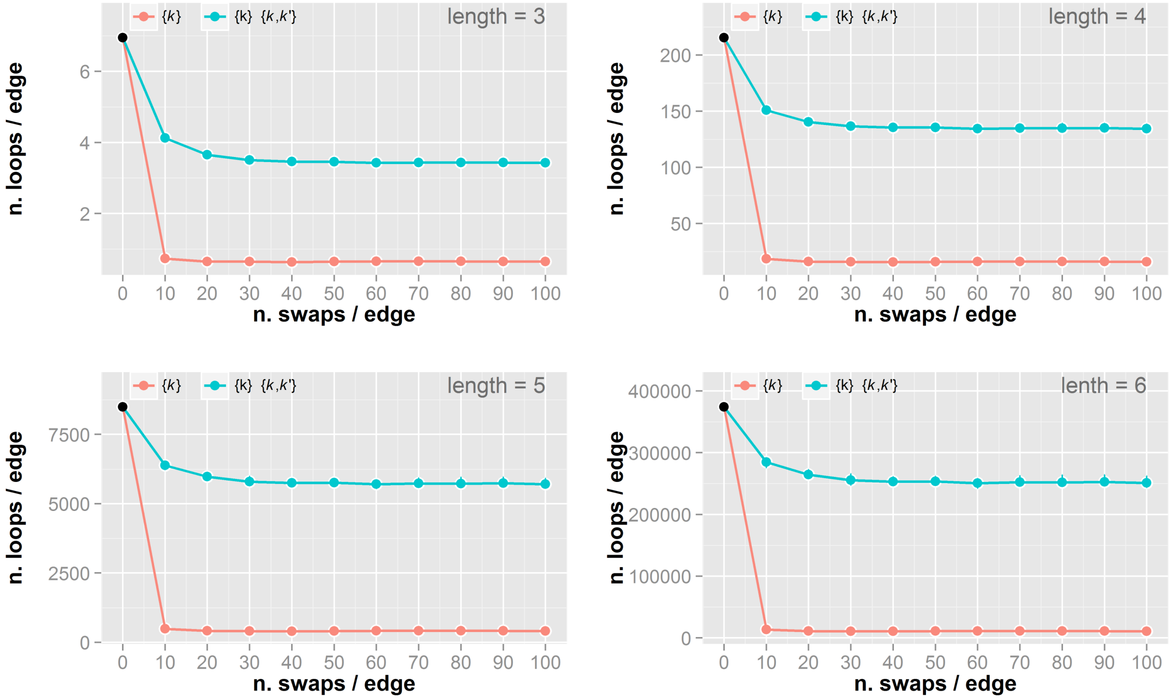
S.cerevisiae VII

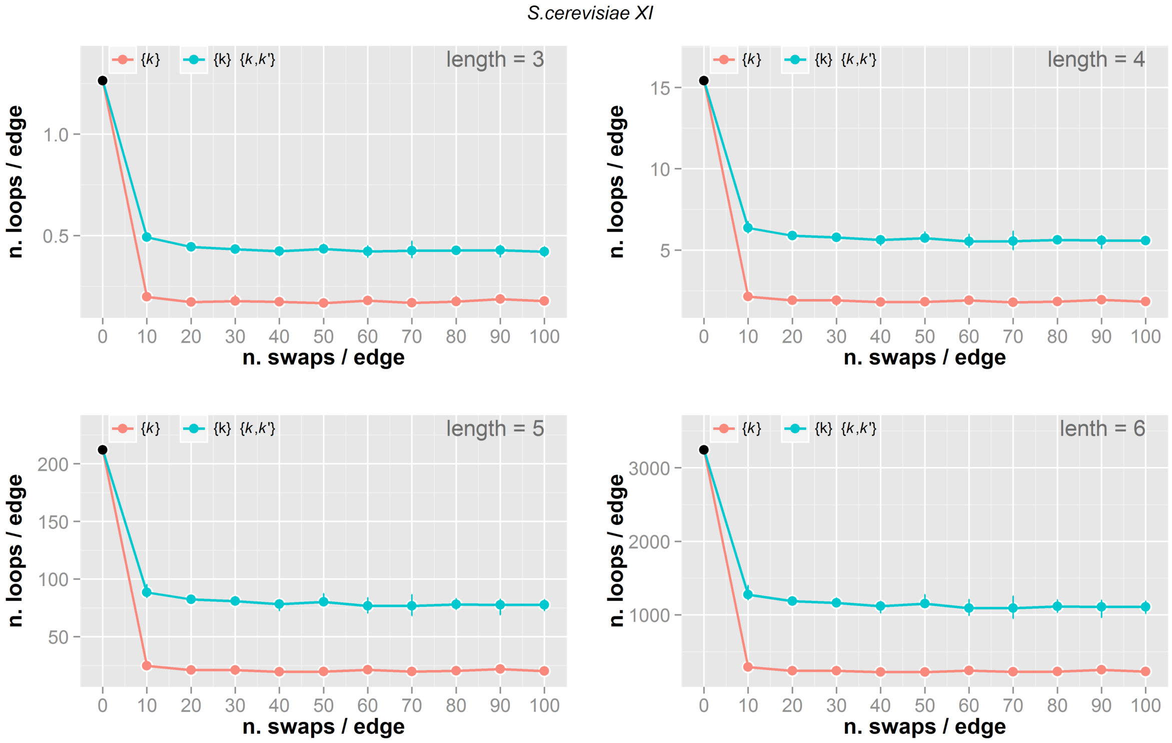


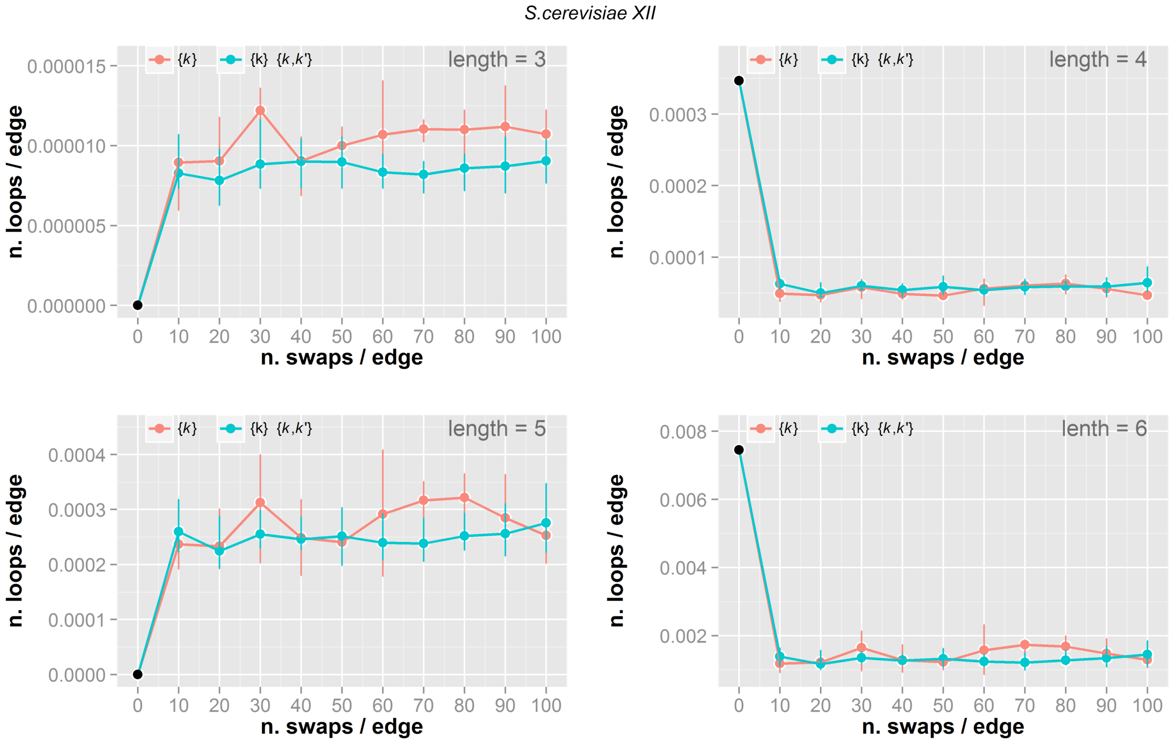
S.cerevisiae VIII



S.cerevisiae X




S.cerevisiae XI
{k}
{k} {k,k'}
length = 3
length = 4
length = 5
lenth = 6
n. loops / edge
n. swaps / edge
1.0
0.5
15
10
5
200
150
100
50
3000
2000
1000
0
10
20
30
40
50
60
70
80
90
100


S.cerevisiae XII
{k}
{k} {k,k'}
length = 3
length = 4
length = 5
lenth = 6
n. loops / edge
n. swaps / edge
0.000015
0.000010
0.000005
0.000000
0.0003
0.0002
0.0001
0.0004
0.0000
0.008
0.006
0.004
0.002
0
10
20
30
40
50
60
70
80
90
100

T.pallldum

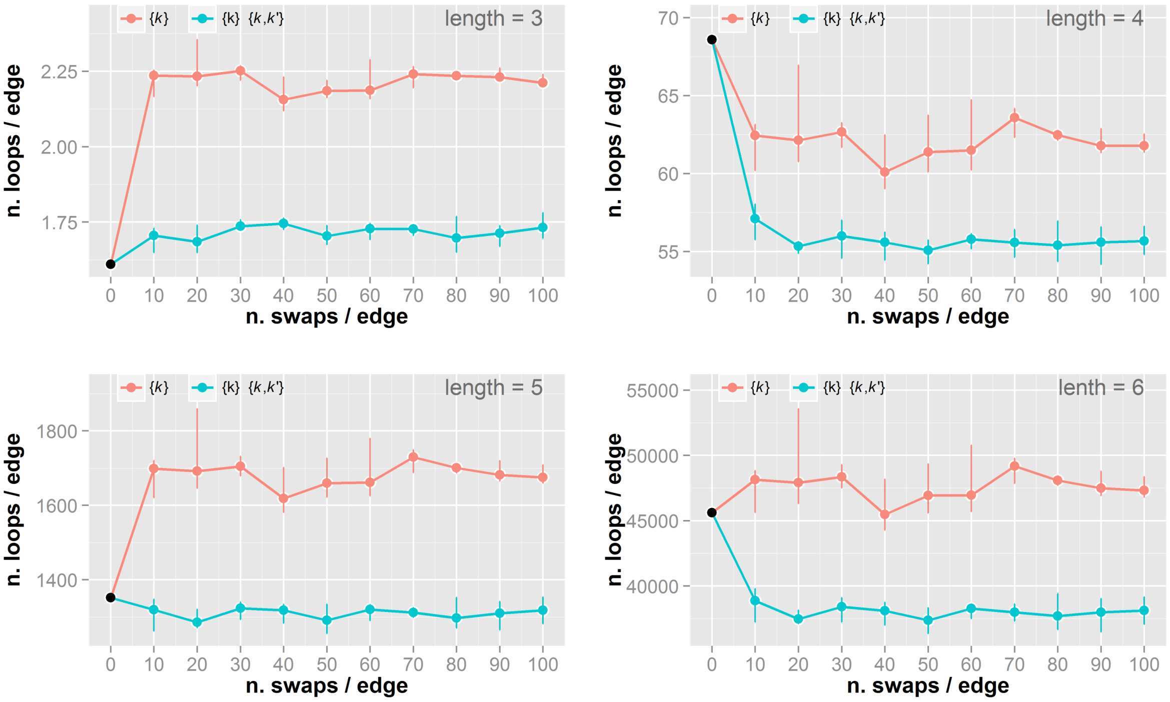
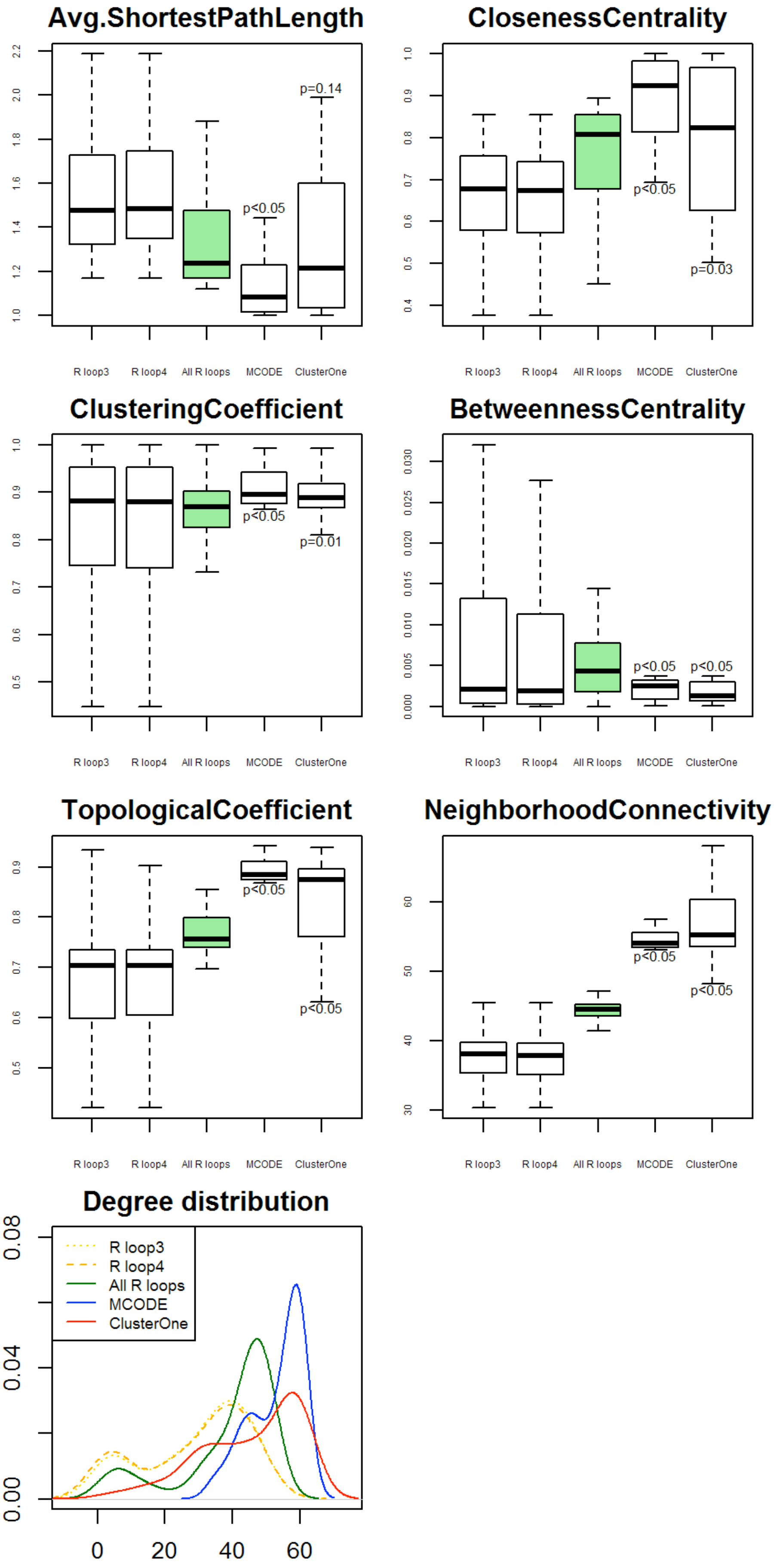

{k}
{k} {k,k'}
length = 3
2.25
2.00
1.75
n. loops / edge
0
10
20
30
40
50
60
70
80
90
100
n. swaps / edge
length = 4
70
65
60
55
length = 5
1800
1600
1400
lenth = 6
55000
50000
45000
40000

Figure S2. Comparison of network properties in the resilient loop set with the 1st cluster obtained by MCODE and by Cluster One

The following topological network properties were obtained with the Network Analyzer function in Cytoscape: average shortest path length, closeness centrality, clustering coefficient, betweenness centrality, topological coefficient, neighborhood connectivity and degree distribution. The distributions of values for the nodes in each set are reported as boxplot. The sets are: resilient loops of length 3 (**R loop3**), resilient loops of length 4 (**R loop4**), resilient loops of length 3 and 4 (**All R loops**), MCODE 1st cluster (MCODE) and Cluster One 1st cluster (Cluster One). Statistical significance of the difference between the distribution for the resilient loop set (**All R loops**) and the clusters identified by MCODE and Cluster One was calculated by Welch t-test in R (Table S3b) and annotated on the plots.

The resilient loop set has generally longer interconnecting paths, smaller Neighborhood Connectivity and smaller Topological Coefficients than MCODE and ClusterOne clusters. The Clustering Coefficient is comparable, but several nodes in the resilient loops have significantly lower value. Closeness Centrality is lower in the loop set, while Betweenness is higher. Differences are more evident between the resilient loop set and MCODE. The trend of all the indices is consistent with the fact that resilient loops have a much lower connectivity (as seen in the shift of the degree distribution towards smaller values). This is expected as the only included edges are “in-loop”.


Avg.ShortestPathLength
2.2
2.0
1.8
1.6
1.4
1.2
1.0
p=0.14
p<0.05
R loop3
R loop4
All R loops
MCODE
ClusterOne
ClosenessCentrality
1.0
0.9
0.8
0.7
0.6
0.5
0.4
p<0.05
p=0.03
R loop3
R loop4
All R loops
MCODE
ClusterOne
ClusteringCoefficient
1.0
0.9
0.8
0.7
0.6
0.5
p<0.05
p=0.01
R loop3
R loop4
All R loops
MCODE
ClusterOne
BetweennessCentrality
0.030
0.025
0.020
0.015
0.010
0.005
0.000
p<0.05
p<0.05
R loop3
R loop4
All R loops
MCODE
ClusterOne
TopologicalCoefficient
0.9
0.8
0.7
0.6
0.5
p<0.05
p<0.05
R loop3
R loop4
All R loops
MCODE
ClusterOne
NeighborhoodConnectivity
60
50
40
30
p<0.05
p<0.05
R loop3
R loop4
All R loops
MCODE
ClusterOne
Degree distribution
R loop3
R loop4
All R loops
MCODE
ClusterOne
0.08
0.04
0.00
0
20
40
60

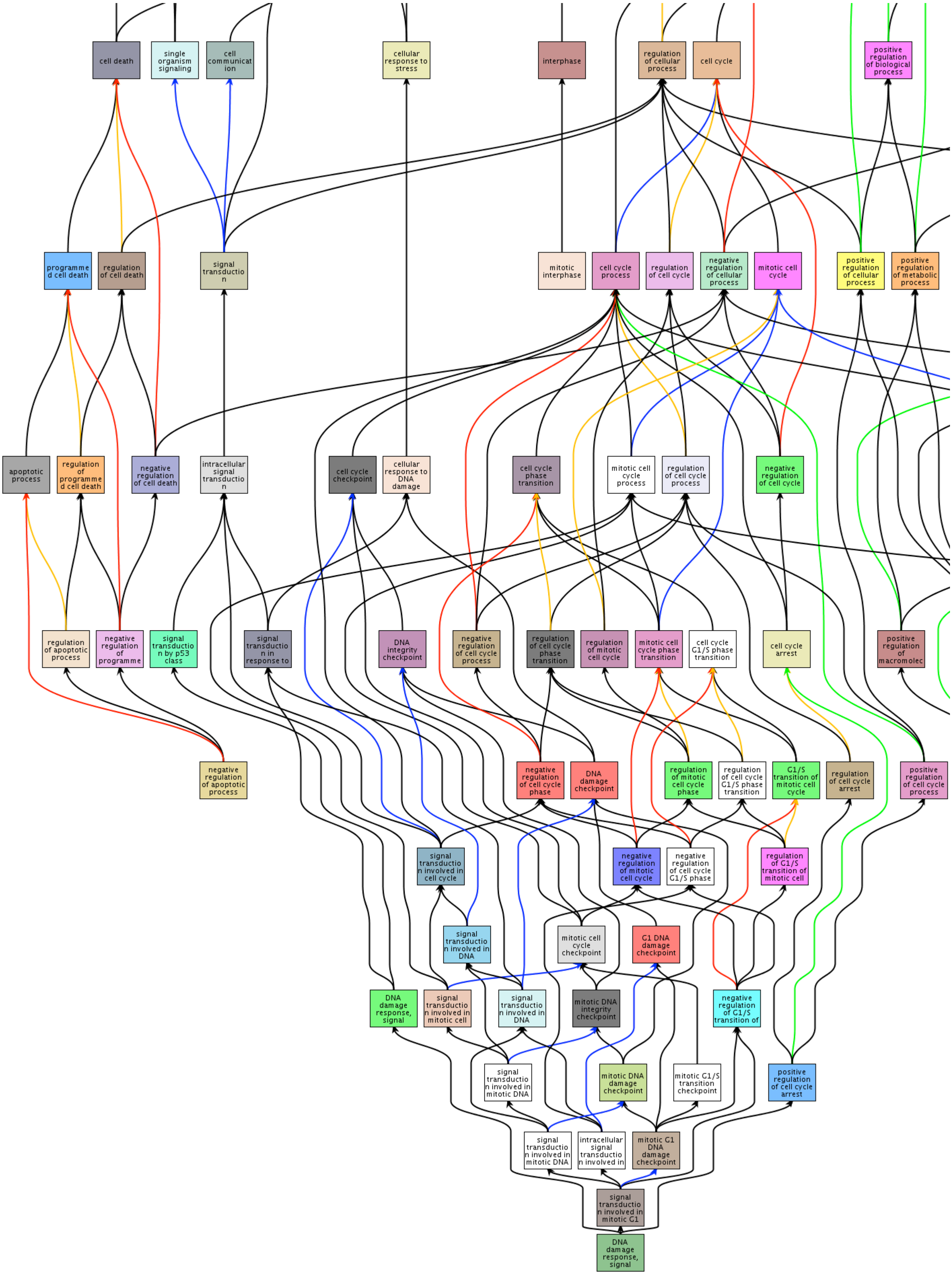


Figure S3. Hierarchical representation of "Cell Cycle" related GO terms in Trend 4 in GO Hierarchy generated by QuickGO

Colored terms are "Cell Cycle" related terms in Trend 4 of Figure 6.

Figure S4. Comparison of a fully random model with an MCGD simulation with constraints on degree distribution only (red) and with both degree distribution and degree-degree correlation (blue).

Evolution of number of loops of length 3 per link in the H. sapiens V (BP-MS) network during randomization via MCGD preserving the degree sequence alone (red) and the degree sequence and the degree-degree correlations (blue). The dynamics constraining the degree sequence converges to the theoretically predicted value, shown by the dashed line, given by formula (5) in the Supplementary material. The expected density of triangles in the fully random i.e. Erdos-Renyi model with the same average degree but Poissonian degree distribution, given by formula (8), is shown as a dotted line for comparison.

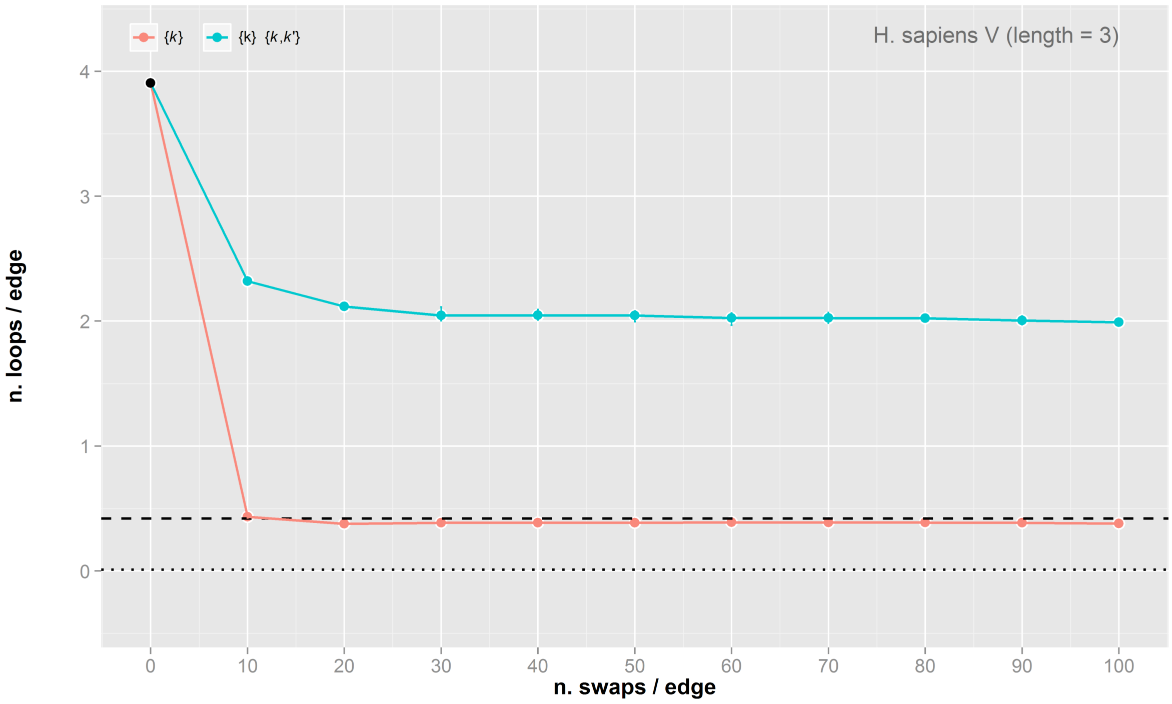
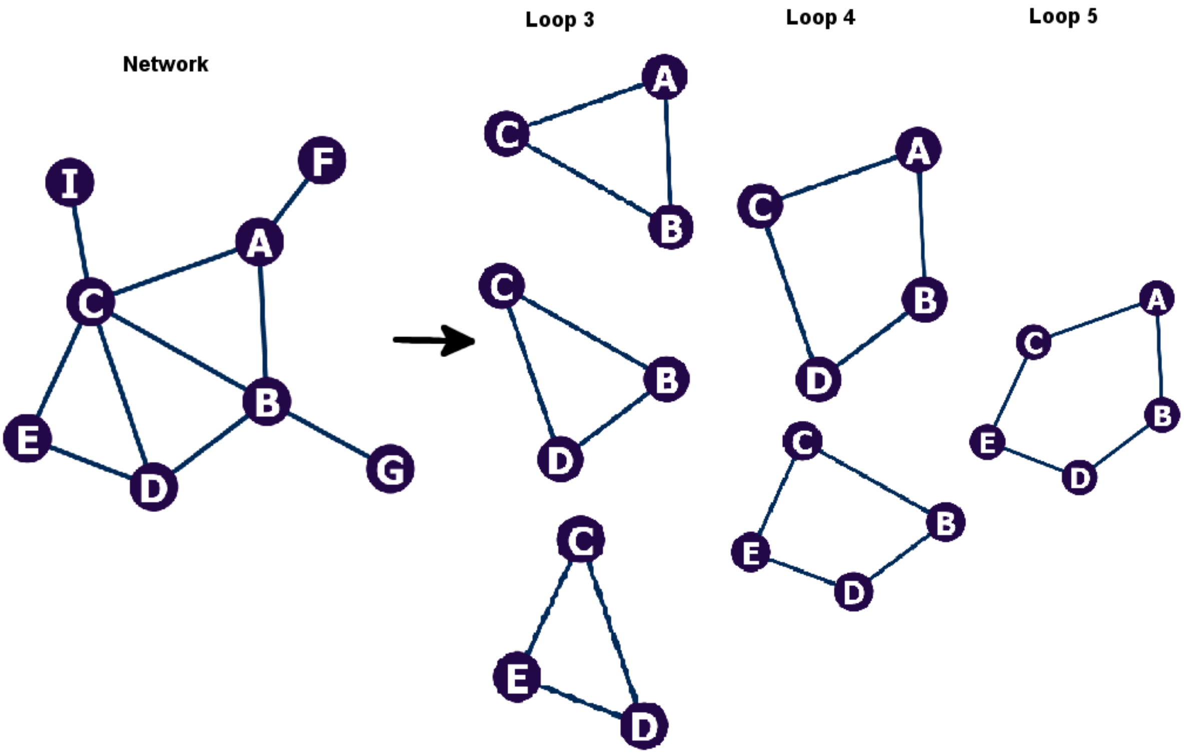


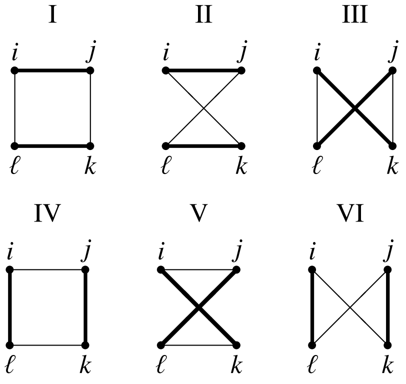
Figure S5. Introductory definition of short loops



Description of the algorithm for Markov Chain Graph Dynamics

1 Degree-Constrained Graph Dynamics Based on Edge Swaps

We use rewiring algorithms that randomize protein interaction networks, yet conserving the degrees of its nodes, by repeated applications of edge swaps that act on quadruplets of nodes. We denote the edge swaps that can act on each quadruplet (i, j, k, ℓ) as



where thick lines indicate existing links and thin lines indicate absent links (that will be swapped with the existing ones) and (IV, V, VI) represent the inverses of (I, II, III). We group the edge swaps into the three pairs (I,IV), (II,V), and (III,VI), and label all three resulting auto-invertible operations for each ordered quadruple (i, j, k, ℓ) by a subscript α and we denote the auto-invertible edge swaps $F_{ijk\ell;\alpha}$, with $i < j < k < \ell$ and $\alpha \in \{1, 2, 3\}$. By repeated applications of the above edge swaps, we can randomly generate graphs from the set $G[\boldsymbol{k}] = \{\boldsymbol{c} \in G|\ \boldsymbol{k}(\boldsymbol{c}) = \boldsymbol{k}\}$ of graphs with the same degree sequence $\boldsymbol{k} = (k_1, \ldots, k_N)$ as the starting graph.

In order to generate graphs with specified probabilities $p(\boldsymbol{c}) = Z^{-1} \exp[-H(\boldsymbol{c})]$ from the set $G[\boldsymbol{k}]$, we define a Markov Chain

$$\forall \boldsymbol{c} \in G[\boldsymbol{k}] : \quad p_{t+1}(\boldsymbol{c}) \quad = \sum_{\boldsymbol{c}' \in G[\boldsymbol{k}]} W(\boldsymbol{c}|\boldsymbol{c}') p_t(\boldsymbol{c}') \qquad (1)$$

where the one-step transition probability $W(\boldsymbol{c}|\boldsymbol{c}')$ from graph $\boldsymbol{c}'$ to $\boldsymbol{c}$ is chosen in such a way that the probability $p_t(\boldsymbol{c})$ of observing graph $\boldsymbol{c}$ at time t in the process, converges to $p(\boldsymbol{c})$ for long times. More specifically, for any set Φ of reversible elementary moves $F : G[\boldsymbol{k}] \to G[\boldsymbol{k}]$, we choose transition probabilities of the form

$$W(\boldsymbol{c}|\boldsymbol{c}') = \sum_{F\in\Phi} q(F|\boldsymbol{c}')\Big[\delta_{\boldsymbol{c},F\boldsymbol{c}'}A(F\boldsymbol{c}'|\boldsymbol{c}') + \delta_{\boldsymbol{c},\boldsymbol{c}'}[1 - A(F\boldsymbol{c}'|\boldsymbol{c}')]\Big] \tag{2}$$

so that at each time step a candidate move $F \in \Phi$ is drawn with probability $q(F|\boldsymbol{c}')$, where $\boldsymbol{c}'$ denotes the current graph, and this move is accepted (and the transition $\boldsymbol{c}' \to \boldsymbol{c} = F\boldsymbol{c}'$ executed) with probability $A(F\boldsymbol{c}'|\boldsymbol{c}') \in [0, 1]$, which depends on the current graph $\boldsymbol{c}'$ and on the proposed new graph $F\boldsymbol{c}'$. If the move is rejected, which happens with probability $1 - A(F\boldsymbol{c}'|\boldsymbol{c}')$, the system stays in $\boldsymbol{c}'$. One can prove that the process (1) will converge towards the equilibrium measure $p_\infty(\boldsymbol{c}) = Z^{-1} \exp[-H(\boldsymbol{c})]$ upon making in (2) the choices [1]

$$q(F|\boldsymbol{c}) = I_F(\boldsymbol{c})/n(\boldsymbol{c}) \tag{3}$$

$$A(\boldsymbol{c}|\boldsymbol{c}') = \left[1 + \frac{n(\boldsymbol{c})}{n(\boldsymbol{c}')}\mathrm{e}^{[H(\boldsymbol{c})-H(\boldsymbol{c}')]}\right]^{-1} \tag{4}$$

Here $I_F(\boldsymbol{c}) = 1$ if the move F can act on graph $\boldsymbol{c}$, $I_F(\boldsymbol{c}) = 0$ otherwise, and $n(\boldsymbol{c})$ denotes the total number of moves that can act on a graph $\boldsymbol{c}$. For the edge-swap dynamics illustrated above, this could be calculated [1], giving (with $\mathrm{Tr}\boldsymbol{A} = \sum_i A_{ii}$):

$$\begin{aligned} n(\boldsymbol{c}) = \sum_{F\in\Phi} I_F(\boldsymbol{c}) &= \frac{1}{4}\Big(\sum_i k_i\Big)^2 + \frac{1}{4}\sum_i k_i - \frac{1}{2}\sum_i k_i^2 - \frac{1}{2}\sum_{ij} k_i c_{ij} k_j \\ &\quad + \frac{1}{4}\mathrm{Tr}(\boldsymbol{c}^4) + \frac{1}{2}\mathrm{Tr}(\boldsymbol{c}^3). \end{aligned} \tag{5}$$

Hence, the graph dynamics algorithm described by (2) prescribes: at each time step (i) pick uniformly at random a quadruplet (i, j, k, ℓ) of sites, (ii) if at least one of the three edge swaps $F_{ijk\ell;\alpha}$ can act on the instantaneous configuration $\boldsymbol{c}'$, select one of these uniformly at random and execute it with an acceptance probability

$$A(\boldsymbol{c}|\boldsymbol{c}') = \left[1 + \mathrm{e}^{E(F_{ijk\ell;\alpha}\boldsymbol{c}') - E(\boldsymbol{c}')}\right]^{-1}, \tag{6}$$

with $E(\boldsymbol{c}) = H(\boldsymbol{c}) + \log n(\boldsymbol{c})$, then return to (i). $H(\boldsymbol{c})$ follows from the probability measure one wants to target. In order to generate graphs with prescribed degree-correlations $W(k, k')$, one has to target the following non-uniform measures [2],

$$p_\infty(\boldsymbol{c}) = \frac{1}{Z}\prod_{i<j}\left[\frac{\bar{k}}{N}\frac{W(k_i, k_j)}{p(k_i)p(k_j)}\delta_{c_{ij},1} + \Big(1 - \frac{\bar{k}}{N}\frac{W(k_i, k_j)}{p(k_i)p(k_j)}\Big)\delta_{c_{ij},0}\right] \times \prod_i \delta_{k_i,k_i(\boldsymbol{c})} \tag{7}$$

leading to

$$H(\boldsymbol{c}) = -\sum_{i<j}\log\left[\frac{\bar{k}}{N}\frac{W(k_i, k_j)}{p(k_i)p(k_j)}\delta_{c_{ij},1} + \Big(1 - \frac{\bar{k}}{N}\frac{W(k_i, k_j)}{p(k_i)p(k_j)}\Big)\delta_{c_{ij},0}\right] \tag{8}$$

with $\bar{k} = N^{-1}\sum_i k_i$, $p(k) = N^{-1}\sum_i \delta_{k_i,k}$, $W(k,k') = (N\bar{k})^{-1}\sum_{ij} c_{ij}\delta_{k_i,k}\delta_{k_j,k'}$ and

$$W(k) = \sum_{k'} W(k,k') = p(k)k/\bar{k} \tag{9}$$

Hence, for the candidate edge swaps $\boldsymbol{c}' \to \boldsymbol{c} = F_{ijk\ell;\alpha}\boldsymbol{c}'$ the acceptance probability (4) can be used where [1]

$$e^{H(\boldsymbol{c})-H(\boldsymbol{c}')} = \prod_{(a,b)\in S_{ijk\ell;\alpha}} \left[L_{ab}\delta_{c_{ab},1} + L_{ab}^{-1}\delta_{c_{ab},0}\right] \tag{10}$$

with

$$\mathcal{S}_{ijk\ell;1} = \{(i,j),(k,\ell),(i,\ell),(k,j)\} \tag{11}$$

$$\mathcal{S}_{ijk\ell;2} = \{(i,j),(\ell,k),(i,k),(\ell,j)\} \tag{12}$$

$$\mathcal{S}_{ijk\ell;3} = \{(i,k),(j,\ell),(i,\ell),(j,k)\} \tag{13}$$

and

$$L_{ab} = N\bar{k}/[\Pi(k_a,k_b)k_ak_b] - 1, \qquad \Pi(k,k') = \frac{W(k,k')}{W(k)W(k')} \tag{14}$$

To fix ideas, if the quadrupole (i,j,k,ℓ) is selected and move I applies (i.e. $\alpha = 1$), we have, from (10)

$$e^{H(\boldsymbol{c})-H(\boldsymbol{c}')} = \frac{L_{i\ell}L_{jk}}{L_{ij}L_{k\ell}} \tag{15}$$

where L_{ab} must be calculated using (14), and $\Pi(k,k')$ is the targeted relative degree correlation. If the aim is to generate uncorrelated random graphs with the same degree sequence as the starting graph, $\Pi(k,k') = 1$ should be targeted. On the other hand, if the objective is to randomise the graph, while preserving its degree sequence *and* its degree correlations, one should target the degree correlations initially present in the network.

In this work we use the algorithm to randomise biological networks while preserving

(i) their degree sequence

(ii) their degree sequence and degree correlation.

Denoting the relative degree correlation initially present in the network as $\Pi_{\text{bio}}(k,k')$, we run the algorithm using $\Pi(k,k') = 1\ \forall k,k'$ for (i) and $\Pi(k,k') = \Pi_{\text{bio}}(k,k')\ \forall\ k,k'$ for (ii). For the two types of dynamics, we monitor the number of short loops, defined as closed paths which do not self-intersect.

References

[1] A. C. C. Coolen, A. de Martino, and A. Annibale. Constrained Markovian Dynamics of Random Graphs. *Journal of Statistical Physics*, 136:1035–1067, September 2009.

[2] C. J. Pérez Vicente and A. C. C. Coolen. Spin models on random graphs with controlled topologies beyond degree constraints. *Journal of Physics A Mathematical General*, 41(25):255003, June 2008.

Relation between the quantities that we monitor or constrain and others commonly used

1 Relation between clustering coefficient and loops of length three in different graph ensembles

- We note that loops of length 3 are related to the clustering coefficient, which is commonly used to characterize network structure, by a simple formula. The clustering coefficient of a node i measures the number of connected pairs of neighbours of this node, normalised by the total number of distinct pairs of neighbours (regardless of whether or not they are connected):

  $$C_i(\boldsymbol{c}) = \frac{\sum_{r\neq s} c_{ir}c_{rs}c_{si}}{\sum_{r\neq s} c_{ir}c_{is}} = \frac{2T_i(\boldsymbol{c})}{k_i^2(\boldsymbol{c}) - k_i(\boldsymbol{c})} \tag{1}$$

  Here $\boldsymbol{c}$ is the $N \times N$ adjacency matrix of the network, $k_i(\boldsymbol{c}) = \sum_j c_{ij}$ is the local degree, and $T_i(\boldsymbol{c})$ denotes the number of loops of length 3 that pass through node i,

  $$T_i(\boldsymbol{c}) = \frac{1}{2}\sum_{r\neq s} c_{ir}c_{rs}c_{si} \tag{2}$$

  The factor $\frac{1}{2}$ prevents double counting of triangles, due to the two possible orientations of closed triangular paths.

- There are several reasons why one might prefer to use triangle statistics over clustering coefficient statistics, as markers of dynamical trends. First, clustering coefficients are defined only for nodes with degree 2 or larger, whereas there is no such limitation for triangle counters. Second, there is a natural generalisation of triangle statistics to statistics of closed paths of arbitrary length (which we indeed exploit in our paper). Third, the total number of closed paths of a given length ℓ (with $\ell = 3$ giving triangles, $\ell = 4$ giving squares, etc) informs us directly on the ℓ-th moment of the eigenvalue spectrum of the graph's adjacency matrix. This spectrum is known to provide important information on relaxation time scales of collective processes defined on the nodes of the network. There is no such connection to dynamical processes for the clustering coefficients.

- Since in our graph randomisation algorithms the degrees of all nodes are preserved, any observed evolution of triangle statistics is directly linked to the evolution of statistics of clustering coefficients (and vice versa). One can calculate exactly the expected values of the global clustering coefficient in the ensemble of uncorrelated graphs with constrained degrees, in the limit of large N, which gives

$$C = \langle C(\boldsymbol{c})\rangle = \frac{1}{N}\sum_i \langle C_i(\boldsymbol{c})\rangle = \frac{\langle k\rangle}{N}\left(\frac{\langle k^2\rangle - \langle k\rangle}{\langle k\rangle^2}\right)^2 (1 - p(0) - p(1)) \tag{3}$$

The $p(k)$ inside the last round brackets is the degree distribution of the constrained degree sequence and is intuitively due to the fact that nodes with degree 1 and isolated nodes (i.e. with degree 0) do not contribute to the clustering coefficient. The average $\langle\cdot\rangle$ is taken with respect to the ensemble probabilities

$$p(\boldsymbol{c}) = \frac{1}{Z}\prod_{i<j}\left[\frac{\langle k\rangle}{N}\delta_{c_{ij},1} + \left(1 - \frac{\langle k\rangle}{N}\right)\delta_{c_{ij},0}\right] \times \prod_i \delta_{k_i,k_i(\boldsymbol{c})} \tag{4}$$

A similar calculation for the expected density of triangles yields

$$T = \langle T(\boldsymbol{c})\rangle = \frac{1}{3N}\sum_i \langle T_i(\boldsymbol{c})\rangle = \frac{\langle k\rangle^3}{6N}\left(\frac{\langle k^2\rangle - \langle k\rangle}{\langle k\rangle^2}\right)^3 \tag{5}$$

where the 3 in the prefactor prevents overcounting of the global number of unoriented triagles by starting the triangular path at each of the 3 different sites. The expected density of triangles and the expected clustering coefficient are related by

$$T = \frac{1}{6(1 - p(0) - p(1))}(\langle k^2\rangle - \langle k\rangle)C \tag{6}$$

Hence, in random graph ensembles with constrained degree sequences, the density of triangles is proportional to the global clustering coefficient through a factor which depends only on the first two moments of the degree distribution, the density of disconnected nodes and the density of nodes with degree 1. In a graph randomization protocol where the degree sequence is preserved, as in our paper, all the moments of the degree distribution are constant over time as well as the density of isolated and degree-one nodes. Hence monitoring the evolution of the density of triangles is fully equivalent to monitoring the evolution of the global clustering coefficient. Formula (1) shows that in this case even local versions of the two quantities are equivalent, as all the local degrees $k_i(\boldsymbol{c})$, $i = 1, \ldots, N$, are constant.

Finally we note that in a fully random graph model, where only the average connectivity is constrained, the degree distribution is Poissonian, so that $\langle k^2\rangle - \langle k\rangle = \langle k\rangle^2$ and we obtain from the above formulae

$$C^{\mathrm{ER}} = \frac{\langle k\rangle}{N}(1 - e^{-\langle k\rangle} - \langle k\rangle e^{-\langle k\rangle}) \tag{7}$$

$$T^{\mathrm{ER}} = \frac{1}{6(1 - e^{-\langle k\rangle} - \langle k\rangle e^{-\langle k\rangle})}\langle k\rangle^2 C^{\mathrm{ER}} = \frac{\langle k\rangle^3}{6N} \tag{8}$$

These expressions coincide with the expected clustering coefficient and density of triangles in the Erdös-Rényi (ER) graph ensemble, obtained from (4) by removing the constraint on the degree sequence

$$p(\boldsymbol{c}) = \frac{1}{Z}\prod_{i<j}\left[\frac{\langle k\rangle}{N}\delta_{c_{ij},1} + \left(1-\frac{\langle k\rangle}{N}\right)\right] \tag{9}$$

In order to compare the performance as null models of our tailored graph ensembles (where degree correlations and/or degree sequences are constrained), to the fully random graph model, we report the theoretical prediction for the expected density of triangles in the ER graph (8) as a dotted line in the plots in Figure S4. We also show the theoretically predicted value for the ensemble of uncorrelated graphs with constrained degree sequence (5), as a dashed line.

2 Relation between degree-degree correlations and assortativity

- We note that the degree-degree correlation function $W(k,k')$ that we use to construct our null models is closely related to another popular measure of graph structure, namely the assortativity. In fact, the latter is simply the Pearson coefficient of the joint distribution $W(k,k')$:

  $$\begin{aligned} a(\boldsymbol{c}) &= \frac{\frac{1}{N\langle k\rangle}\sum_{ij} c_{ij}k_i(\boldsymbol{c})k_j(\boldsymbol{c}) - \left(\frac{1}{N\langle k\rangle}\sum_i k_i^2(\boldsymbol{c})\right)^2}{\frac{1}{N\langle k\rangle}\sum_i k_i^3(\boldsymbol{c}) - \left(\frac{1}{N\langle k\rangle}\sum_i k_i^2(\boldsymbol{c})\right)^2} \\ &= \frac{\langle k\rangle^2 < kk' >_W - \langle k^2\rangle^2}{\langle k\rangle\langle k^3\rangle - \langle k^2\rangle^2} \end{aligned} \tag{10}$$

  where $\langle kk'\rangle_W = \sum_{k,k'} W(k,k')kk'$. For uncorrelated graphs, where $W(k,k') = W(k)W(k')$ we have

  $$\langle kk'\rangle_W = \sum_{k,k'} p(k)p(k')\frac{k^2k'^2}{\langle k\rangle^2} = \frac{\langle k^2\rangle^2}{\langle k\rangle^2} \tag{11}$$

  and the assortativity vanishes. Hence, there is by definition no information on the network in the assortativity that is not contained in the distribution $W(k,k')$. $W(k,k')$ is more informative than the assortativity.

- One could in principle construct stochastic processes for network evolution in which, instead of degree correlations, alternative observables are preserved. See the general theory in [Coolen ACC, De Martino A, Annibale A, J Stat Phys 2009, 1035-1067]. However, the distribution $W(k,k')$, *which measures the statistics of the immediate local environment of links*, can be regarded as the natural complement of the degree distribution, *which measures the statistics of the immediate* *local environment of nodes*. Moreover, since PPIN are known to have correlated degrees, the degree correlation kernel $W(k, k')$ is the natural choice to be used in addition to $p(k)$.