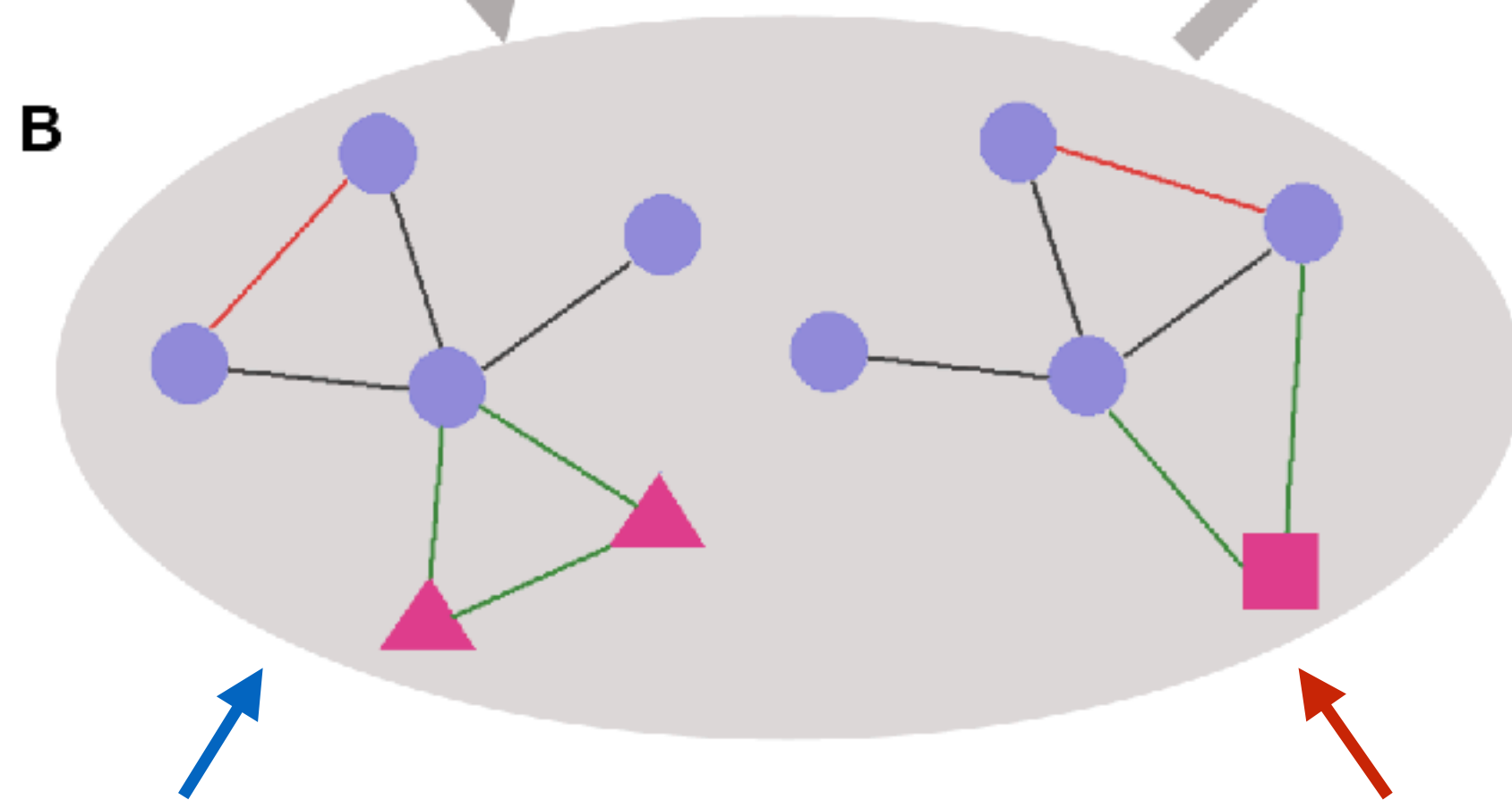
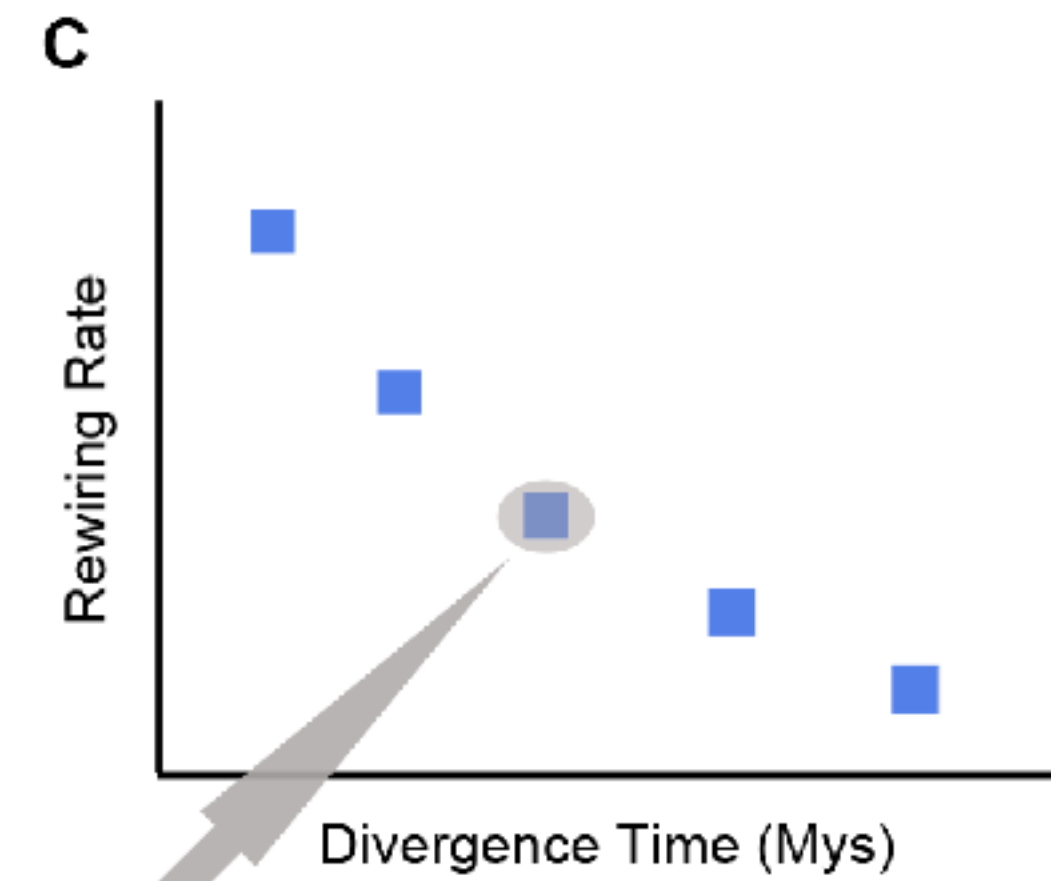
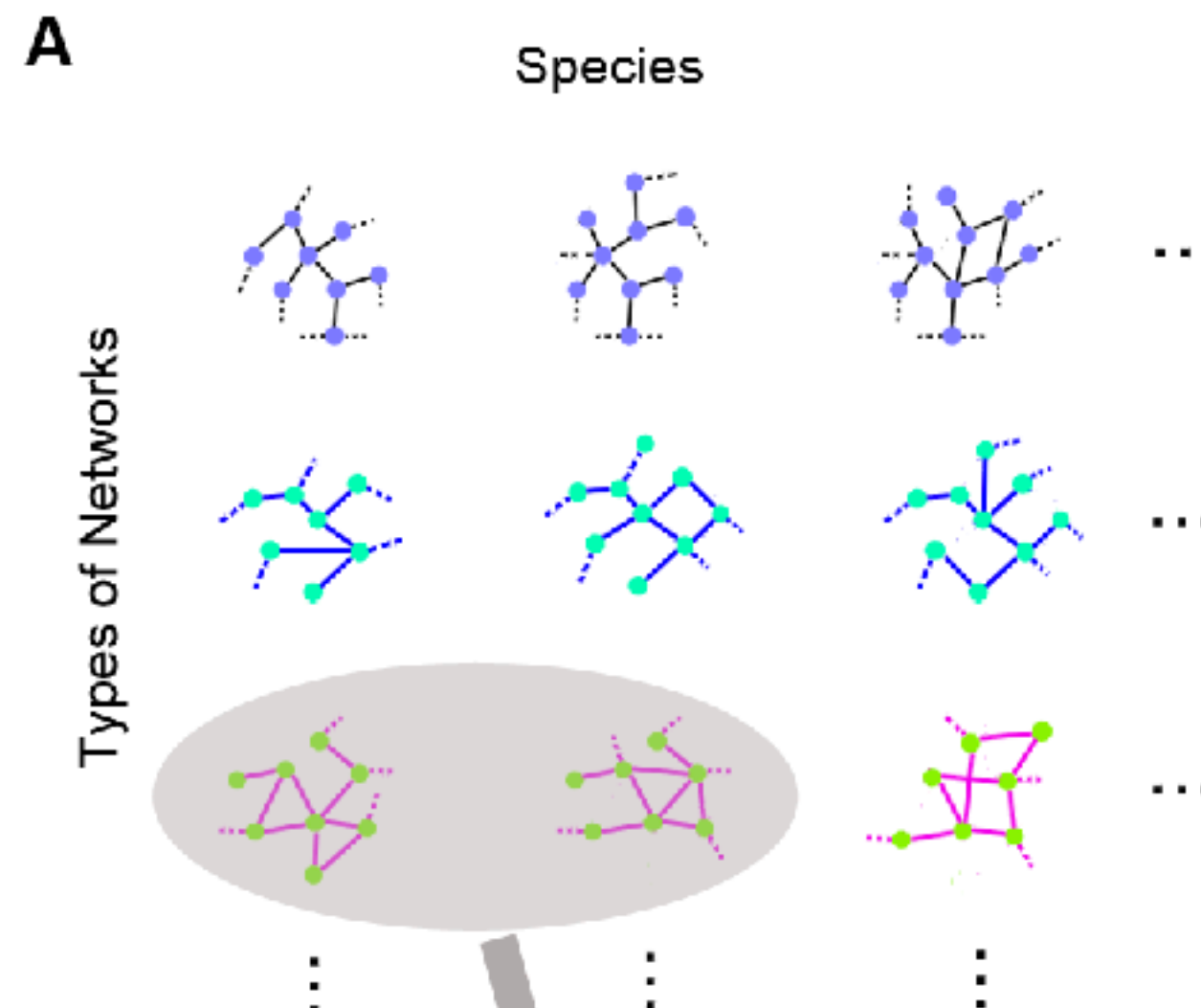
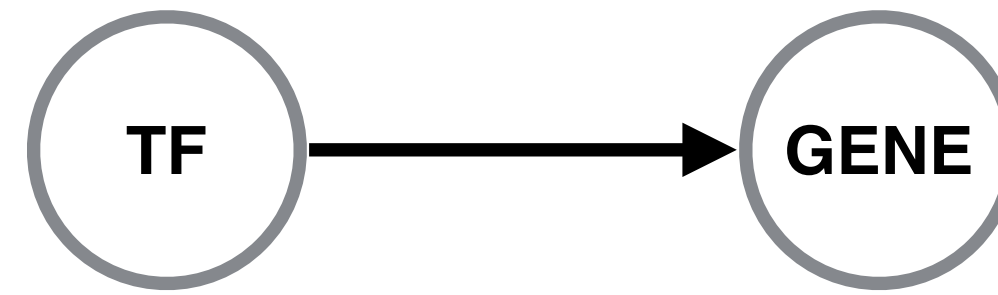


Quantifying “rewiring” of TF-Gene Network



- Common Node
- Gain Node
- ▲ Loss Node
- Common Edge
- Rewired Edge Between Common Nodes
- Rewired Edge Involving Gain or Loss Nodes

GM12878

K562

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PLoS COMPUTATIONAL BIOLOGY

Measuring the Evolutionary Rewiring of Biological Networks

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- TF-Gene network can be represented as a DAG (directed acyclic graph)
 - Common Nodes (CNs) are nodes present in both networks
 - Loss Nodes (LNs) only in reference network (GM12878 only)
 - Gain Nodes (GNs) only in the other compared network (K562 only)
- Four types of “rewired” edges
 - gain or loss edges between CNs
 - gain edges involving GNs
 - loss edges involving LNs

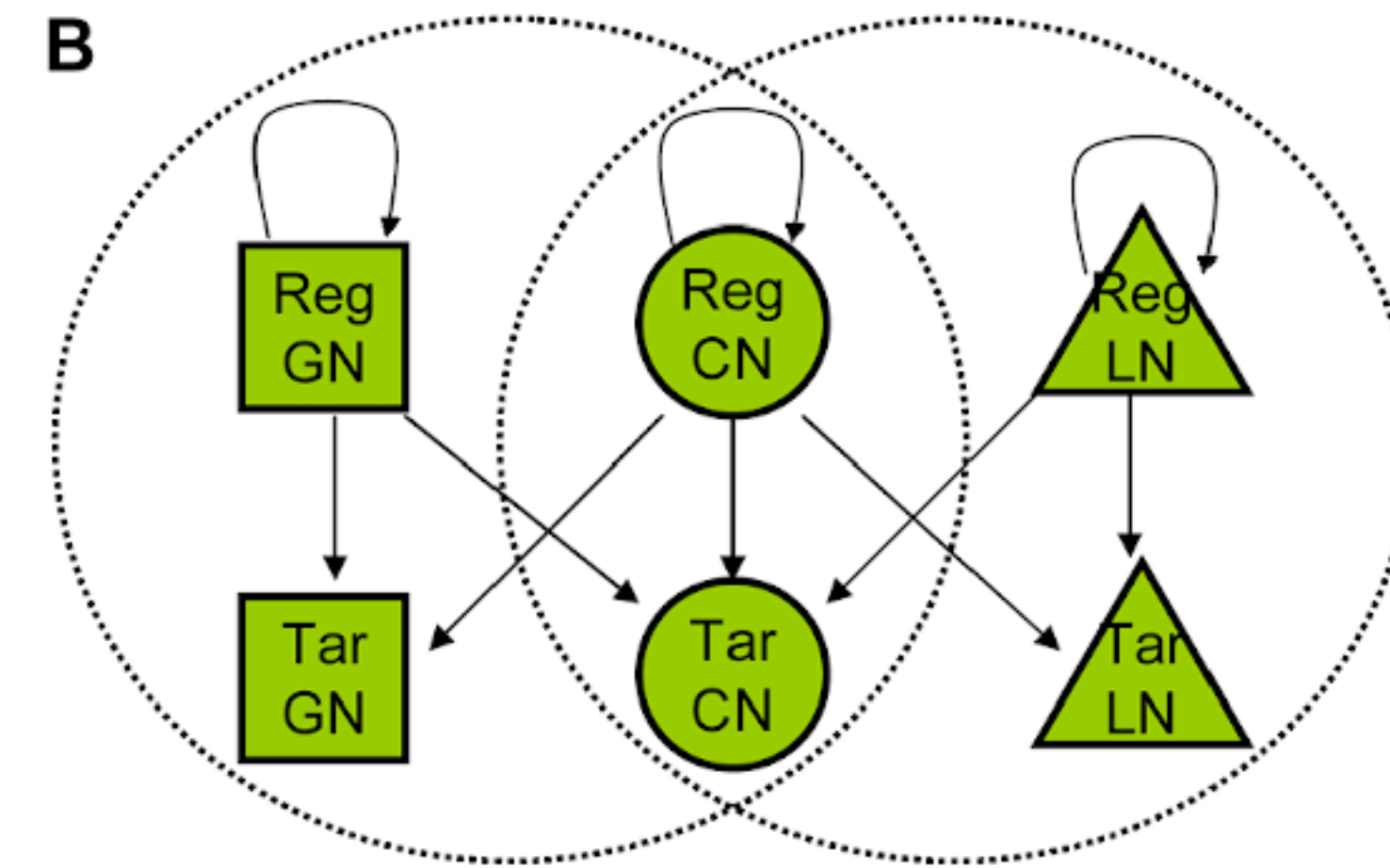
$$\text{Rewiring rate} = \frac{R}{C \times \text{Time divergence}}$$

TF or Kinase network C =

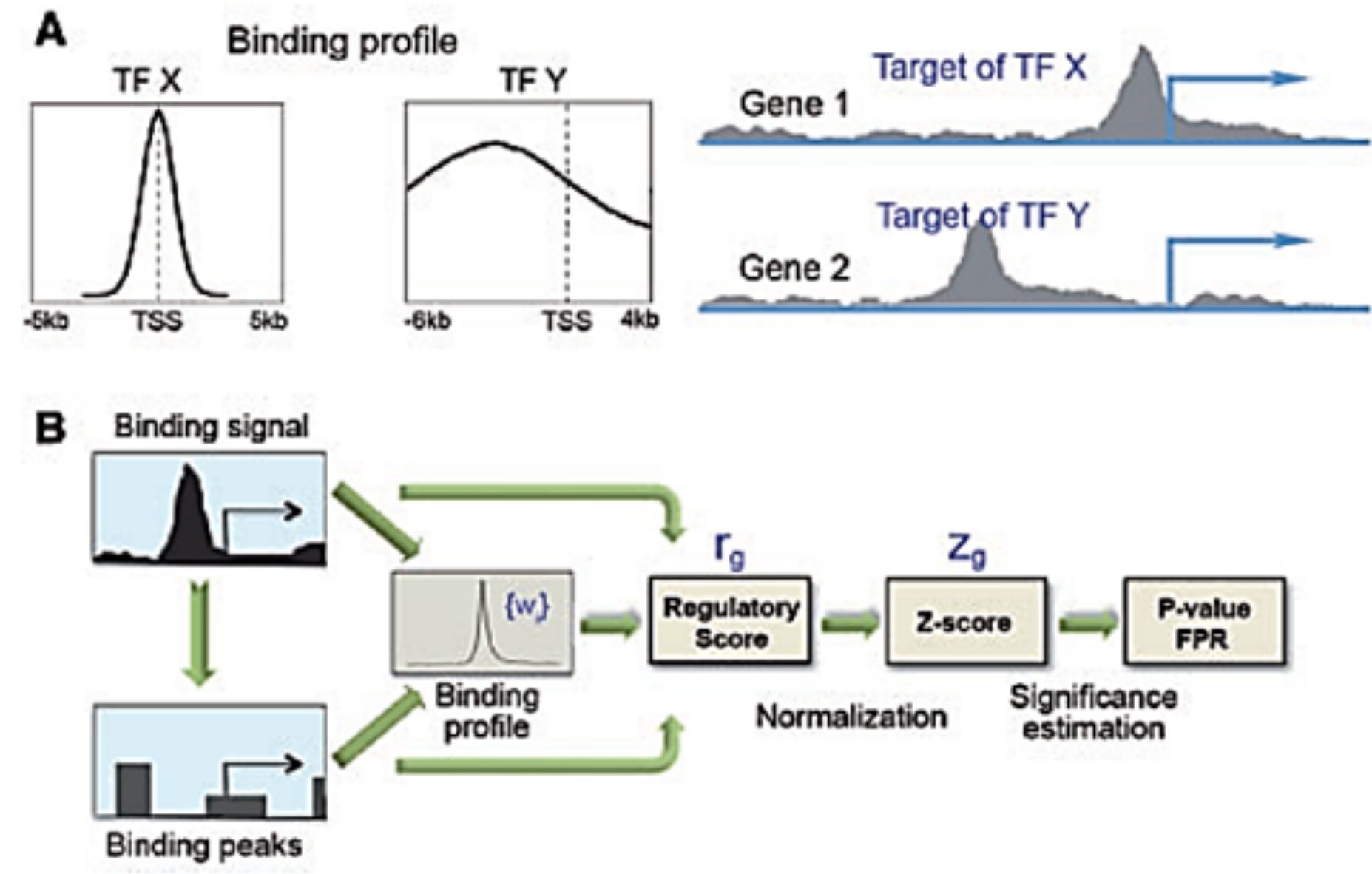
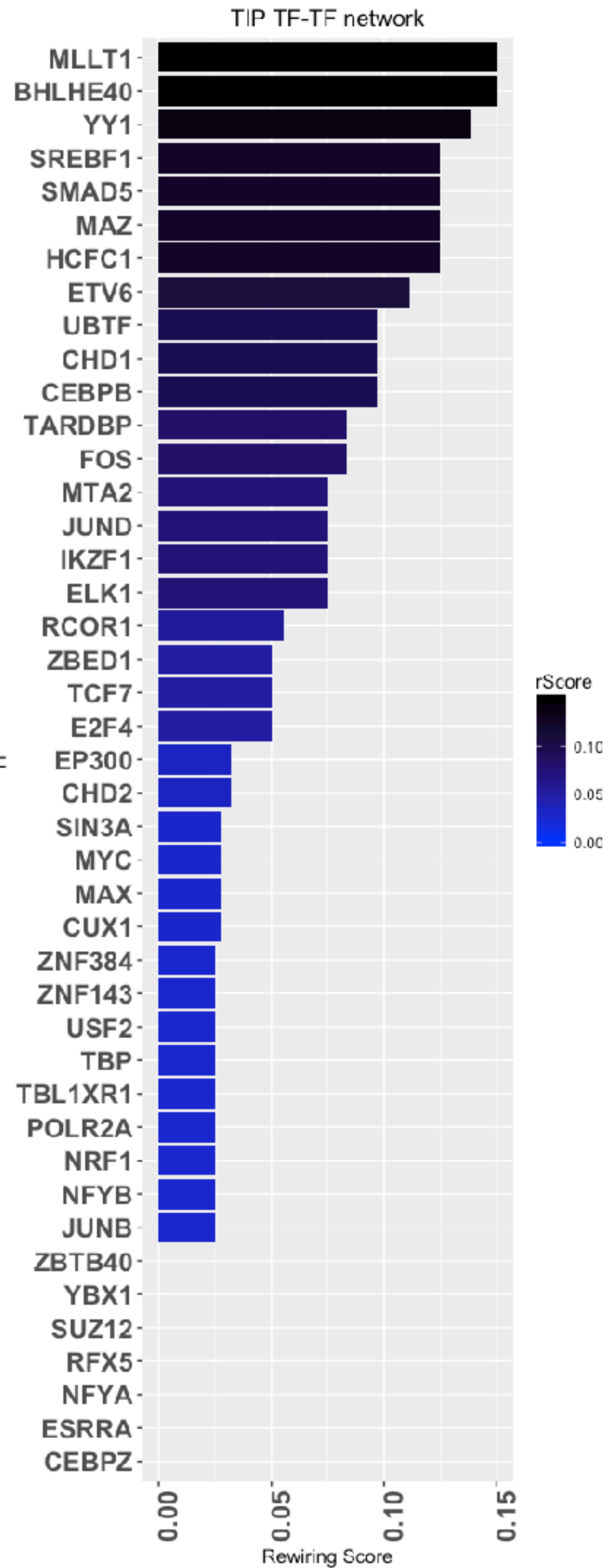
$$\frac{\text{Reg CNs} \times (\text{Reg CNs}-1) + \text{Reg GNs} \times (\text{Reg GNs}-1) + \text{Reg LNs} \times (\text{Reg LNs}-1)}{2}$$

$$+ \text{Reg CNs} \times \text{Tar CNs} + \text{Reg GNs} \times \text{Tar GNs} + \text{Reg LNs} \times \text{Tar LNs}$$

$$+ \text{Reg CNs} \times (\text{Tar GNs} + \text{Tar LNs}) + \text{Tar CNs} \times (\text{Reg GNs} + \text{Reg LNs})$$



- **R_{TF}** - Total number of rewired edges (R) between two networks: union of edges between pairs of CNs that only present in one network and all edges involving LNs and GNs
- **C_{TF}** - Total number of possible edges (C) in the two networks: number of non-redundant edges if two networks are both fully connected
- **Rewiring-Score_{TF}** = R_{TF} / C_{TF}
- C_{TF} = CN_{TF} × (CN_{GENE} + GN_{GENE} + LN_{GENE}) + GN_{TF} × (CN_{GENE} + GN_{GENE}) + LN_{TF} × (CN_{GENE} + LN_{GENE})



TIP network is too sparse!

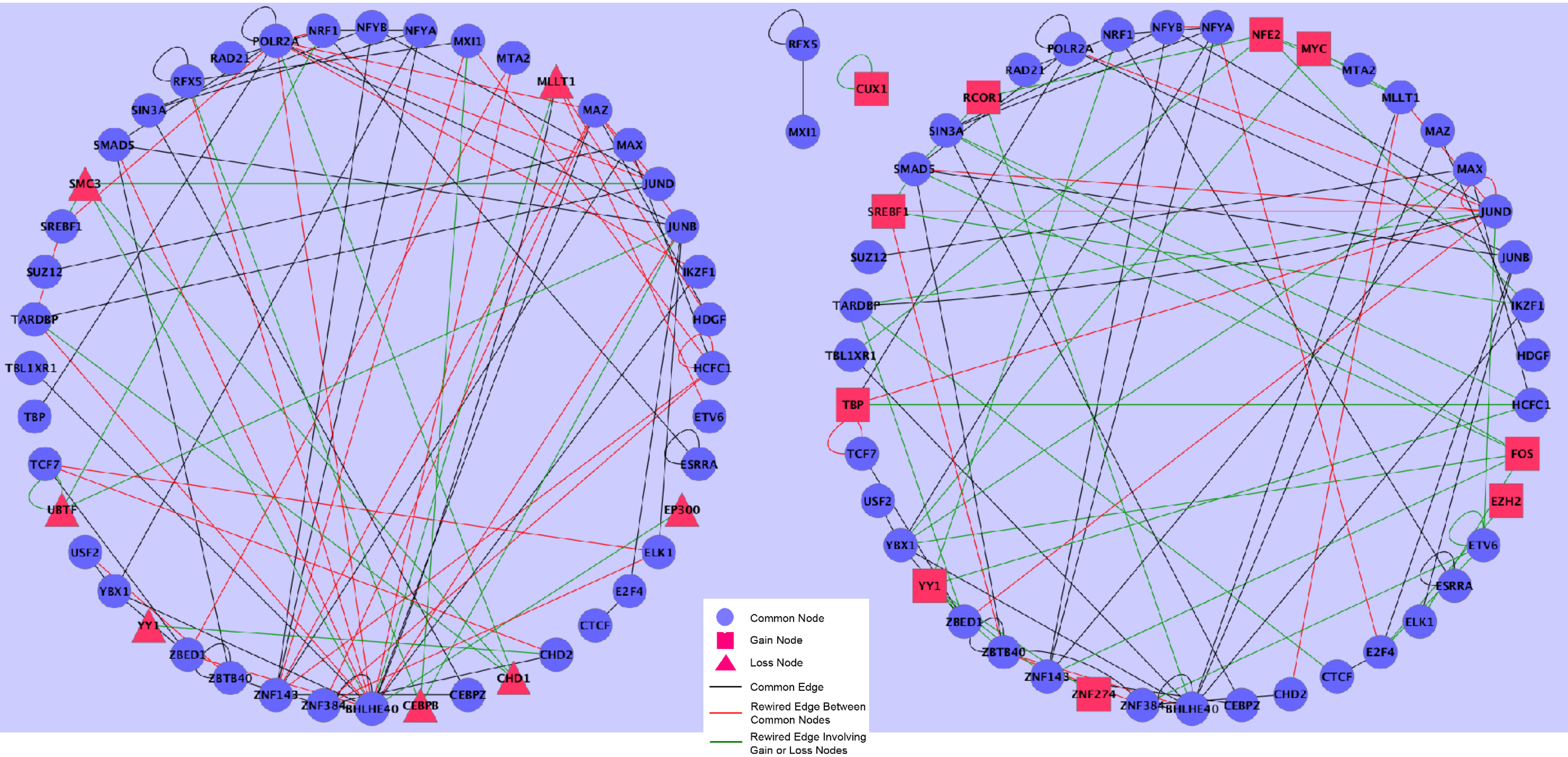
TIP TF-TF network

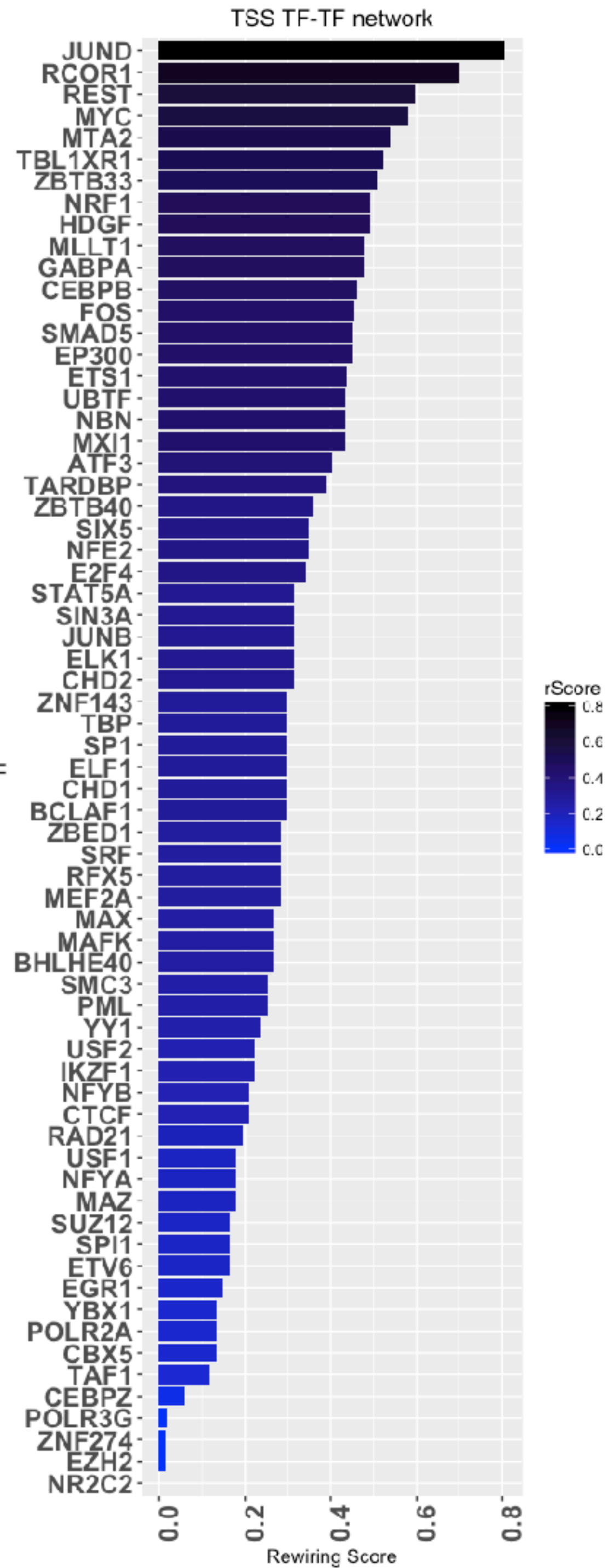
	TF		GENE	
CN	29	67.4%	28	70.0%
GN	9	20.9%	8	20.0%
LN	5	11.6%	4	10.0%
common edge	82		46.6%	
rewired CN	47		26.7%	
rewired GN or LN	47		26.7%	

GM12878

TIP

K562





Top 10 Rewired TFs

TF	rScore	Literature
JUND	0.8060	“a double-edged sword in tumorigenesis”; JunD is a versatile AP-1 transcription factor that can activate or repress a diverse collection of target genes. Precise control of junD expression and JunD protein–protein interactions modulate tumor angiogenesis, cellular differentiation, proliferation and apoptosis.; Whereas c-JUN is oncogenic, JUNB and JUND can have anti-oncogenic effects.
RCOR1	0.7015	An RCOR1 loss–associated gene expression signature identifies a prognostically significant DLBCL subgroup
REST	0.5821	A genetic screen for candidate tumor suppressors identifies REST; REST/NRSF was first identified as a transcriptional repressor of neuronal genes in non-neuronal cells. Recent studies have now revealed seemingly paradoxical roles for REST/NRSF in neurogenesis, neural plasticity, tumour suppression and cancer progression.
MYC	0.5672	The MYC oncogene contributes to the genesis of many human cancers.; A NOTCH1-driven MYC enhancer promotes T cell development, transformation and acute lymphoblastic leukemia
MTA2	0.5522	MTA2 is a member of the metastasis tumor-associated family of transcriptional regulators and is a central component of the nucleosome remodeling and histone deacetylation complex. MTA2 acts as a central hub for cytoskeletal organization and transcription and provides a link between nuclear and cytoskeletal organization.
TBL1XR1	0.5373	TBL1XR1 mutations detected in our patient cohort are predicted to be monoallelic loss-of-function mutations, suggesting that reduction in TBL1XL1 activity is probably mechanistically involved in leukemogenesis.
ZBTB33	0.5075	ZBTB33 has been mapped to Xq23 and CTNND1 has been mapped to 11q11. According to the Cancer Chromosomes Entrez database of the NCBI, deletion or translocation of these regions has been reported in a number of solid tumours such as colon, pancreatic and ovarian cancer, and in acute myeloblastic leukaemia.
HDGF	0.4776	HDGF is an important regulator of a broad range of cancer cell activities and plays important roles in cancer cell transformation, apoptosis, angiogenesis and metastasis. Such a divergent influence of HDGF on cancer cell activities derives from its multiple inter- and sub-cellular localizations where it interacts with a range of different binding partners. Interestingly, high levels of HDGF could be detected in patients’ serum of some cancers.
NRF1	0.4776	c-MYC apoptotic function is mediated by NRF-1 target genes
GABPA	0.4776	GABP transcription factor is required for development of chronic myelogenous leukemia via its control of PRKD2

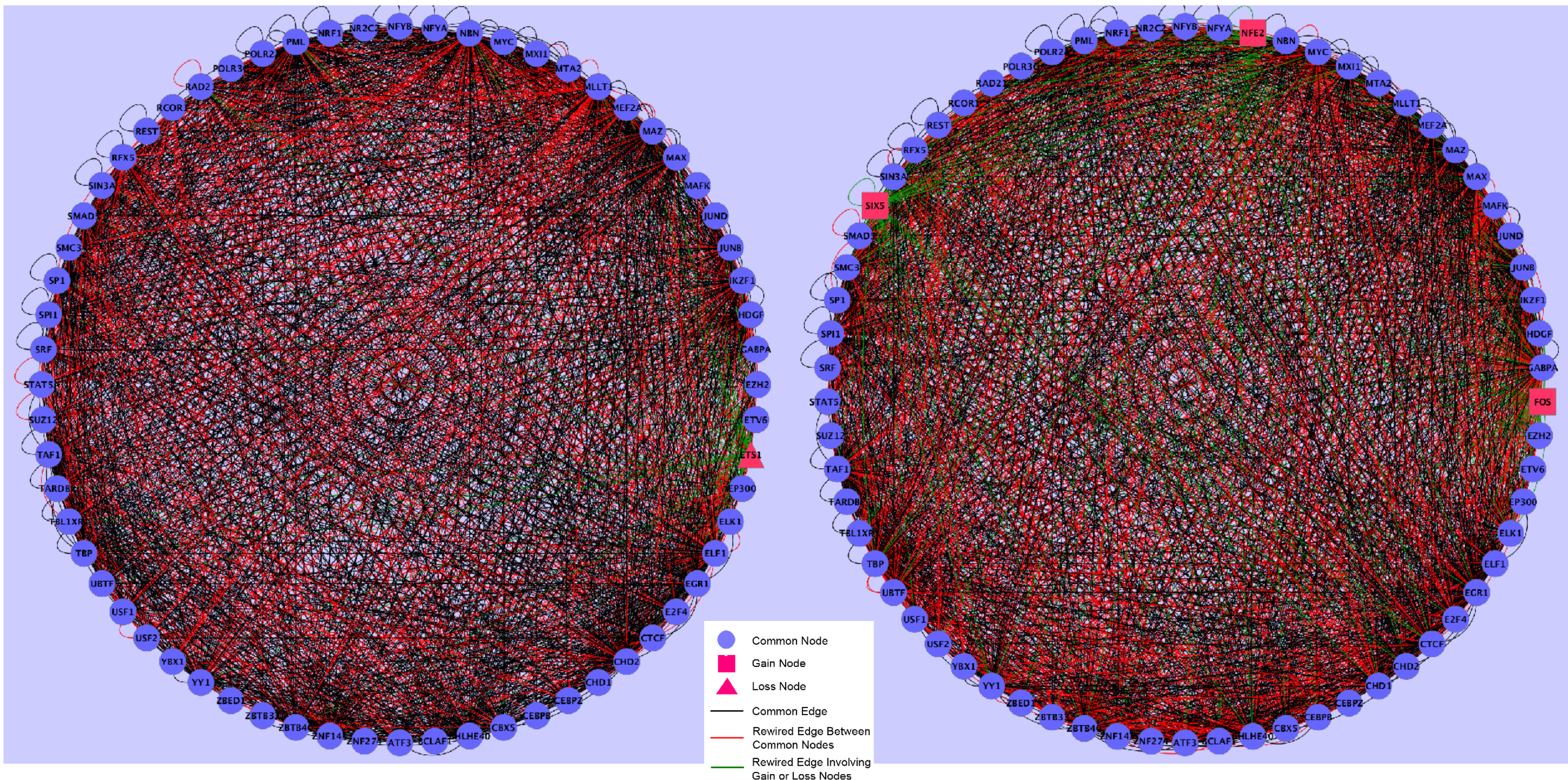
TSS TF-TF network

	TF		GENE	
CN	61	91.0%	66	98.5%
GN	4	6.0%	0	0.0%
LN	2	3.0%	1	1.5%
common edge	2886		67.9%	
rewired CN	1235		29.0%	
rewired GN or LN	131		3.1%	

GM12878

TSS

K562



GM12878

TSS

K562

