Meeting 10/5/15

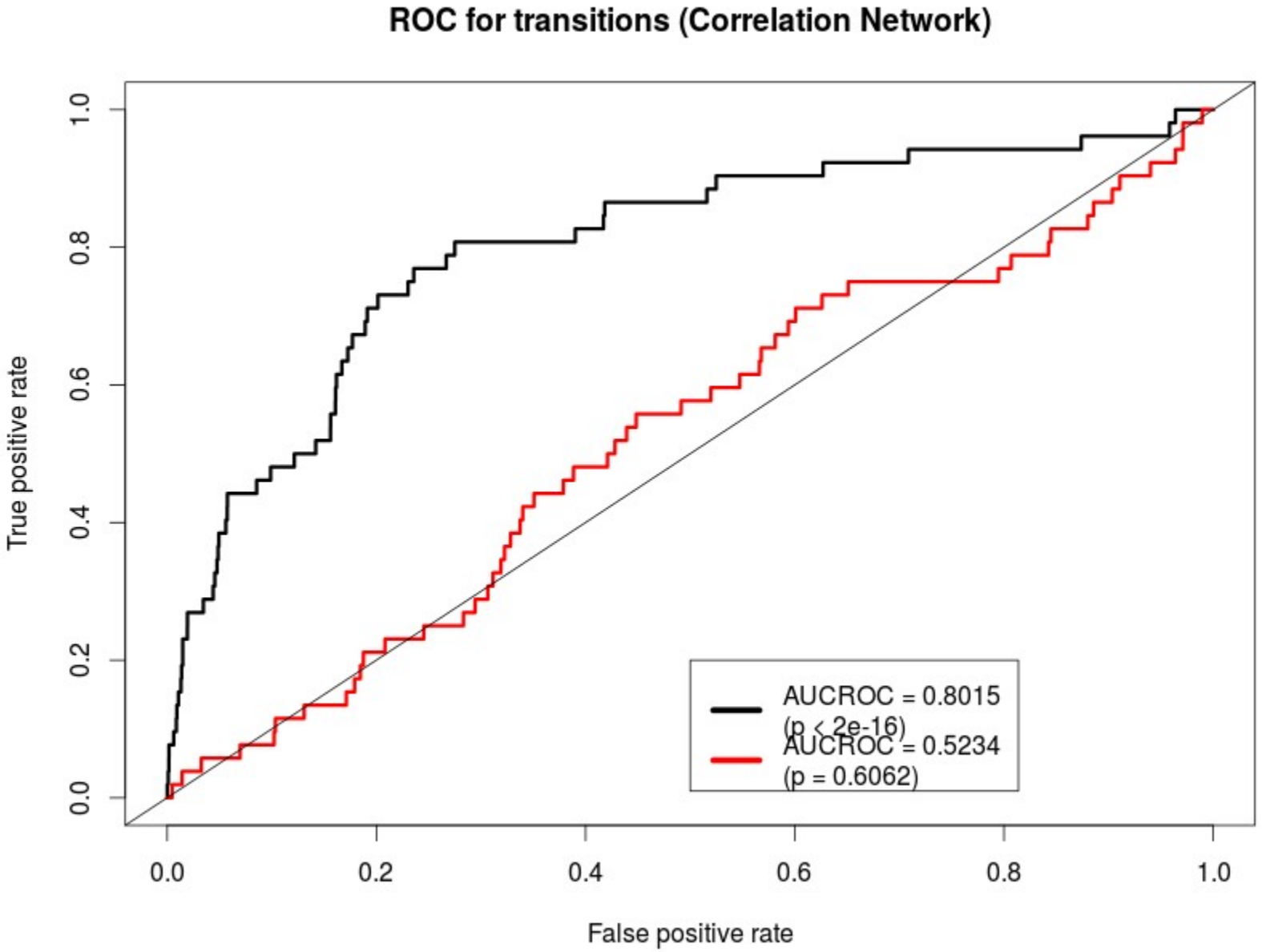
Work in progress

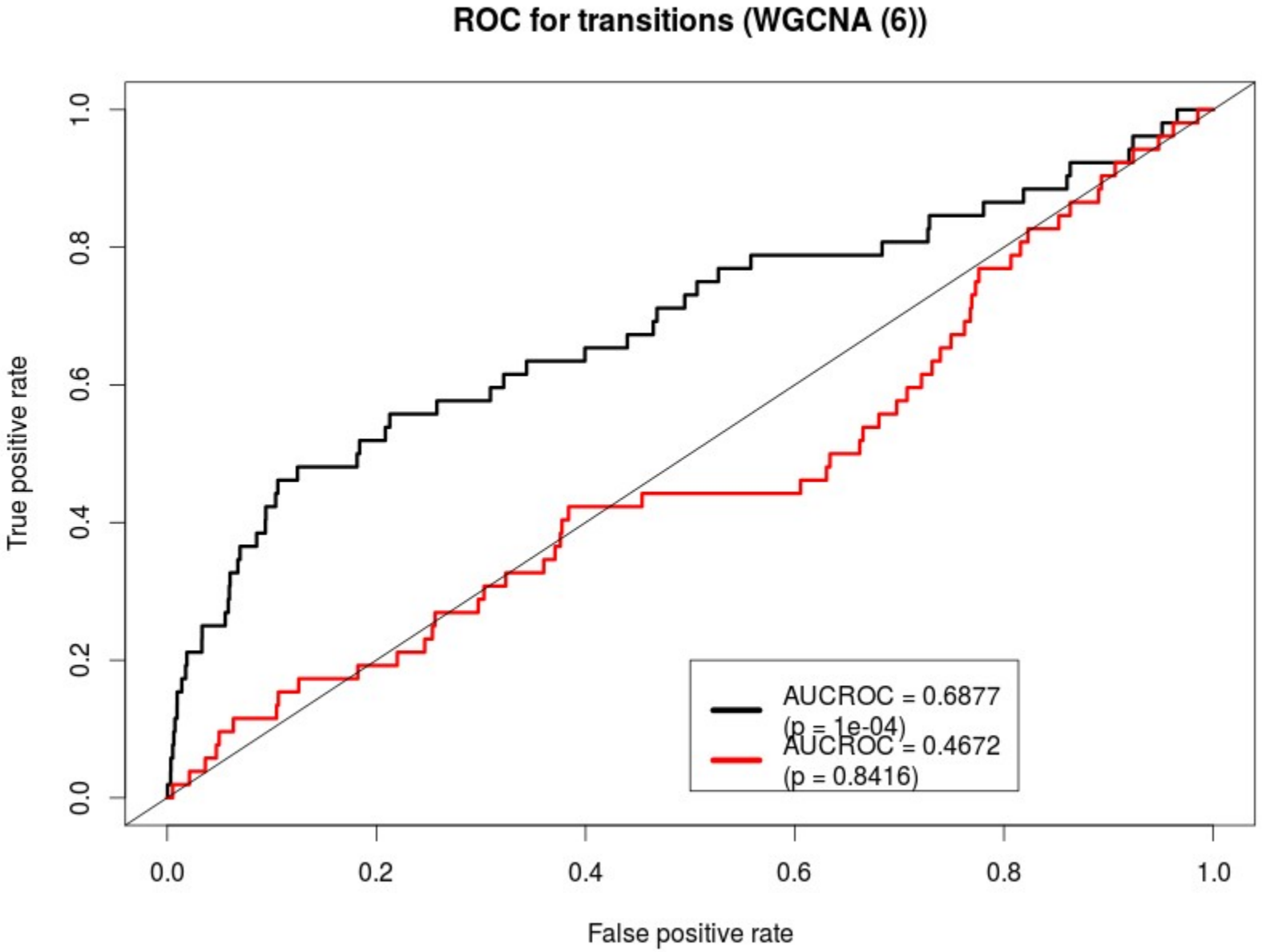
1.) Evaluation of TM of published NI algorithms

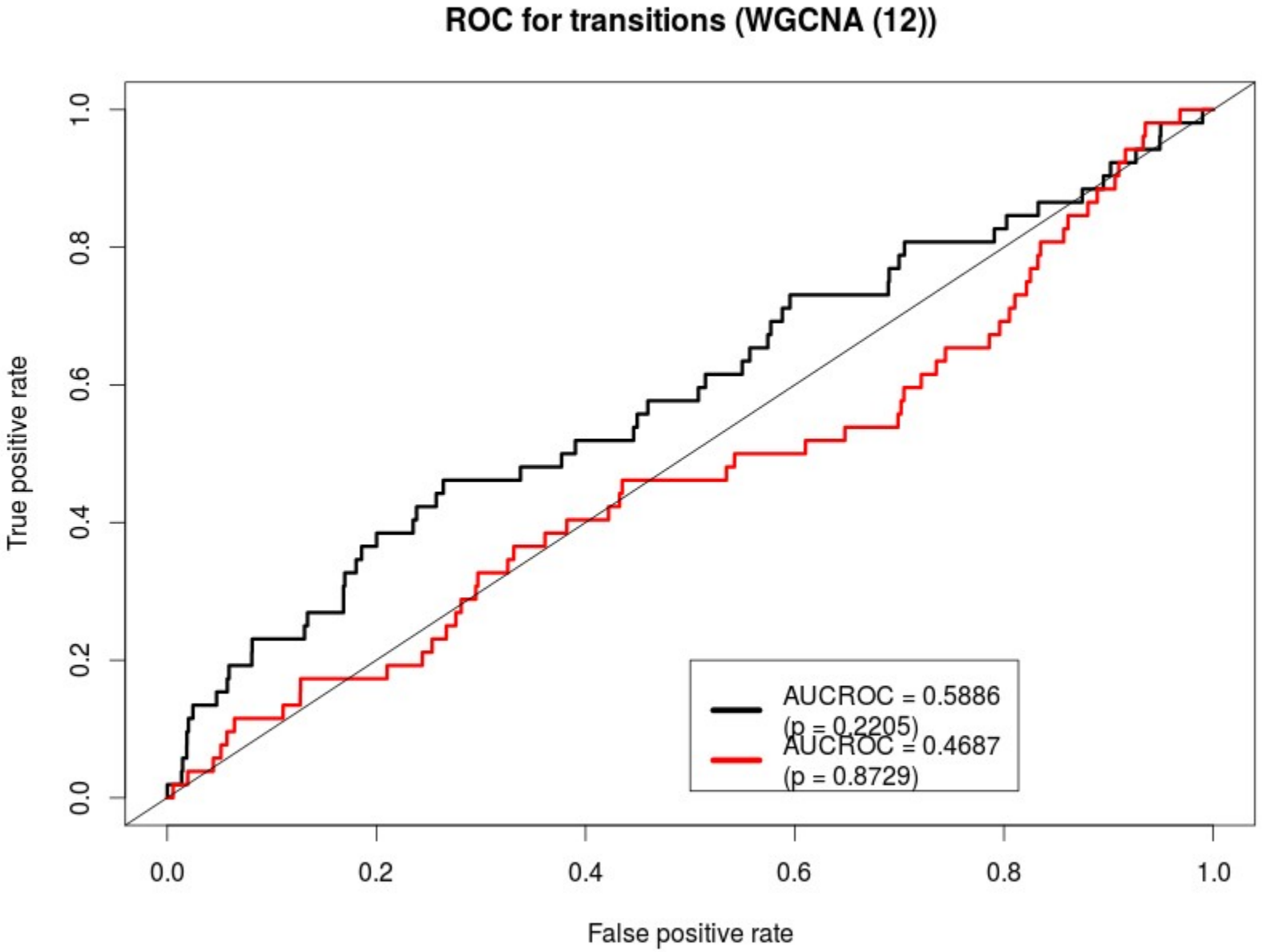
- Pearson
- WGCNA (with differing beta parameters)
- Topological Overlap Measure
- CLR
- ARACNE
- PANDA

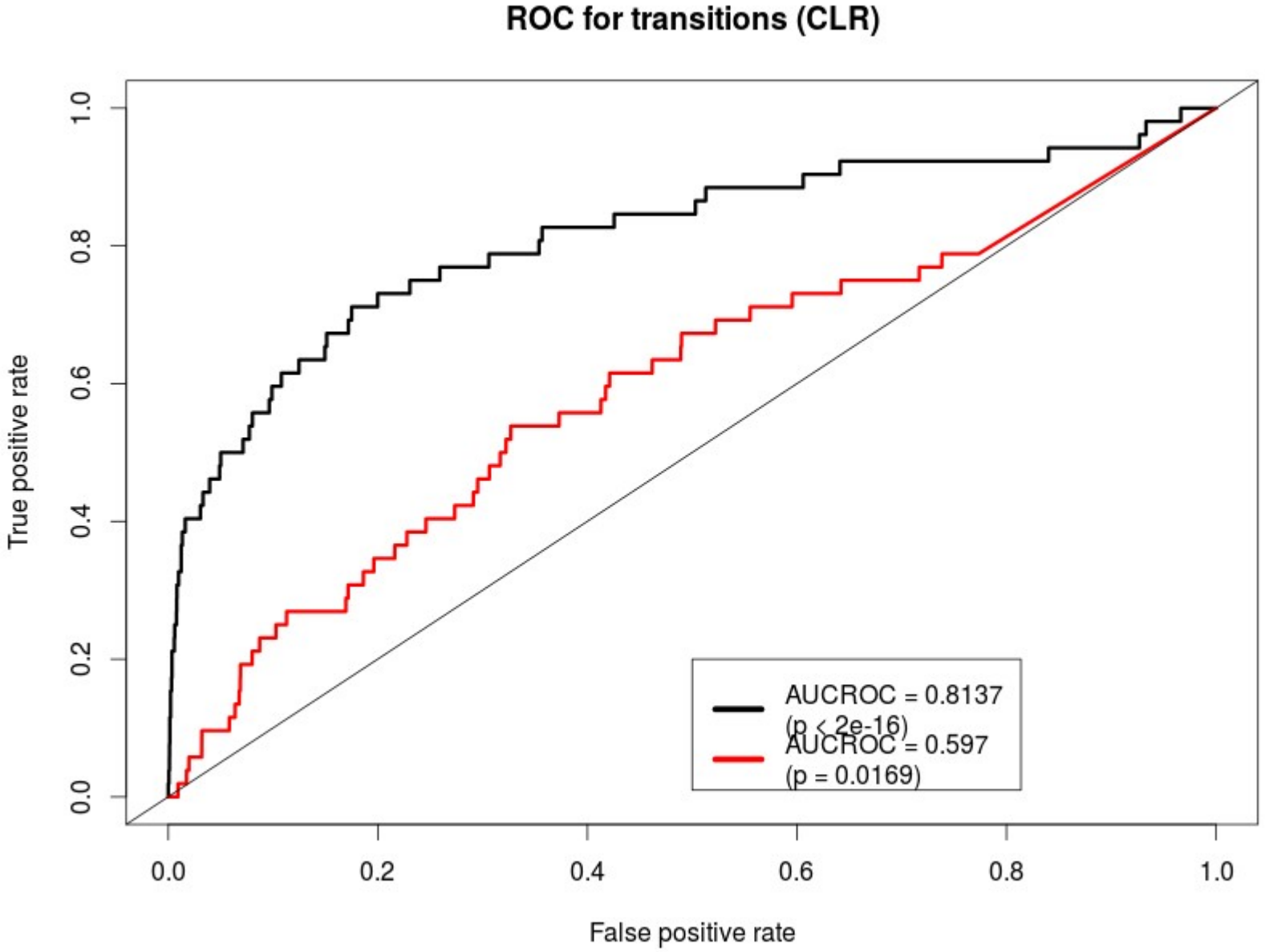
2.) Comparison to direct edge difference to find TF-TF interaction.

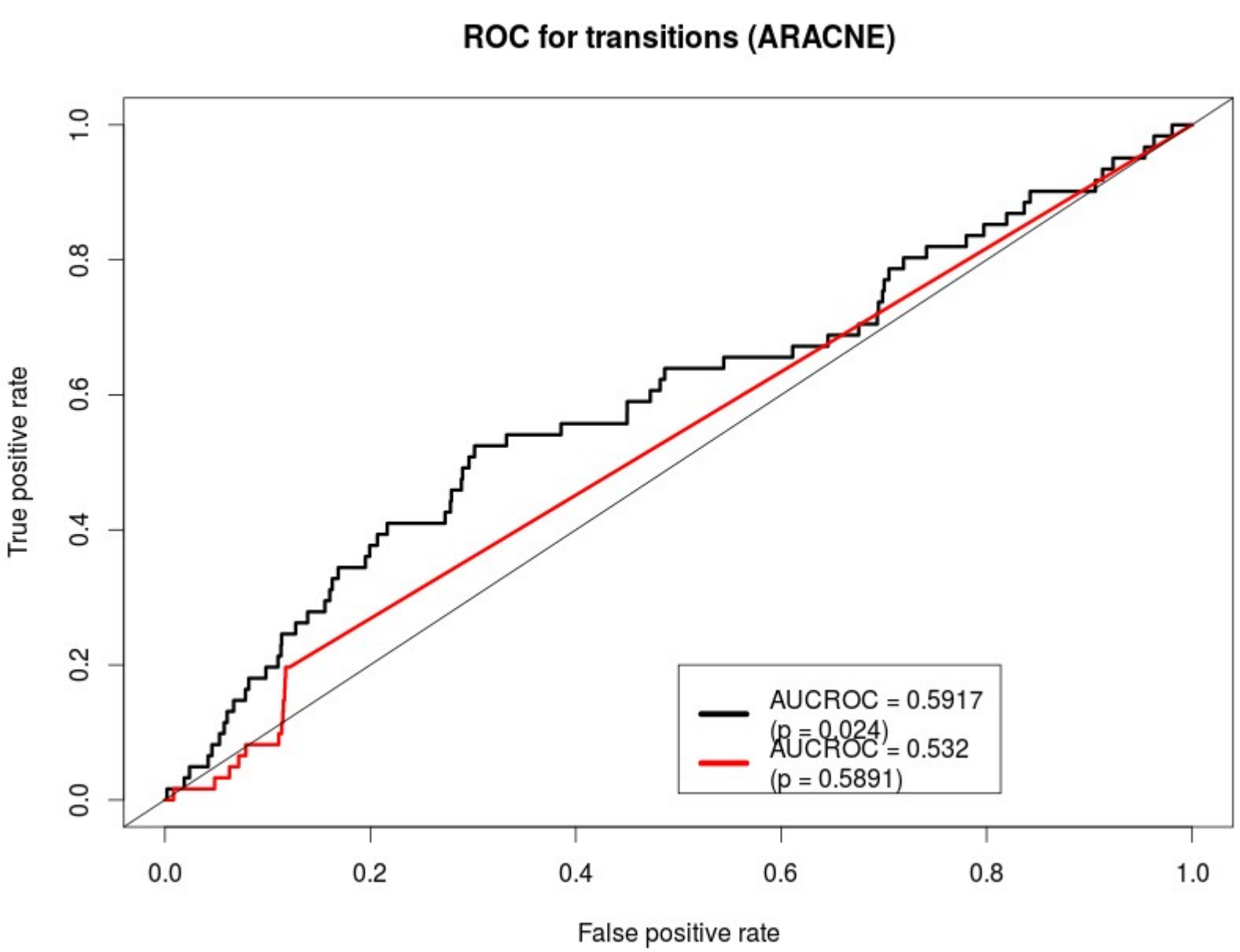
- Pearson
- WGCNA (with differing beta parameters)
- Topological Overlap Measure
- CLR
- ARACNE

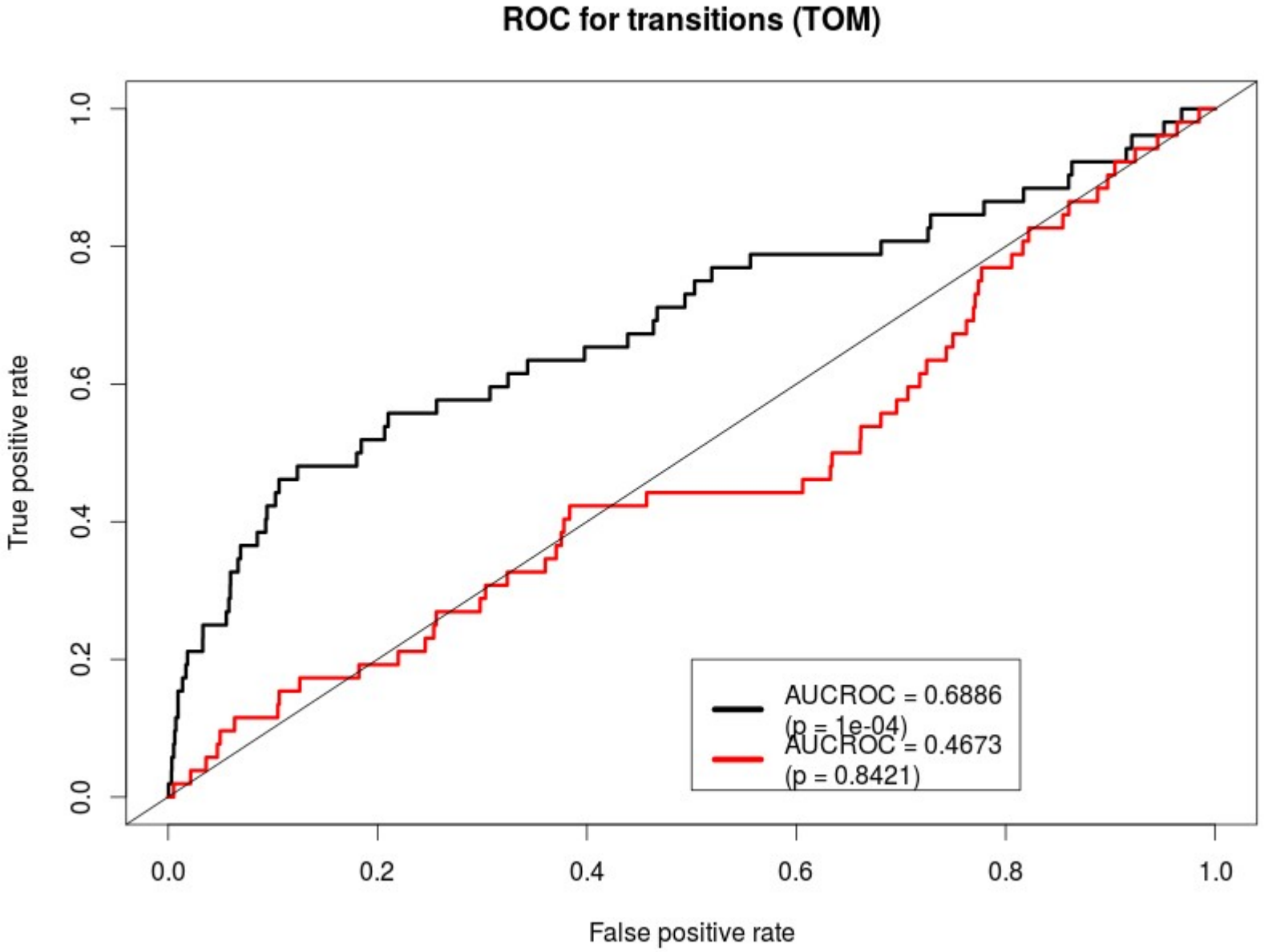

ROC for transitions (Correlation Network)
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUCROC = 0.8015
(p < 2e-16)
AUCROC = 0.5234
(p = 0.6062)

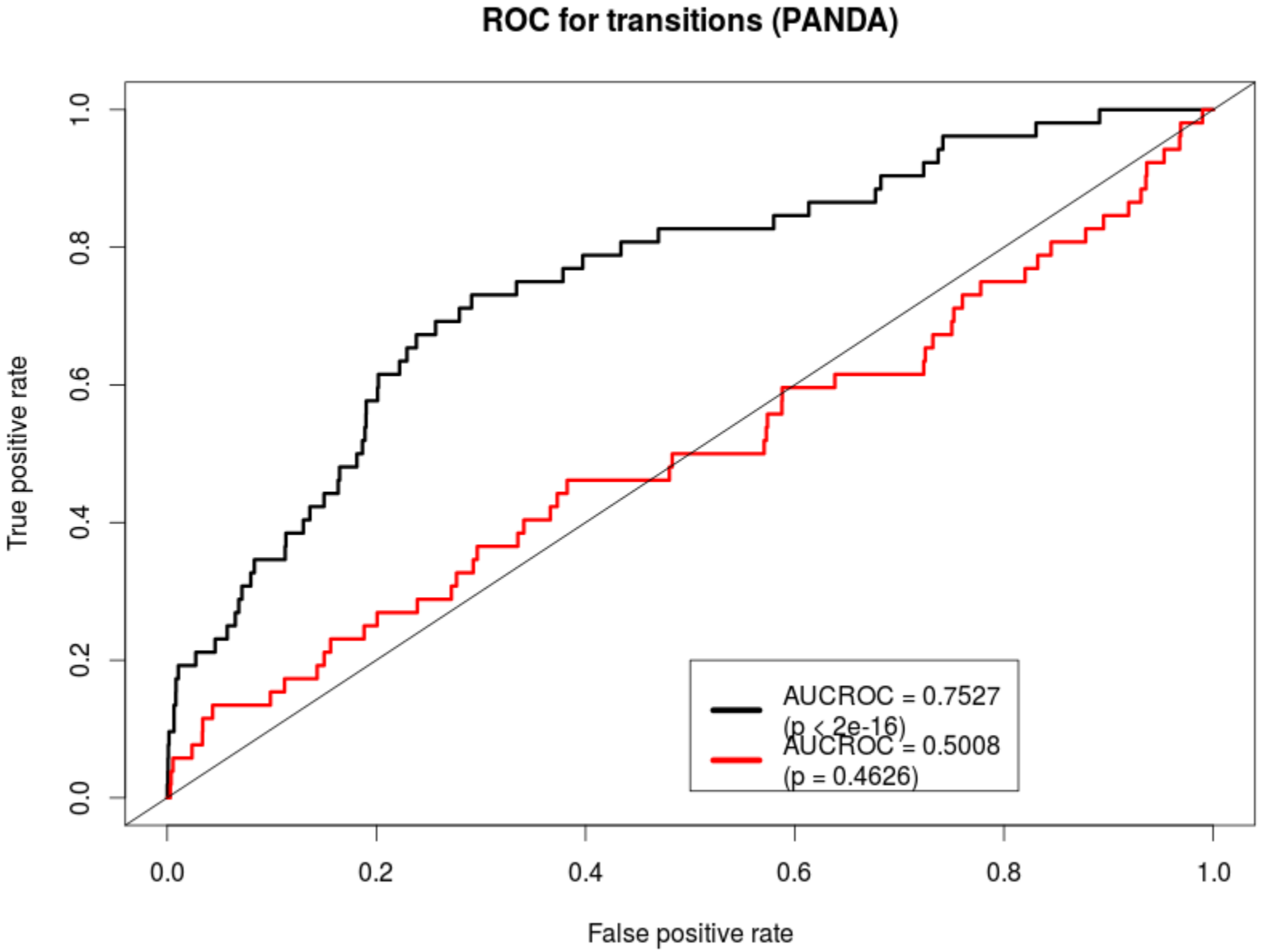

ROC for transitions (WGCNA (6))
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUCROC = 0.6877
(p = 1e-04)
AUCROC = 0.4672
(p = 0.8416)


ROC for transitions (WGCNA (12))
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUCROC = 0.5886
(p = 0.2205)
AUCROC = 0.4687
(p = 0.8729)


ROC for transitions (CLR)
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUCROC = 0.8137
(p < 2e-16)
AUCROC = 0.597
(p = 0.0169)


ROC for transitions (ARACNE)
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUCROC = 0.5917
(p = 0.024)
AUCROC = 0.532
(p = 0.5891)


ROC for transitions (TOM)
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUCROC = 0.6886
(p = 1e-04)
AUCROC = 0.4673
(p = 0.8421)


ROC for transitions (PANDA)
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUCROC = 0.7527
(p < 2e-16)
AUCROC = 0.5008
(p = 0.4626)

Comparison of NI methods

	Pearson	WGCNA(6)	WGCNA(12)	ARACNE	CLR	TOM	PANDA1	PANDA2
Network AUC	.701 (p<.0001)	.701 (p<.0001)	.701 (p<.0001)	.515 (p<.0001)	.691 (p<.0001)	.700 (p<.0001)	.740 Motif=.570 (p<.0001)	.676 Motif = .547 (p<.0001)
Direct AUC	.510 (p=.72)	.512 (p=.61)	.52 (p=.10)	.523 (p=.58)	.57 (p=.19)	.51 (p=.62)	.520 (p<.13)	.509 (p<.43)
Transition AUC	.802 (p<.0001)	.688 (p<.0001)	.589 (p=.02)	.566 (p=.09)	.814 (p<.0001)	.689 (p<.0001)	.793 (p<.0001)	.66 (p<.0001)

ECLIPSE results, top TF-TF interactions

Changing TF	Trainer TF	Gain/Loss	p-value	FDR
GABPA	SPIB	Loss	1.07E-009	3.82E-005
E2F4	PAX2	Loss	1.22E-008	2.17E-004
ELK4	SPIB	Loss	1.83E-008	2.18E-004
E2F4	SPIB	Loss	3.53E-008	3.15E-004
E2F4	ZEB1	Gain	4.70E-008	3.36E-004
E2F4	YY1	Gain	6.76E-008	4.02E-004
E2F4	SREBF2	Gain	1.46E-007	7.46E-004
NRF1	SPIB	Loss	3.64E-007	1.63E-003
E2F4	FOXL1	Gain	4.10E-007	1.63E-003
E2F1	YY1	Gain	4.23E-007	1.51E-003
E2F4	FOXD1	Loss	5.07E-007	1.65E-003
NRF1	BACH1::MAFK	Gain	5.39E-007	1.61E-003
E2F4	BACH1::MAFK	Gain	6.25E-007	1.72E-003
E2F4	PPARG	Gain	8.24E-007	2.10E-003
NRF1	YY1	Gain	1.26E-006	3.00E-003
NRF1	PPARG	Gain	1.46E-006	3.27E-003
E2F4	GABPA	Gain	1.62E-006	3.40E-003
ELK4	MYOG	Loss	2.11E-006	4.19E-003
GABPA	ZEB1	Gain	2.24E-006	4.22E-003
GABPA	MYOG	Loss	3.27E-006	5.83E-003

Checking this list for differential methylation may be our best hope for biological validation in humans.

Conclusions

- The transition matrix approach finds TF-TF interactions dramatically better than using pairwise NI approaches.
- Effectiveness of TM *does* depend on network inference method, but is always superior to pairwise approach.

Story

- 1.) Method works?
  - TM approach has strong theoretical basis with clearly defined assumptions and conditions.
    - Can be proven to be most efficient unbiased estimator of our defined transitions for *any* edge distribution.
  - TM approach validates in *in silico*, *E. coli*, and *Yeast* datasets
- 2.) Method replicates?
  - TM approach finds dramatic and significant improvement upon TF-TF edge prediction in all tested NI methods.
    - Pearson, WGCNA(6 and 12), TOM, CLR, ARACNE, PANDA
  - Method finds highly concordant results in different datasets studying the same disease.
    - COPDGene, ECLIPSE, LGRC (note, this fact *does* depend on NI method)
- 3.) Method is useful?
  - Method predicts TF-TF targeting substantially better than existing methods in *Yeast* and *in silico* datasets.
  - Method predicts many TF interactions as well as TFs which have non-specified behavioral changes

- Yes, yes and yes?