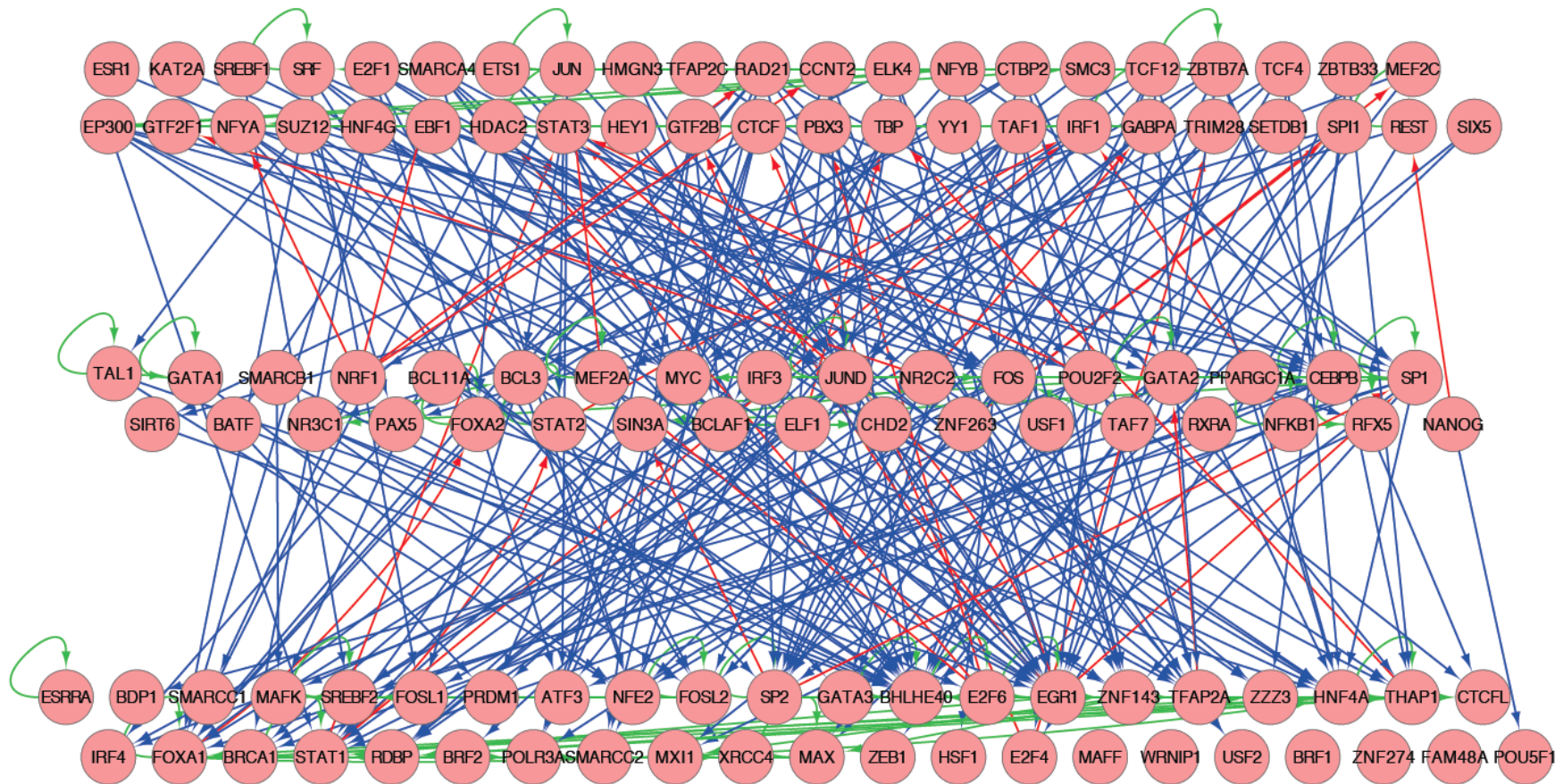# Construction of
# a network hierarchy
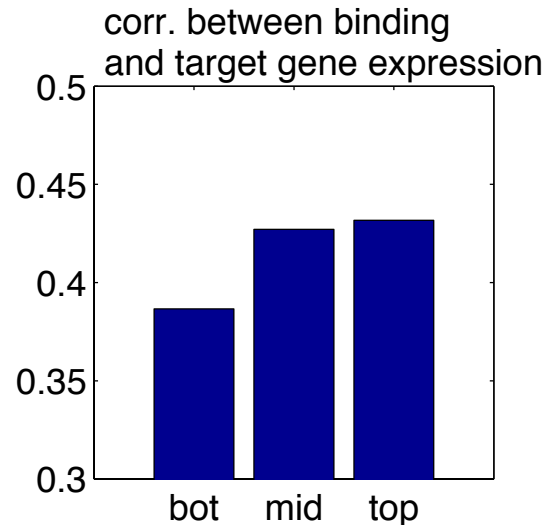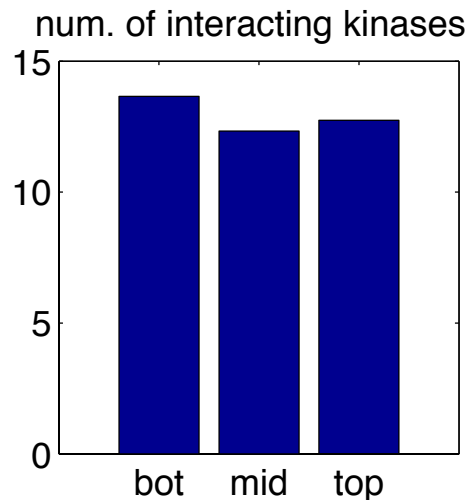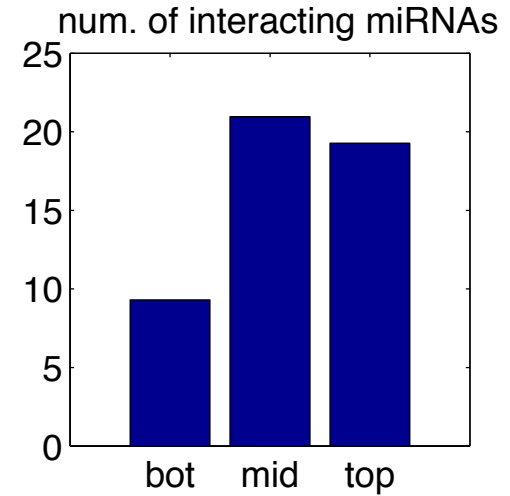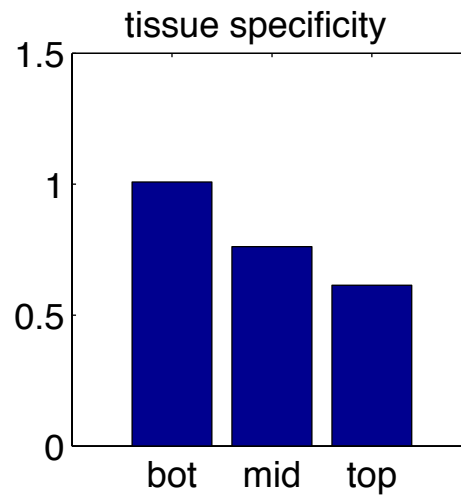
- Essential idea: an hierarchical network possesses an intrinsic direction of information flow. The majority of edges should go along the preferred direction. Edges along the direction (forward edges), and edges opposite to the direction (feedback edges)

- An optimization problem: how to place nodes in different levels such that the number of feedback edges (forward edges) is minimal (maximal) --- approximate solution obtained by an Metropolis algorithm

# Construction of
# a network hierarchy



Forward edges (245 ), feedback edges (31), within the same level (42) +28 autoregulation
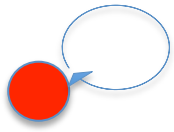
# Mapping TF properties to the hierarchy



num. of PPI partners

tissue specificity

num. of interacting miRNAs

num. of interacting kinases
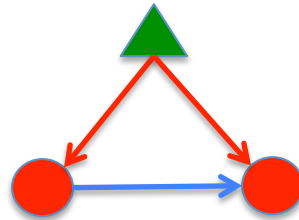
corr. between binding and target gene expression
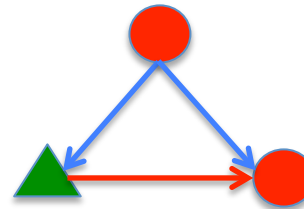
and many more .....

# Mapping motifs to the hierarchy



autoregulator
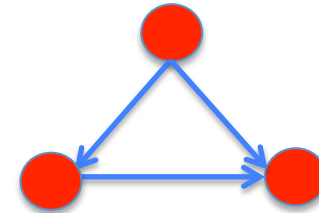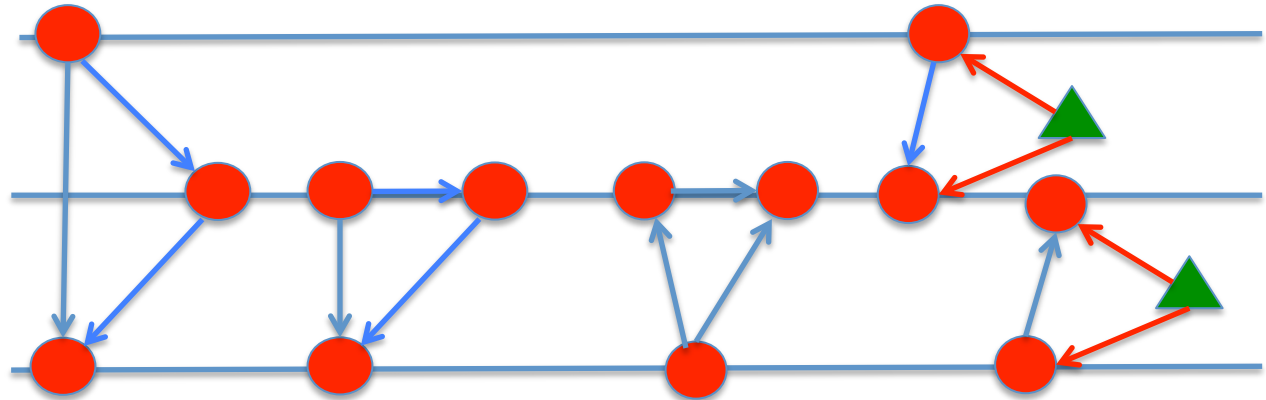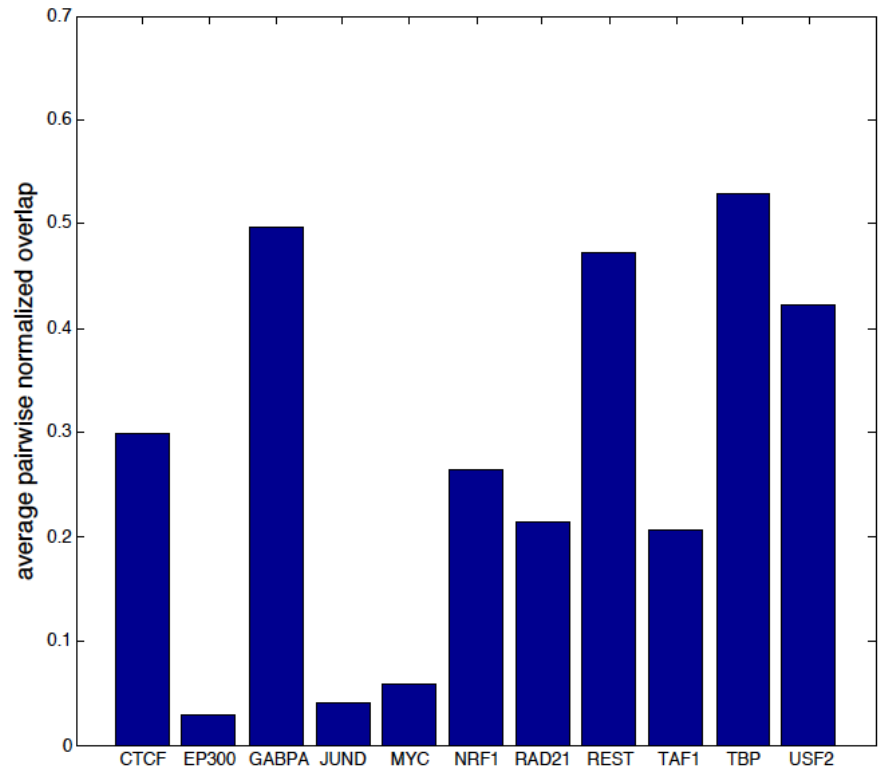
28

59

29

123

Auto-regulation is depleted at the top layer: 6 auto regulator out of 43 TFs (28 out of 119 in the whole system)
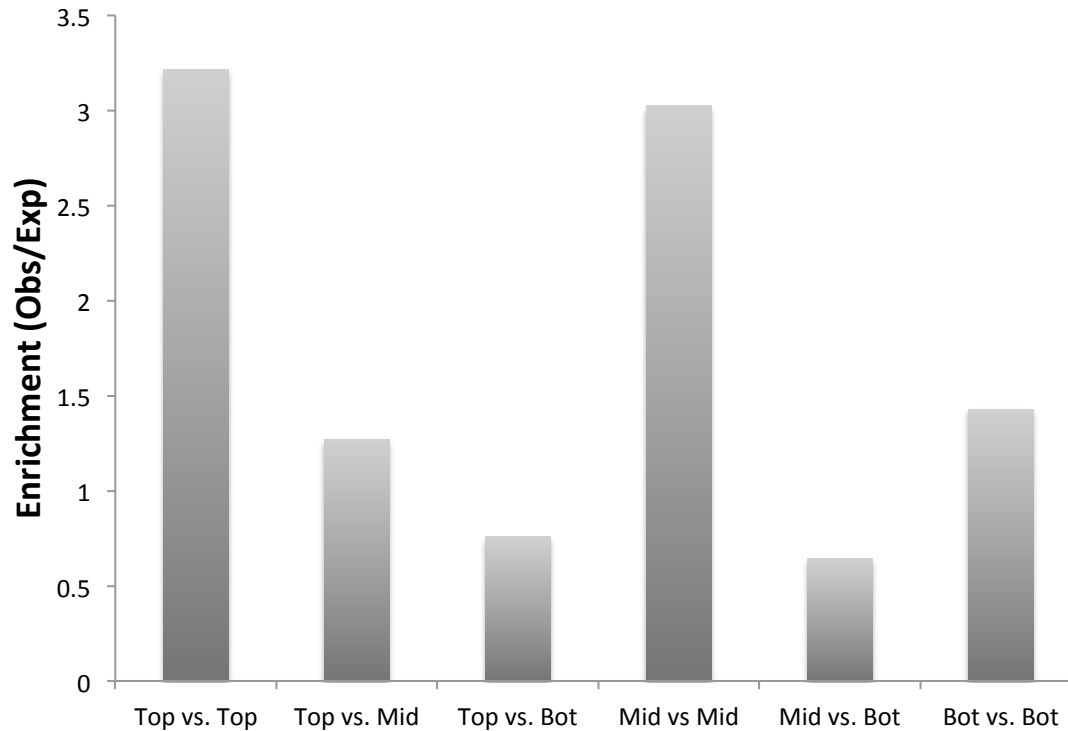
# TF Dynamics

- Only 11 TFs (CTCF, EP300, GABPA, JUND, MYC, NRF1, RAD2, REST, TAF1, TBP, USF2) with tracks in 5 major cell lines (Gm12878, H1hesc, Helas3, Hepg2, K562)

- Quantify the average pairwise rewiring (intersection/union) of these TFs in the 5 cell lines

# TFs in the same level are more interacted

| | Lev1 | Lev2 | max.num | exp.num | obs.num | fraction | ratio | pvalue |
|---|---|---|---|---|---|---|---|---|
| Top vs. Top | top | top | 861 | 39.18584071 | 126 | 0.146341463 | 3.215447154 | 2.81E-30 |
| Top vs. Mid | top | mid | 1230 | 55.97977244 | 71 | 0.057723577 | 1.268315266 | 0.02665771 |
| Top vs. Bot | top | bot | 1681 | 76.505689 | 58 | 0.034503272 | 0.758113557 | 0.989383011 |
| Mid vs Mid | mid | mid | 465 | 21.1630847 | 64 | 0.137634409 | 3.024133811 | 6.26E-15 |
| Mid vs. Bot | mid | bot | 1230 | 55.97977244 | 36 | 0.029268293 | 0.643089431 | 0.998528953 |
| Bot vs. Bot | bot | bot | 861 | 39.18584071 | 56 | 0.06504065 | 1.429087624 | 0.005546014 |

# TF-TF pairs showing additive effect

- 239 TF/cell-line tracks
- For a pair of  TFs: A and B

  - identify A-unique (A), B-unique (B), AB-shared genes (AB)

  - compare their expression levels

  - AB ≠A & AB≠B pairs
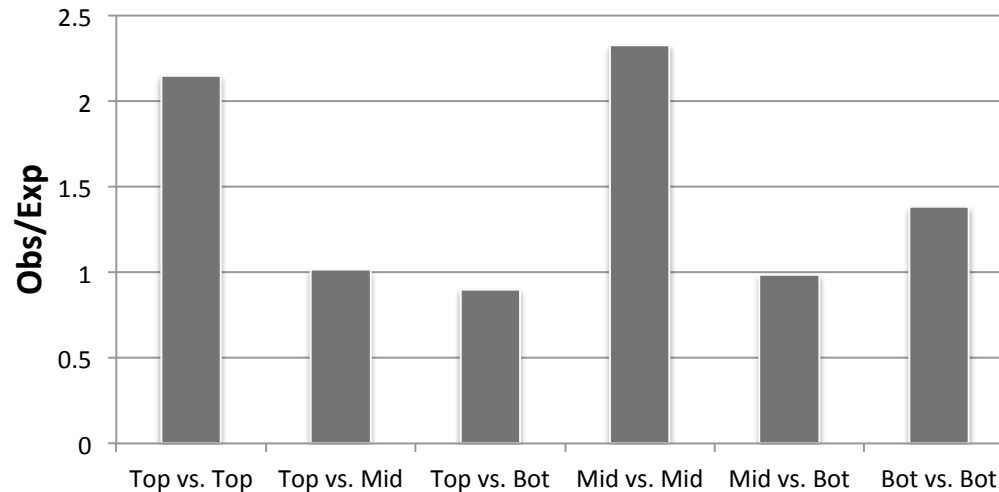
  - more interestingly, AB>max(A,B) or AB<min(A,B)

# K562

For (A,B)
[A,B] shows P(AB>A);
[B,A] shows P(AB>B);

Cut-off for P-value is 0.001

# TFs in the same layer are more additive for regulating gene expression



K562

| | Lev1 | Lev2 | max.num | exp.num | obs.num | fraction | ratio | pvalue |
|---|------|------|---------|---------|---------|----------|-------|--------|
| Top vs. Top | top | top | 120 | 36.31349782 | 78 | 0.65 | 2.147961631 | 4.69E-15 |
| Top vs. Mid | top | mid | 368 | 111.3613933 | 113 | 0.3070652171 | 1.014714316 | 0.445705663 |
| Top vs. Bot | top | bot | 224 | 67.78519594 | 61 | 0.2723214290 | 0.899901507 | 0.855650617 |
| Mid vs. Mid | mid | mid | 253 | 76.56095791 | 178 | 0.7035573122 | 2.324944787 | 2.95E-39 |
| Mid vs. Bot | mid | bot | 322 | 97.44121916 | 96 | 0.2981366460 | 0.985209348 | 0.590123577 |
| Bot vs. Bot | bot | bot | 91 | 27.53773585 | 38 | 0.4175824181 | 1.379924632 | 0.013096259 |