Supplementary

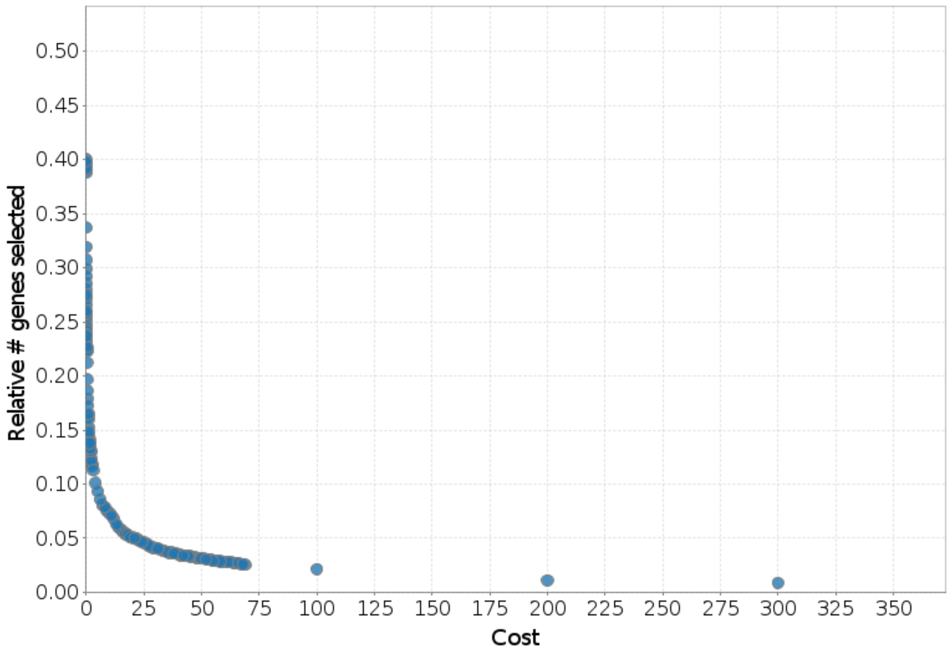

Figure S1 – Effect of varying gene selection cost on the size of the selected sub-network, The relative number of genes selected by the PheNetic algorithm by increasing gene selection cost. As the gene selection cost increases the number of selected genes decreases. Number of genes selected when varying the gene selection cost, while keeping all other parameters constant. As the cost increases gradually less genes will be selected.

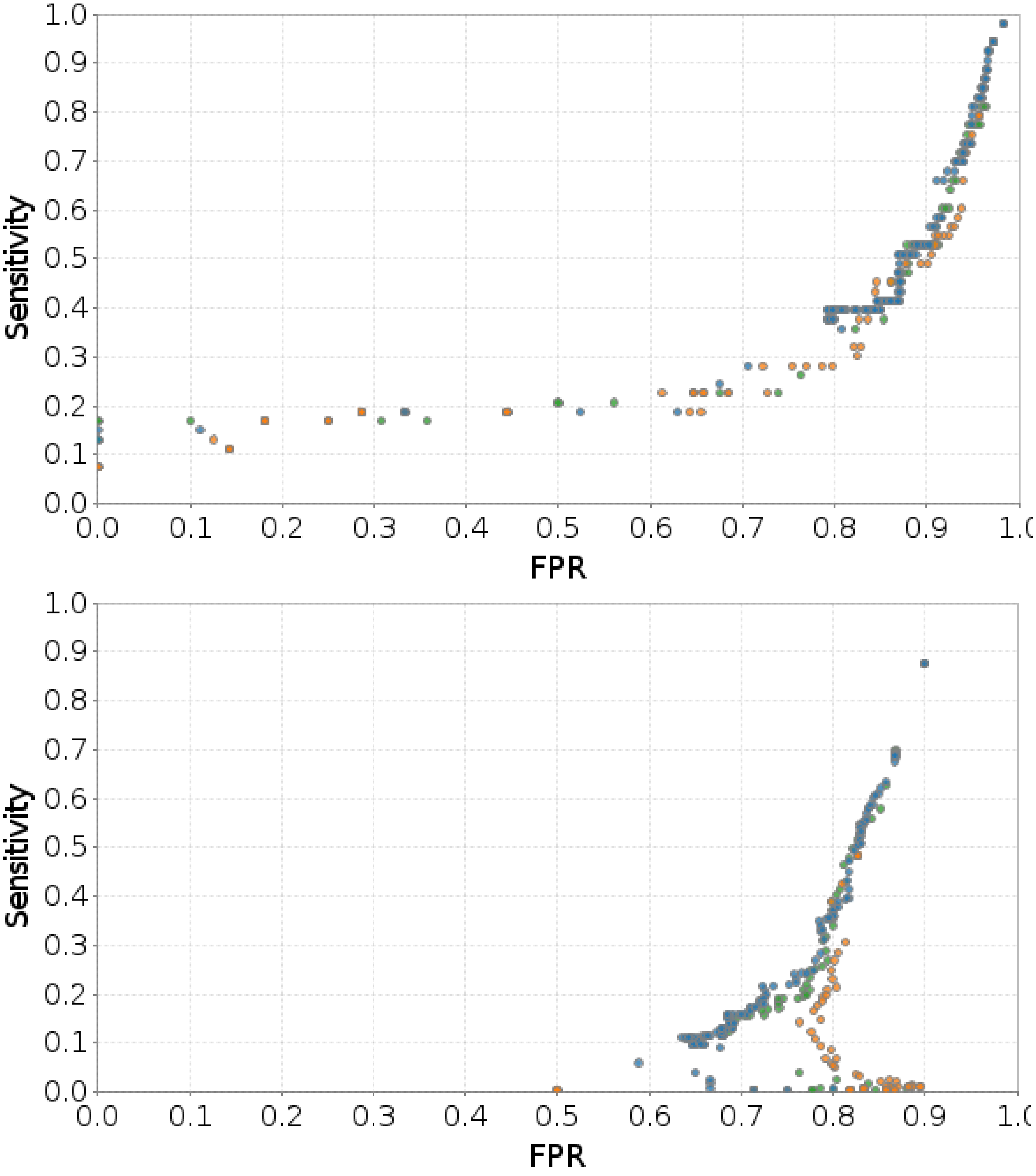

Figure S2 – The effect of different reward functions for PheNetic. Performance comparison was based on a sensitivity –FPR analysis as described in Materials and Methods using the literature (top panel) and the differential expression (bottom panel) benchmark sets. A comparison of the reward function based on the fifth power of the differential expression of an explained effect (blue), a reward function based on the absolute value of the differential expression of an explained effect (green) and a reward function based on a constant value independent of differential expression (orange) was made. The results were obtained using the 1000 best cause-effect pairs per mutant and a sweep over the gene selection cost. Using the fifth power of the differential expression as a reward function yielded best overall performance.

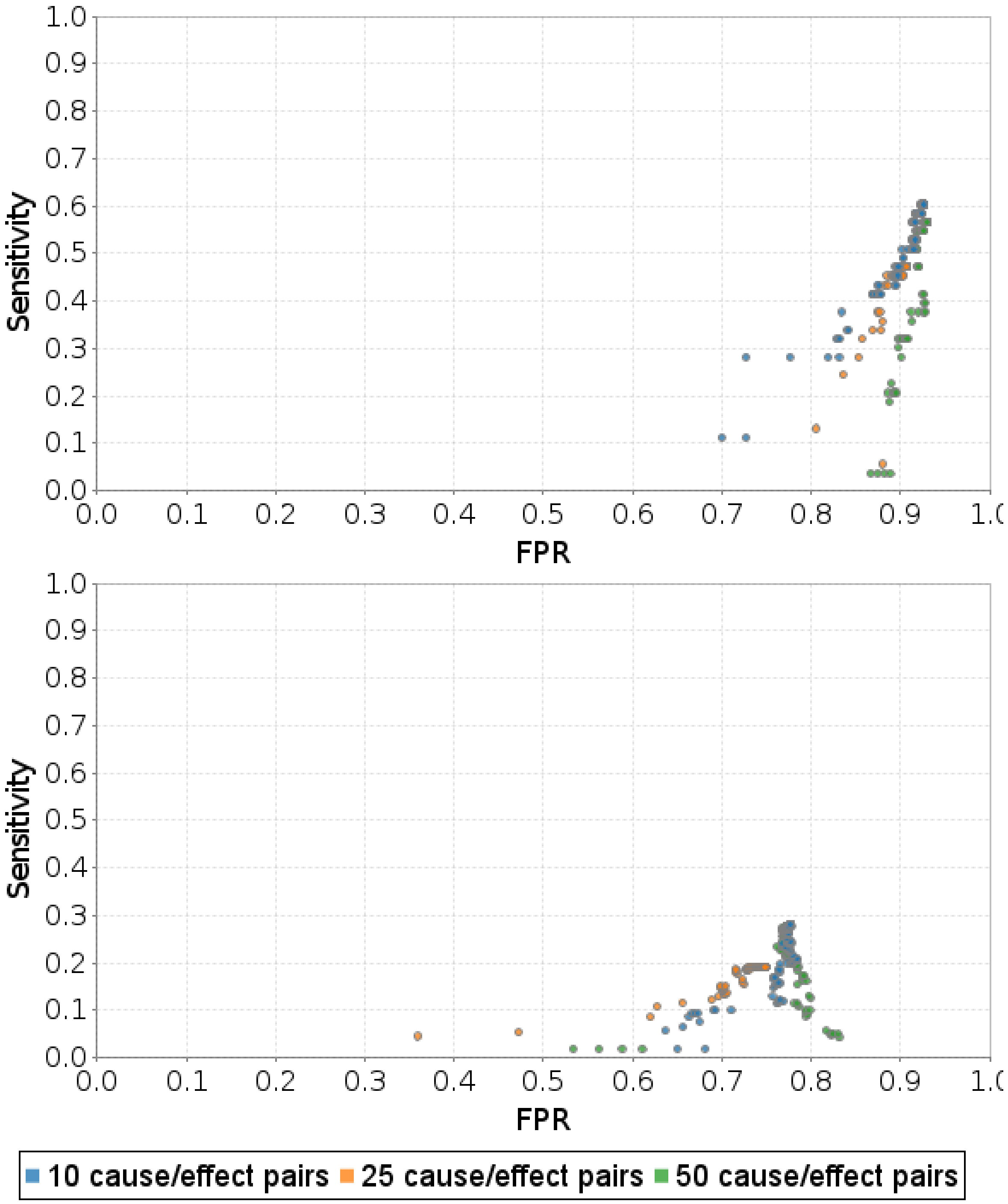

Figure S3 – The effect of selecting a different number of differentially expressed genes per mutant as input for eResponseNet. Performance comparison was based on a sensitivity –FPR analysis as described in Materials and Methods using the literature (top) and the differential expression (bottom) benchmark sets. A comparison for the 10 (blue), 25 (orange) and 50 (green) most differentially expressed genes as input using the interaction network without the metabolic interaction layer was made. In general using a low number (10-25) of differentially expressed genes as input for eResponseNet results in a better performance than using a larger number of differential expressed genes (effect is already visible when using 50 genes and deteriorates much further when adding more genes).

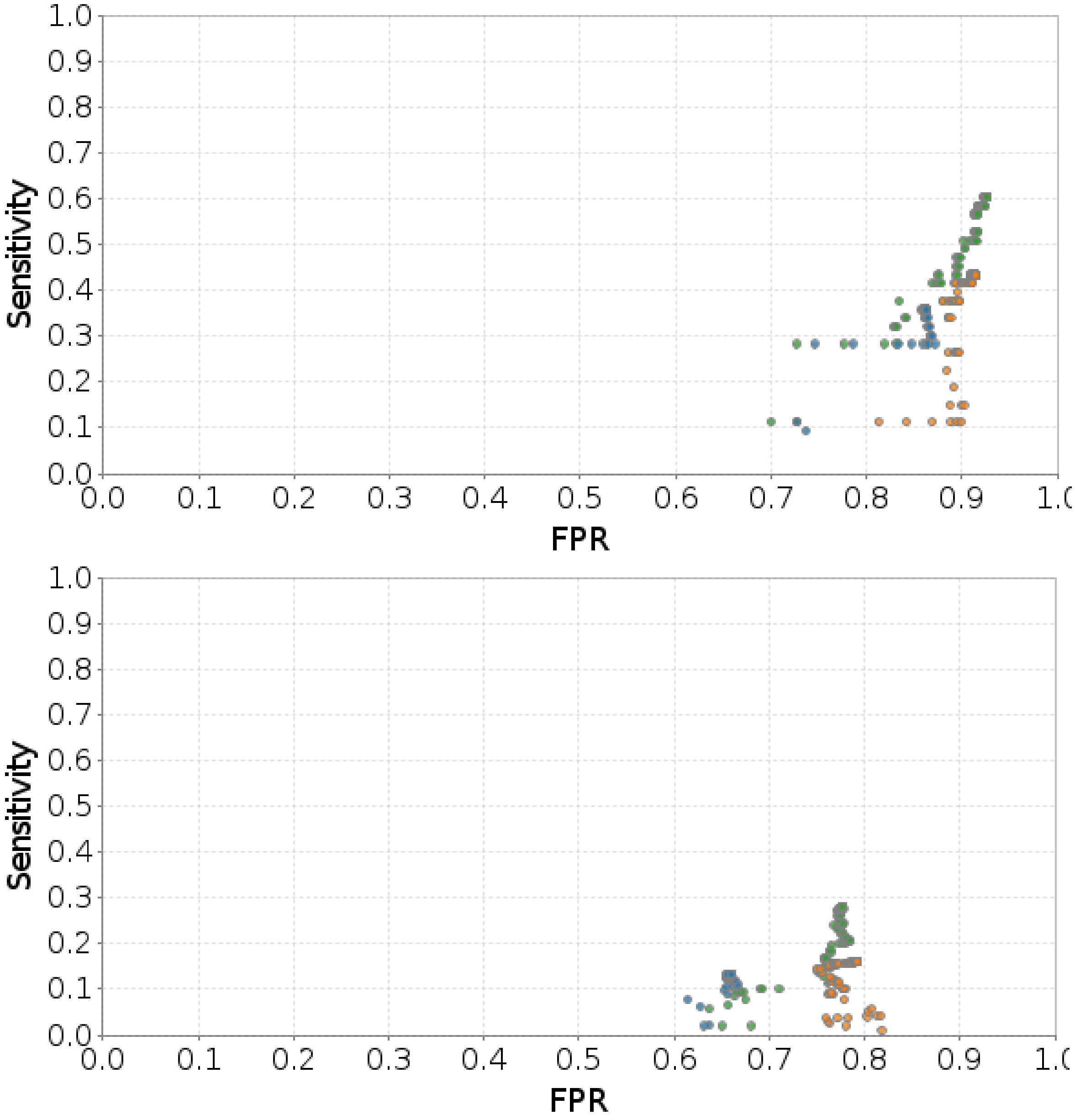

Figure S4 – The effect of adding metabolic interactions to the interaction network to be used in combination with eResponseNet. Performance comparison was based on a sensitivity –FPR analysis as described in Materials and Methods using the literature (top) and the differential expression (bottom) benchmark sets. Results are shown of runs with eResponseNet in combination with the original network developed in this study (interaction network containing both directed and indirected metabolic interactions) (orange), an interaction network without metabolic interactions (green), and an interaction network with all metabolic interactions added as undirected interactions (blue). All runs were performed using the 10 most differentially expressed genes as input. Optimal performance on the literature benchmark set was obtained using an interaction network without metabolic interactions.

Network visualization

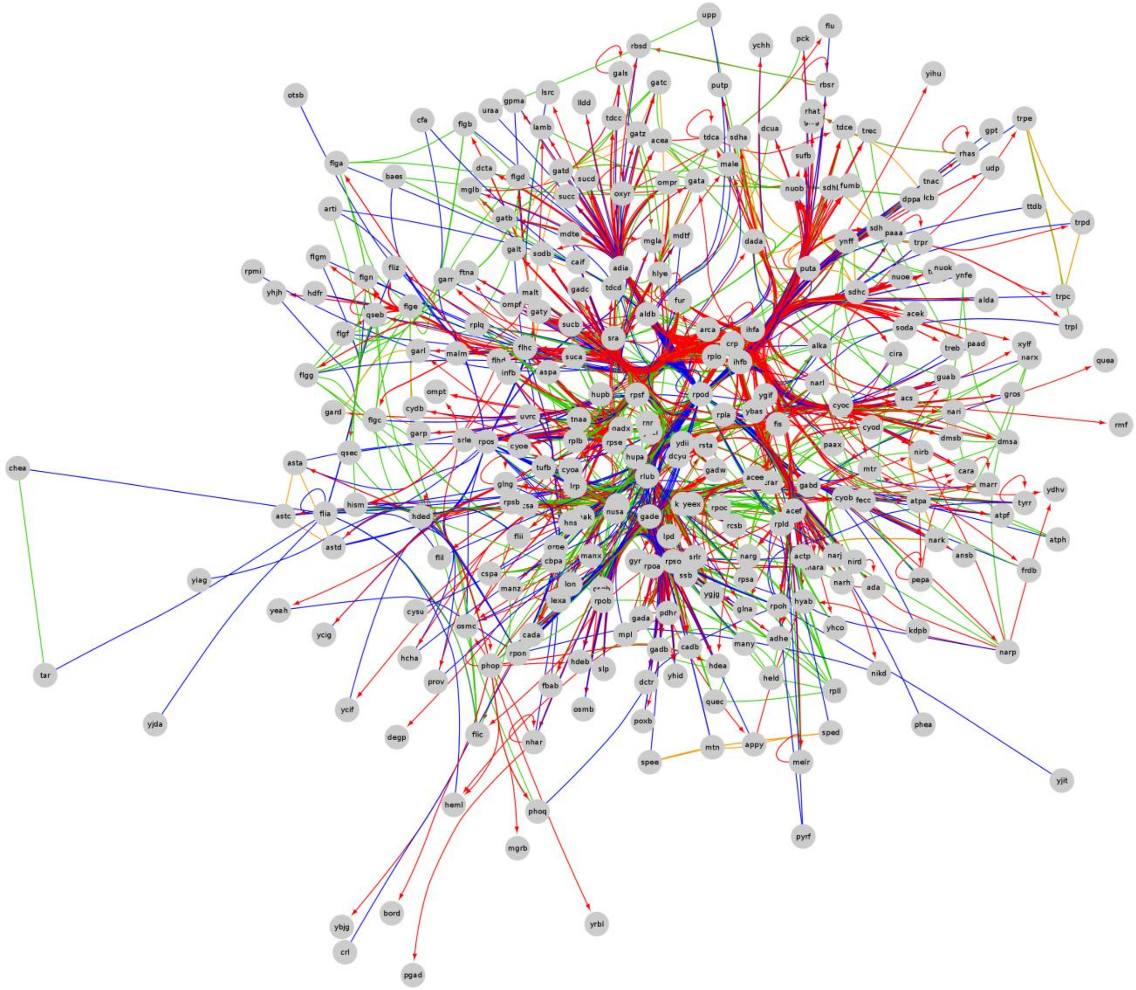

Figure S5 – Sub-network consisting of the 287-best ranked genes obtained by PheNetic. Red lines indicate protein-DNA interactions, blue lines interactions between sigma factors and their targets, green lines protein-protein interactions and orange lines metabolic interactions.

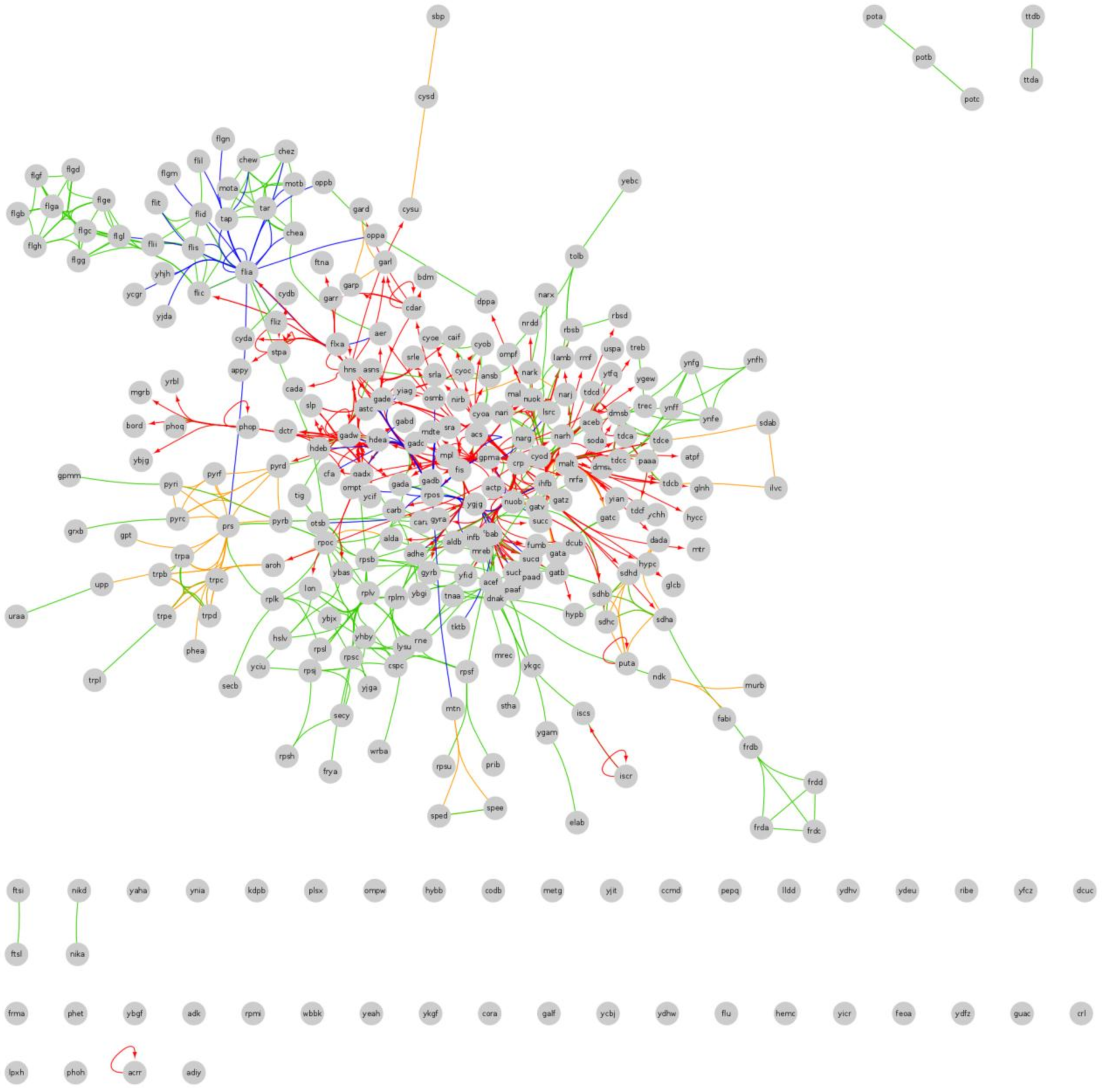

Figure S6 – Sub-network consisting of 293 genes selected by the differential expression-based ranking. Red lines indicate protein-dna interactions, blue lines interactions between sigma factors and their targets, green lines protein-protein interactions and orange lines metabolic interactions.

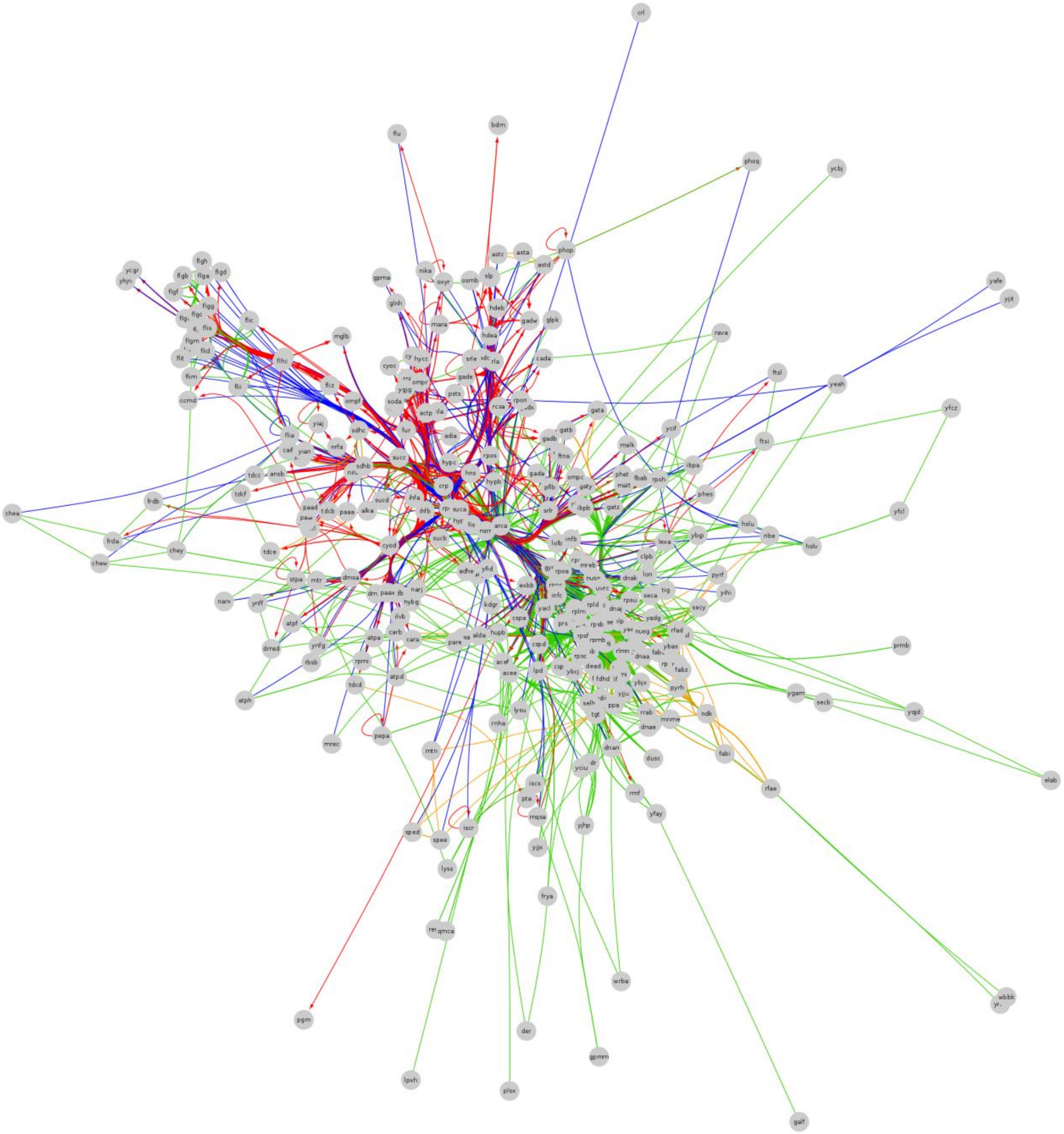

Figure S7 – Sub-network consisting of 292 genes selected by eResponseNet. Red lines indicate protein-dna interactions, blue lines interactions between sigma factors and their targets, green lines protein-protein interactions and orange lines metabolic interactions.