

Supplementary table S1: Summary features of the complex-complex predictions

	Human	Yeast
Distinct complexes	1216	471
Protein network size (# of edges)	63358	75090
Proteins in the PPI networks (# nodes)	11359	5959
Proteins in curated complexes not in the PPIs	247	40
Total proteins used in the analysis	11606	5999
Proteins not in curated complexes	9468	4398
Proteins in the PPIs mapped to a curated complex	2138	1601
Number of complex-complex predictions at <10% FDR, ICE rule	375	428
Number of complex-complex predictions at <10% FDR, BSO rule	1262	188

Descriptive statistics of the complex-complex interactions in human and yeast: The summary features of the source interactome data, protein complexes, and predictions from both organisms are depicted. For the physical complex-complex predictions, many complex pairs gave weaker predictions when the BSO rule was applied in yeast compared to the ICE rule. The reverse trend was observed in human. This particular effect in yeast was not a global phenomenon and largely occurred in complexes that contained many intra-complex interactions within either of the complex pair. When the ICE rule was applied in yeast, the intra-complex interactions were removed in these complex pairs, thus reducing the degrees of the proteins and that of the complexes. As a result, the complex-complex degrees were lowered for these complex pairs, and their expected number of random interactions was reduced accordingly. This led to more predictions for the ICE rule in yeast than in human. Due to the far greater tendency of complexes to share protein membership in human, the opposite phenomenon occurred: the ICE rule had the effect of being very strict across many complex pairs in the human interactome, and the BSO rule resulted in lower expected random values (due to lowered complex-complex degree among many complex pairs), leading to an increased number of predictions for BSO in human.