

## Supplementary Methods

The  $Z_{res}$  [Little and Chen(2009)Little and Chen] and  $Z_{i \times j}$  statistics were very similar; the plot in Figure 1B shows a slope of 0.9998, an intercept of 0.0005 and an  $r^2$  value of 0.9998. However, since the  $Z_{i \times j}$  statistic is a multiplicative  $Z$  score, it greatly expands the extreme tail of the distribution and is not easily interpretable. Thus, we chose to use  $\sqrt{Z_{i \times j}}$  since this value maintains the same order of scores without unduly over-representing the difference between covarying and non-covarying pairs. We refer to the  $\sqrt{Z_{i \times j}}$  as the  $Z_{px}$  score.

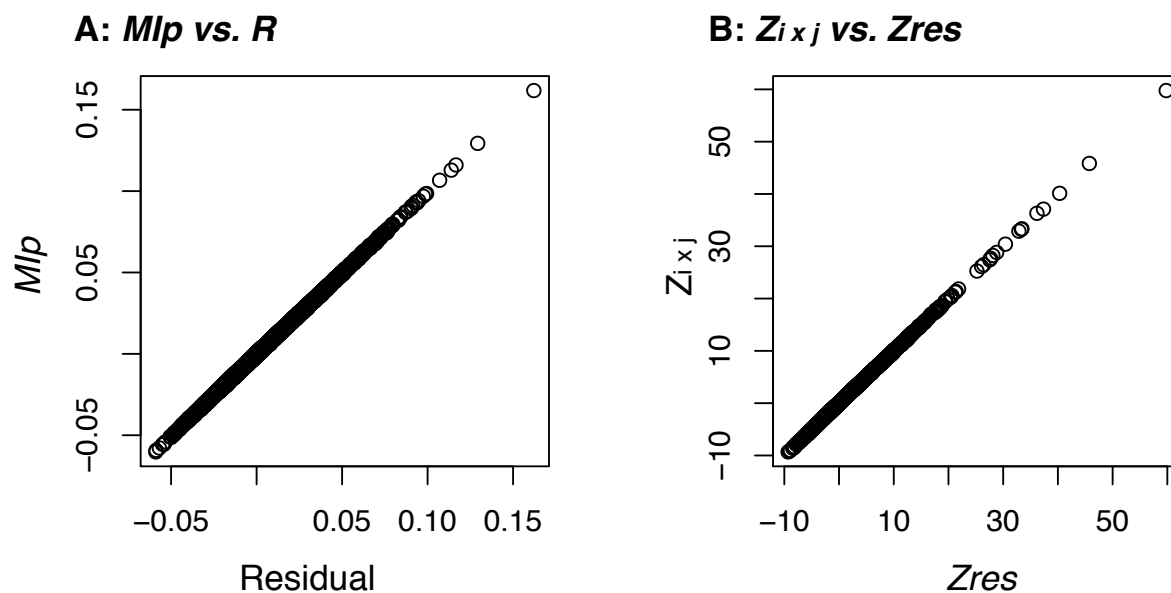


Figure 1:  $MIP$  and  $ZRes$  are essentially the same statistic. Panel A shows a plot of  $MIP$  vs. the residual of a linear regression between  $MI_{ij}$  and  $\overline{MI}_i \times \overline{MI}_j$  [Little and Chen(2009)Little and Chen]. Panel B shows a plot of  $Z_{i \times j}$  vs.  $Zres$ . The data were calculated using the repaired lactate dehydrogenase alignment. These statistics were very similar. In A,  $r^2 = 0.9994975$  with a slope and intercept of: 1.000 and  $6.185e-05$ . In B,  $r^2 = 0.9998498$  with a slope and intercept of 0.9998193, 0.0005206.

## References

[Little and Chen(2009)Little and Chen] Little, D. Y. and Chen, L. (2009). Identification of coevolving residues and coevolution potentials emphasizing structure, bond formation and catalytic coordination in protein evolution. *PLoS ONE*, 4(3), e4762.