



**Supplemental Figure S2. Characterization of the Distribution of structural similarity and sequence identity through random sampling**

Overlay of 2D scatter plot and 2D contour plot depicting the distribution of structural similarity and sequence identity of the proteins. The subfigures compare the proteomes of *E. coli* vs *H. sapiens* (A), *M. jannaschii* vs *H. sapiens* (B) and *M. jannaschii* vs *E. coli* (C). A total number of 1,000,000 unique pairs of proteins were randomly selected to compare *E. coli* and *H. sapiens*, and 500,000 unique pairs were selected for comparing *M. jannaschii* with either *H. sapiens* or *E. coli*. The vertical dashed lines indicate the sequence identity of 0.2 and 0.25, and the horizontal dashed line indicates the structural similarity of 0.5.