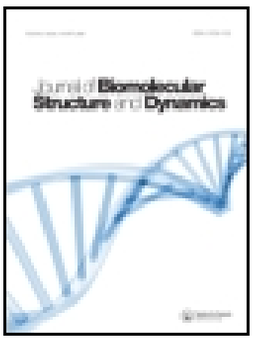

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Deciphering the cause of evolutionary variance within intrinsically disordered regions in human proteins

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Abstract

Why the intrinsically disordered regions evolve within human proteome has became an interesting question for a decade. Till date it remains an unsolved yet an intriguing issue to investigate why some of the disordered regions evolve rapidly while the rest are highly conserved across mammalian species. Identifying the key biological factors, responsible for the variation in the conservation rate of different disordered regions within the human proteome, may revisit the above issue. We emphasized that among the other biological features (multifunctionality, gene essentiality, protein connectivity, number of unique domains, gene expression level and expression breadth) considered in our study, the number of unique protein domains acts as a strong determinant that negatively influences the conservation of disordered regions. In this context, we justified that proteins having a fewer types of domains preferably need to conserve their disordered regions to enhance their structural flexibility which in turn will facilitate their molecular interactions. In contrast, the selection pressure acting on the stretches of disordered regions is not so strong in the case of multi-domains proteins. Therefore, we reasoned that the presence of conserved disordered stretches may compensate the functions of multiple domains within a single domain protein. Interestingly, we noticed that the influence of the unique domain number and expression level acts differently on the evolution of disordered regions from that of well-structured ones.

Keywords: Conservation score; protein domain; selection pressure; unstructured; protein folding.

A**bbreviations:** IDP - Intrinsically disordered proteins, CDP - Conserved disordered protein, NDP - Non-conserved disordered protein, SP - Structured protein, MIP - Multi-interfaced proteins, SIP - Single interfaced proteins, UDN - Unique domain number.

1. Introduction

Advances in the field of structural biology have claimed that there exist some portions of certain proteins or a protein as a whole that lack well-defined structural conformation under normal physiological conditions. These proteins are termed as intrinsically disordered or unstructured proteins (IDPs) (Dunker et al., 2000; Dunker et al., 2001; Tompa, 2002; Uversky, 2002; Uversky et al., 2000). Gradually, with the advent of the concept of IDPs, protein's flexibility comes into existence masking Fischer's theory of "lock and key hypothesis" related to protein structure and its rigidity. Literature claimed that the eukaryotic proteome comprises approximately 30% of disordered residues (Pentony and Jones, 2010; Ward et al., 2004). The functional role of IDPs allows them to behave as flexible linker, recognition sites, entropic chain and small linear motifs (Dyson and Wright, 2005; Gunasekaran et al., 2003; Uversky et al., 2000; Wright and Dyson, 2009). A significant difference in amino acid composition is noticed within intrinsically disordered and well-structured regions in a protein (Williams et al., 2001). Disordered residues are largely enriched in polar, charged, hydrophilic residues and are abundant at low complexity regions (Lise and Jones, 2005; Tompa, 2003). Furthermore, it is reported that structural disorder prevails in negligible amounts in lower species (e.g. *Saccharomyces*), and gradually increases as the organism becomes more complex (e.g. *Homo sapiens*) (Peng et al., 2015; Schad et al., 2011; Ward et al., 2004). The distribution of intrinsic disorders across the animal kingdom evokes the question how differently the molecular evolution acts upon IDPs or particularly the disordered regions within a protein.

In the above context, several evolutionary studies concentrated on understanding the pattern of molecular evolution within IDPs and well-structured proteins (SPs). Brown et al. (Brown et al., 2002) explored if there is any significant difference in the evolutionary rate of IDPs and SPs within 26 protein families based on pairwise genetic distances between them. They reported that 19 families out of 26 showed a higher evolutionary rate in disordered regions than their structured regions, 2 families (adenovirus ssDNA binding protein and flagellin) exhibited a reverse trend of high evolution in structured regions than disordered ones, whereas remaining 5 families revealed no such significant difference in the rate of evolution between disordered and structured

regions. In this context, some of the studies questioned the reason behind such variation in the rate of evolution within the set of protein families (Brown et al., 2011; Brown et al., 2002; Schlessinger et al., 2011). Further several studies showed that intrinsically disordered regions usually evolve faster compared to those of well-structured or ordered ones resulting from the difference in their rate of point mutations (Liu et al., 2008), amino acid substitution (Brown et al., 2010), and repeat expansions (Light et al., 2013). Researchers reasoned that disordered residues evolve rapidly because they usually do not participate in the long-range interactions (Dunker et al., 2008). Although, the amino acid residues forming disordered segments evolve rapidly, the intrinsically disordered behavior of the disordered region is highly conserved through evolution (Daughdrill et al., 2007). This characteristic of disordered regions is considered to be advantageous since they tolerate random mutations without modifying the functions of corresponding disordered segments (Schlessinger et al., 2011). However, how often an intrinsically disordered region evolves to a well-structured region or the probability of evolving the reverse is still not explored intensively.

On the other hand, some studies claimed that the underlying sequences bearing disordered regions are not always fast evolving (Chen et al., 2006a; Chen et al., 2006b; Dunker et al., 2008). The disordered residues, residing within the protein domains, are seen to be highly conserved in terms of sequence and behavior (Chen et al., 2006a; Chen et al., 2006b; Tompa et al., 2009). It indicates that the disordered residues are evolutionarily favored, and therefore, are maintained particularly in domain regions. A study on yeast proteome observes that a set of proteins exhibits high conservation in sequences as well as in disordered behavior across 23 yeast strains and is termed them as “constrained disorder” (Bellay et al., 2011). These instances imply that there exists a diversification in evolutionary rates within disordered regions. Furthermore, Schaefer et al. perceived the evolutionary variance of intrinsically disordered regions in a different way (Schaefer et al., 2010). They suggested that highly structured regions (helices, strands) are the intrinsic property of a protein sequence, and therefore, are easily maintained through evolution. On the other hand, maintaining or acquiring flexible disordered regions in course of evolution becomes relatively strenuous (Schaefer et al., 2010). Supporting the above statement, Schlessinger et al. also mentioned the difficulties in evolution and maintenance of disordered residues regardless of random mutations (Schlessinger et al., 2011). The above studies pose a question: What is

the probable stimulating force responsible for maintaining disordered regions across evolution? Addressing this question, we tried to endeavor the reasons - why some of the intrinsically disordered stretches are highly conserved (or maintained across evolution) compared to other rapidly evolving disordered regions within the same (or different) protein(s). Identifying the biological features responsible for the wide variation in conservation level of disordered regions will make us aware of their importance within the human proteome. In order to resolve these issues, we analyzed the influence of various genomic and proteomic features resulting in the evolutionary disparity among disordered regions in proteins.

We identified a set of IDPs evolving with highly conserved and non-conserved disordered regions across mammalian orthologous sequences. We termed them as conserved disordered proteins (CDPs) and non-conserved disordered proteins (NDPs), respectively (Section 2.2). We observed that there exists a variation in the distribution of conservation scores of disordered regions across the human proteome.

In order to explore the reason why disordered regions are exposed to such varying degree of conservation, we analyzed the influence of certain biological features, like protein functionality, gene essentiality, protein connectivity, the number of unique protein domains, gene expression breadth and expression level. Linear regression analysis reported that among all the above features, unique domain number (UDN) acts as a strong determinant, independently controlling the selection pressure acting on the conserved and non-conserved disordered regions within a protein. Strikingly, we observed that the domain number negatively correlates with the conservation rate of disordered regions, unlike the case of well structured proteins, where the number of unique domain interfaces positively correlates with the protein's conservation rate. We also clarified how the effect of different biological features, changes from well-structured to disordered proteins. We noticed that expression breadth, rather than expression level, controls the degree of evolutionary conservation of disordered regions. According to Park et al. (Park and Choi, 2010), well-structured proteins, having high expression breadth tend to have a high expression level, remarkably which is not followed by CDPs. In contrast, CDPs having a high expression breadth usually exhibit low expression level. A detailed study of the above

perspectives will help us to understand why intrinsically disordered regions are evolutionarily favored in some cases while in others, they are not.

2. Materials and Methods

2.1 Identification of intrinsically disordered proteins

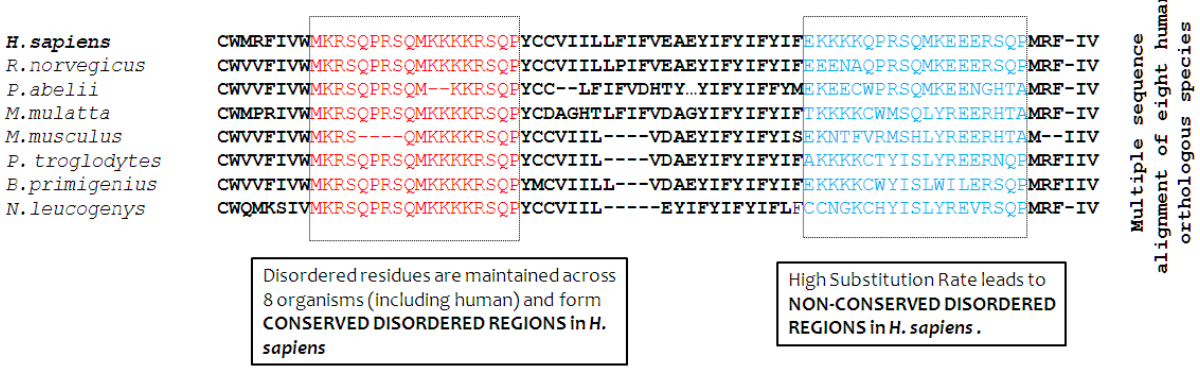
IUPred algorithm is widely used for predicting disorder content of the protein. According to the IUPred server (Dosztányi et al., 2005), an amino acid residue within a protein sequence is considered as disordered if its value is greater than 0.5 or else ordered. It gives the total number of disordered residues within a protein. We considered the normalized value of disorder content (D_C) of each protein by obtaining the fraction of total disordered residues within an entire protein sequence (i.e.,D_C/Protein length × 100). The stretch of 30 or more disordered residues is considered as a disordered region. Each protein in the human proteome was categorized as IDP following two criteria as: (i) the D_C value should be greater than 30% (Gsponer et al., 2008), and (ii) at least one stretch of a minimum of 30 consecutive disordered residues should exists whereas, in the case of ordered (structured) proteins the D_C value should be at the most 10%. Accordingly, we obtained 4816 IDPs and 11,523 SPs within the total set of 18,996 human proteins, while the remaining 7132 proteins are moderately disordered or ordered (i.e., neither IDPs nor SPs) where $10\% < D_C < 30\%$. In order to maintain the stringency of the categorization, we considered only the extreme classes of highly structured (SPs) and disordered proteins (IDPs). Furthermore, we also predicted the disordered residues using the prediction tools like PONDR-FIT (Xue et al., 2010) and ESpritz (Walsh et al., 2012) to have the results independent of the prediction methods used to measure the disordered residues (Extended Results in Supplementary file 2, Figures S1 and S2).

2.2 Classification of disordered proteins based on the conservation scores

Eight orthologous species, including human (*Homo sapiens*, *Rattus norvegicus*, *Pongo abelii*, *Macaca mulatta*, *Mus musculus*, *Pan troglodytes*, *Bos primigenius* and *Nomascus leucogenys*) were considered to estimate proteome-wide conservation scores involving only the disordered segments. The whole protein sequences of all the eight species are obtained from the NCBI Refseq server (Pruitt et al., 2005). Here, we purposely selected

these eight mammalian species because phylogenetically they appear closer to the human outgroup and share almost similar evolutionary history. On the other hand, increasing the number of species may return less number of orthologous sequences, due to the reduced probability of obtaining similarity within the aligned sequences from distant species. Next, we identified the disordered residues for all the protein sequences from eight species using three different disorder prediction tools: IUPred, PONDR-FIT and ESpritz (Dosztányi et al., 2005; Walsh et al., 2012; Xue et al., 2010).

Then we aimed at finding the human orthologous proteins in these seven species, and for this purpose, we executed standalone BLAST program downloaded from BLAST 2.2.29+ released (Altschul et al., 1997). The criteria to extract the orthologous human proteins is set as: (i) the sequences having e-value (according to BLAST program) less than 10^{-5}, (ii) minimum sequence length overlap should be 70% or more, (iii) gaps allowed in the alignment should be less than 5%, and (iv) sequences should fulfill the above three criteria in at least four out of remaining seven orthologs. We retrieved 18,996 orthologous human sequences, applying the above criteria. Further, the multiple sequence alignment of this set of 18,996 sequences was done using MAFFT algorithm (Katoh et al., 2002). Further, we marked the disordered and ordered residues along the alignment (Katoh et al., 2002). We considered only the disordered segments (i.e., where the number of consecutive disordered residues is at least 30) of a human IDP for calculating the parameters, called disorder conservation score (D) and amino acid conservation score (A) (Figure 1).



Disorder promoting residues : M, K R, S, Q, P and E
Order promoting residues: C, W, Y, I, F, V and L
Neutral residues : H, T, N, D, A and G

Figure 1: Identification of conserved and non-conserved disordered regions within human proteome. Schematic diagram showing the alignment of a stretch of a protein sequence obtained from 8 organisms [*Rattus norvegicus* (Norway rat), *Pongo abelii* (Sumatran orangutan), *Macaca mulatta* (rhesus monkey), *Nomascus leucogenys* (northern white chick gibbon), *Mus musculus* (house mouse), *Pan troglodytes* (chimpanzee) and *Bos primigenius* (cattle) including *Homo sapiens* (human)]. Here the regions (≥ 30 residues at a stretch) that are conserved (in terms of both disorderedness and amino acid residues) are considered as conserved disordered segments and the consecutive residues which are substituted several times to become a disordered region specifically in human protein sequences from pre-existing ordered region in other orthologs are considered to be non-conserved disordered segments.

The disorder conservation for an IDP is defined, similar to that in Bellay et al. (Bellay et al., 2011), as

$$D = \frac{1}{N}\sum_{s}\sum_{i} d_{si}$$

Here d_{si} denotes the number of orthologs, including human, in which the amino acid residue in i^{th} position (i.e., the same i^{th} position in all the orthologs) of s^{th} segment is disordered, and N stands for the number of orthologs including human (N = 8). That is, we considered only the disordered regions of human IDPs for calculating D. Normalized D value (D_{nor}) of an IDP is obtained dividing D (disorder conservation score) by the total length of all the disordered regions in an IDP, i.e., D_{nor} = (D / Total length of the disordered regions) × 100%.

Similarly, we calculated the amino acid conservation score (A) of disordered residues within the disordered regions of a human IDP. Thus the amino acid conservation score (A), for an IDP, is defined as

$$A = \frac{1}{N}\sum_{s}\sum_{i} a_{si}$$

where a_{si} denotes the number of orthologs having identical amino acid residue in i^{th} position within s^{th} segment, and N stands for the total number of orthologs including human. We further obtained the normalized A-value (A_{nor}) of the IDP, dividing A (amino acid conservation score) by the total length of all of the disordered segments in the IDP, i.e., A_{nor} = (A / Total length of the disordered region) × 100%.

We divided the values D and A by the total length of the disordered regions in an IDP for calculating D_{nor} and A_{nor}, respectively. This is done because D_{nor} indicates the proportion of conserved disordered portion within the disordered region in human IDP, while A_{nor} depicts the proportion of conserved amino acid residues within the disordered segments. Therefore, the scores are related specifically to the conservation of the disordered regions only and not to the whole protein. On the basis of these D_{nor} and A_{nor} values, the whole set of IDPs was further classified as conserved disordered proteins (CDPs) and non-conserved disordered proteins (NDPs).

Here, we considered the median values of D_{nor} and A_{nor} (i.e., ≈93% and ≈86%, respectively) over all the IDPs (i.e., 4816 out of 18 996 proteins), as a threshold value for measuring the CDPs ($D_{nor} > 93\%$ and $A_{nor} > 86\%$) and NDPs ($D_{nor} \leq 93\%$ and $A_{nor} \leq 86\%$). It resulted in about 37.8% (1822 out of 4816 IDPs) CDPs and about 41.7% (2008 out 4816 IDPs) NDPs. Remaining 986 IDPs failed to follow the cut-offs of both the parameters (D_{nor} and A_{nor}) simultaneously, and thus were ignored for further analysis (List of IDPs is provided in Supplementary file 1 along with their D_{nor} and A_{nor} values). However, to test the robustness of the categorization, we varied the cut-offs over a wide range of values and observed that our conclusion remains unchanged in all instances (Section 3.7).

2.3 Measurement of the evolutionary rate of intrinsically unstructured and well-structured regions

In order to measure the evolutionary rates, we calculated d_N/d_S ratio, which denotes the ratio of the number of non-synonymous substitutions per non-synonymous site (d_N) to the number of synonymous substitutions per synonymous site (d_S). We calculated d_N/d_S ratio by comparing human *(Homo sapiens)* gene sequences against one to one orthologous sequence from that of the mouse *(Mus musculus)*. We obtained the whole coding sequences of both human and mouse genome from the NCBI RefSeq server (Pruitt et al., 2005). Then, we translated these coding sequences into protein sequences using the EMBOSS Transeq program (Rice et al., 2000). We further obtained the orthologous sequences using BLAST program identified previously in Section 2.2. We used ClustalW (version 2.0) (Larkin et al., 2007) to obtain the pairwise alignment for each set of orthologous proteins. Then, we aligned the corresponding nucleotide sequences based on the protein alignments removing the gaps using in-house Perl script. The evolutionary rates (d_N/d_S) of the whole protein sequence were

calculated based on the pairwise alignment by Yang and Nielsen method (Yang and Nielsen, 2000) using yn00 control file with default parameters within the PAML package (version 4) (Chen et al., 2007; Yang, 1997). Furthermore, we splited up the corresponding nucleotide sequences of the disordered regions and the structured regions from pairwise nucleotide sequence alignment, using in-house Perl script, and estimated the evolutionary rates of disordered and structured regions separately, in the similar way as mentioned above.

2.4 Measure of multifunctionality and essential genes

In order to measure the multifunctionality of proteins, we calculated the number of biological processes (BP) and molecular functions (MF) separately in which the proteins are involved. The associated BPs and MFs for each protein were provided by the Gene Ontology database (Barrell et al., 2009) (http://www.geneontology.org/). The set of human essential genes were downloaded from the OGEE - Online GEne Essentiality database (http://ogeedb.embl.de) (Chen et al., 2012). We mapped these genes to our dataset of IDPs for further analyses.

2.5 Human protein-protein interactions

Human protein interaction data were downloaded from BioGRID Version 3.2.114 Release (http://thebiogrid.org/) (Chatr-Aryamontri et al., 2015). Then the file was manually curated to eliminate the redundant and irrelevant data. Here, we considered Entrez Gene id of both Interactor A and Interactor B. The interactors having no Entrez gene id were discarded. We did not consider the data related to interaction detection method, like “psi-mi: MI: 0686 (unspecified method)" and "psi-mi: MI: 0254 (genetic interference)". Moreover, some of the data corresponding to "colocalization" and “self-interaction” type were removed from the dataset. We calculated the interaction degree (i.e., the number of interacting proteins) of each protein from this non-redundant dataset, and considered them for further analysis.

2.6 Detection of protein interacting domains

We obtained the set of protein domains from the Pfam repository (Bateman et al., 2002; Punta et al., 2012). The following cut-off values were used for domain assignment: (1) e-value of alignment $< 1.0\times10^{-4}$; (2) matched

sequence length > 95% of Pfam domain length, and (3) domain length > 5 residues (Kim et al., 2008). In the study, we counted only the number of unique type of domains (UDN) and not the repetitive ones. We preferred to choose the non-redundant domains for our study since it captures i) the extent of diversity in the types of domain regions within a protein sequence, and ii) the extent of distinct interactions that a protein can perform. Consequently, we calculated the UDN for each protein in our dataset, and categorized them into single-interfaced protein (SIP, having only one or two domains) and multi-interfaced protein (MIP, having more than two domains) depending on the number of their unique domains (UDN) (Kim et al., 2008).

2.7 Determining expression level and expression breadth from normal human gene expression data

The normal expression data of the human genome were downloaded from GNF Gene Atlas (http://biogps.org/downloads/) (filename: Human U133A/GNF1H Gene Atlas; GEO code: GSE1133) (Su et al., 2004; Su et al., 2002; Wu et al., 2009). The data comprises the genome wide expression of human genes across 84 normal human tissues. The number of tissues in which a gene is expressed is termed as "expression breadth", and the extent of the expression in a particular tissue is termed as "expression level". Thus to measure the gene expression breadth, a gene, according to Su et al. (Su et al., 2002), is considered to be expressed in a particular tissue if the expression value is more than 200. We calculated the number of tissues where a particular gene is expressed, i.e., expression value is above 200. To measure the expression level, we calculated the normalized expression value of each gene across 84 tissues provided by the dataset of Su et al. (Su et al., 2002).

2.8 Statistical Analysis

All the statistical analyses, i.e., Mann-Whitney U test, Fisher's exact test, Z-test, Shapiro-Wilk test of normality, Kernel density estimation and multiple linear regression analyses are conducted using SPSS version 20.0 and R statistical software (Team, 2011). Since our datasets including the values of A_{nor} and D_{nor} are not normally distributed (significance level of A_{nor} and D_{nor} values according to Shapiro-Wilk test of normality = 1.0×10^{-6}), we therefore, used non-parametric tests like Kernel density estimation, Fisher's exact test, Mann-Whitney U test, and Spearman's rank correlation test. In case of our study, the non-parametric test is appropriate as it does

not make any prior assumptions about the probability distributions of the variable factors being measured. Moreover, we compared the median values of a particular feature (rather than the mean values) because the mean values seldom get affected by the values being too high or too low in certain cases, while median values pose to be a better measure in estimating two non-normally distributed populations. Kernel density estimation (KDE) is used as a data smoothing problem, to measure the degree of variation in the conservation scores (D_{nor} and A_{nor}, Figure 2). Fisher's exact test is used to examine the significance of the association between the two kinds of classification, and is conducted to measure the distribution of the data (the set of IDPs) categorized as essential or non-essential. We performed multiple regression analysis in order to measure the relationship between the independent impact of each biological feature (considered as the independent variable) on the conservation scores, i.e., D_{nor} and A_{nor} (considered as the dependent variable) of disordered regions. We performed separate regression tests for each of the dependent variables D_{nor} and A_{nor}, and generated a set of regression coefficients corresponding to the independent variables (details in Section 3.8).

3. Results

3.1 Exploring the effects of evolutionary rates on disordered and structured regions of a protein

We categorized the set of IDPs into conserved (≈ 1822) and non-conserved (≈ 2008) disordered proteins depending on the conservation scores (i.e., D_{nor} and A_{nor} values), calculated only on the disordered regions of the respective protein (Section 2.2) and not considering the whole protein sequence. This is done in order to capture the exclusive effects of the biological features acting only on the evolution of the disordered regions. The wide variation in the conservation scores (Figure 2) across all the IDPs indicates that the selection pressure acting upon all the disordered regions is not uniform within the human proteome. While considering the groups of IDPs and SPs, we observed a very little difference in their evolutionary rate (median d_N/d_S: IDP = 0.20 and SP = 0.18; Mann-Whitney U test, $P = 1.8\times10^{-2}$, Figure 3A). Additionally, we also observed no significant difference between the groups of IDPs and SPs obtained using the other disordered prediction tools like PONDR-FIT (Figure S1A) and ESpritz (Figure S2A). This may happen because IDPs contain both disordered and structured regions within their sequences. In order to measure the independent effect of intrinsically

disordered and structured regions on the evolution of the entire protein sequence, we performed a linear regression test. We noticed that the evolutionary rate of a disordered protein is strongly influenced by the selection pressure acting on the disordered stretches rather than the structured regions of the protein ($\beta_{disordered}$ = 0.316, $P = 1.0\times10^{-6}$; $\beta_{structured}$ = 0.091, $P = 2.0\times10^{-6}$). In support to this result, we also observed that the evolutionary rates (d_N/d_S) between the whole protein sequences of CDPs (median d_N/d_S: 0.14) and NDPs (median d_N/d_S: 0.26) produce a sharp difference (Figure 3A). The difference of the evolutionary rate between CDPs and NDPs also become prominent while analysing the outcome from PONDR-FIT (median d_N/d_S of CDP: 0.13; median d_N/d_S of NDP: 0.26, Figure S1A) and ESpritz (median d_N/d_S of CDP: 0.14; median d_N/d_S of NDP: 0.25, Figure S2A) prediction algorithms. The outcome is quite obvious as we categorized the groups based on the conservation scores of disordered regions.

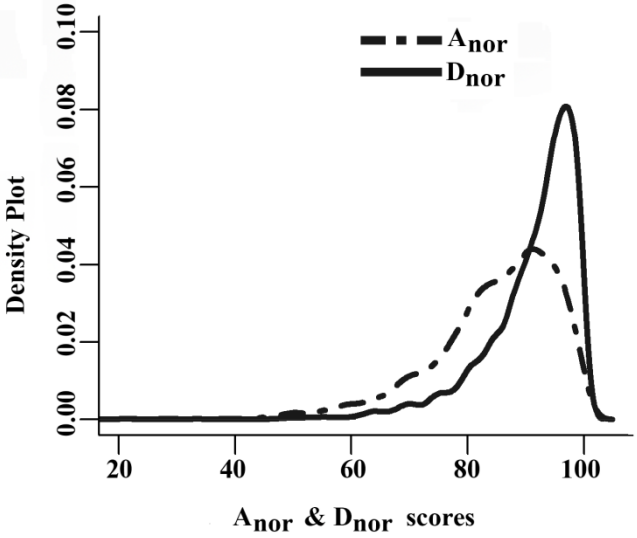


Figure 2: Density plots of both the conservation scores - A_{nor} (shown in dotted line) and D_{nor} (shown in continuous line). Plot is generated using Kernel density estimation. It is used to calculate the density function of the random variables (A_{nor}, D_{nor}). The plot indicates the variation in the conservation scores (A_{nor}, D_{nor}) of the disordered regions of 4816 IDPs within the human proteome.

Recently, the study of Mahani et al. (Mahani et al., 2013) showed that the disordered stretches within Myc protein family remain conserved than widely diverging amino acids in structured regions. As stated earlier, Brown et al. (Brown et al., 2002) reported that in a small dataset of 26 protein families, even though most of the experimentally determined disordered regions evolves rapidly compared to the structured regions in them, the evolutionary pattern is not same for all the proteins. Although, the small set of examples may not be illustrative in proteome wide analysis, it indicates that this trend of molecular evolution of certain disordered regions, if not all, is a step towards purposeful adaptation. The observation evokes a very crucial question: What does actually lead this differential pattern of molecular evolution within intrinsically disordered regions, leaving some regions highly conserved while others are subjected to rapid evolution? It motivated us to study the biological features determining the variation in the conservation scores within different disordered regions within IDPs. We also focused how the classes – (i) IDPs and SPs, and (ii) CDPs and NDPs are subjected differently to the influence of these features.

3.2 Role of protein functionality and gene essentiality determining evolutionary conservation of disordered regions

Literature depicts that the selection pressure acts on protein's flexibility to optimize cellular functions (Liu et al., 2009). According to functional genomics, a protein functionality subjects them to the varying degree of evolutionary pressure (Wall et al., 2005). However, the functional importance of protein's flexibility remains uncertain (Fuxreiter and Tompa, 2012; Jeffery, 2003; Radivojac et al., 2007; Tompa and Fuxreiter, 2008). We explored if the functionality influences the evolutionary diversity within intrinsically disordered regions. According to our results obtained using IUPred and ESpritz prediction tools, there is no difference in the number of biological processes (BP) between both the groups of IDPs versus SPs and CDPs versus NDPs. (Figures 3B, S1B, S2B). Similarly, while considering the distribution of biological processes (BP) between IDPs versus SPs and CDPs versus NDPs, we did not find any significant differences except between IDPs and SPs obtained using PONDR-FIT (Figure S1C). It indicates that structural disorder inducing flexibility within a protein may not have any remarkable impact on functionality. Considering the outcome, we interpreted that multifunctionality may not influence the selection pressure acting upon the disordered regions. However, the result can be misleading given that the information on protein functionality extracted from the Gene Ontology is redundant (Park et al., 2011). On the other hand, since the functional annotations of the SPs are possibly more complete, equal medians between IDPs and SPs may suggests that functions are often deduced from structure. Thus, assuming that our results can be an outcome of such redundancy, we further extended our study using the dataset of human essential genes (Chen et al., 2012).

Essential genes are the set of few genes, the knockout of which causes the phenotypes with lethality or sterility in an organism (Dickerson et al., 2011). This set of genes encode for the proteins having indispensable functionalities. According to our observation, comparatively more CDPs (10.04%), in our dataset, are encoded by the class of essential genes compared to the group of NDPs (7.62%). The level of significance of the distribution of essential genes according to the Fisher's exact test, $P = 2.1\times10^{-3}$. The result thus indicates that gene essentiality may favor the advantageous selection of disordered regions against the random mutations and conserves them in the course of mammalian evolution. It predicts that vital functionalities may constrain the evolution of disordered regions, both in terms of sequence and behavior. The work of Nguyen et al. supports our findings, asserting that functionally enriched short linear motifs, rich in disordered residues, should have a

higher degree of protein sequence conservation compared to the adjacent non-disordered regions (Nguyen Ba et al., 2012).

3.3 Conserved disordered proteins serve as core signaling components in developmental processes

In order to support our result stated in Section 3.2, we considered the role of IDPs in signaling pathways, particularly related to the developmental processes of the organism. Here, we used SignaLink 2.0 database to extract the information related to the proteins participating in pathways, like Receptor Tyrosine Kinase (RTK) pathway (including EGF/MAPK and Insulin/IGF), Hedgehog, JAK-STAT, NHR (nuclear hormone receptor), Notch, TGF-β and WNT pathways (Korcsmáros et al., 2010). It is believed that these seven major pathways exhibit active participation during the process of development, and are conserved across the species (Fazekas et al., 2013). Integrating our dataset with the data provided by SignaLink 2.0, we observed that CDPs are more enriched with the core components of the aforesaid signaling pathways compared to that of the NDPs (proportion of proteins acting as core components: CDP = 58.92% and NDP = 41.08%, $P = 2.7\times10^{-2}$; Fisher's exact test). According to the database, a core component of a signaling pathway is considered to be essential for transmitting the signals. In contrast, non-core components reside in the periphery of the signaling pathways and assist in the proper functioning of core components. The instance indicates the functional importance of CDPs.

3.4 Protein connectivity as one of the determinants influencing the variation in conservation of disordered regions

According to the literature, evolutionary rates of proteins depend on the property of their interacting partners (Makino and Gojobori, 2006). Furthermore, protein connectivity is negatively correlated with their evolutionary rates in yeast as well as in human (Batada et al., 2006; Brown and Jurisica, 2007; Chakraborty and Ghosh, 2013; Fraser et al., 2003; Fraser et al., 2002). However, the study of Jordon et al. contradicts the association between protein's degree of interactions and evolutionary rate (Jordan et al., 2003). Here, we explored how protein connectivity guides the conservation pattern of disordered regions within a protein. We measured the difference in protein connectivity within SPs and IDPs, and noticed that IDPs have significantly higher protein

connectivity compared to SPs (median protein connectivity: 6 for IDPs and 3 for SPs; Mann-Whitney U test, $P = 1.0\times10^{-6}$; Figure 3D). Some of the recent studies support our result, which states that hub proteins are mostly disordered in nature (Dosztányi et al., 2006; Haynes et al., 2006; Patil et al., 2010). Further, while considering the difference in protein connectivity among the classes of IDPs (CDPs and NDPs), we noticed that CDPs are associated with significantly higher numbers of protein–protein interactions compared to NDPs (median protein connectivity: 7 for CDPs and 4 for NDPs; Mann-Whitney U test, $P = 1.0\times10^{-6}$; Figure 3D). We observed a similar pattern of distribution of protein connectivity between SPs versus IDPs (median protein connectivity: 6 for IDPs and 3 for SPs; Mann-Whitney U test, $P = 1.0\times10^{-6}$; Figure S1D), and CDPs versus NDPs (median protein connectivity: 7 for CDPs and 5 for NDPs; Mann-Whitney U test, $P = 1.0\times10^{-6}$) using the other datasets of PONDR-FIT and ESpritz (Figure S1D).

Although, the distribution establishes an association between the conservation of disordered regions and the protein's degree of interaction, it is not the appropriate test to claim that protein connectivity is the cause behind the conservation of disordered regions across human proteome. In order to estimate the influence of protein connectivity on the conservation of disordered regions, we performed conditional probability test. Eventually, we observed that the probability of finding a protein with conserved disordered regions within the set of proteins having high connectivity is pretty higher than the probability of finding a protein with high connectivity within the set of CDPs (p[CDPs given high protein connectivity] = 0.72 and p[high protein connectivity given CDPs] = 0.58; details in Table S1 in Supplementary file 2). It indicates that protein connectivity has an impact on the evolutionary pressure acting on disordered regions. However, the lower probability value (0.58) denotes that the conservation rate of disordered regions of a protein is unlikely to influence the degree of protein connectivity. Additionally, it indicates that a gradual increase in the protein connectivity will eventually increase the conservation rate of disordered regions within a protein (Case D of Table S1 in Supplementary file 2). Thus the gradual increase in the protein connectivity level (PPI = 1, 2 to PPI > 5) may constrain the rapid evolution of disordered regions and conserve them (Case B and C of Table S1 in Supplementary file 2).

We assumed that the flexibility and dynamicity of disordered regions within a globular protein benefit them in mediating an efficient protein-protein interaction (Dunker et al., 2005). The molecular binding of unfolded disordered regions with other interacting partners is considered to be the most favorable conformation (Boehr et al., 2009; Gunasekaran et al., 2003; Wu et al., 2015). For instance, the binding of unfolded KID region of CERB to the KIX domain of the other interacting partner, CBP undergoes induced folding and forms a stable complex without dissociating either of the domains (Dyson and Wright, 2002; Sugase et al., 2007). Hence, the prevalence of disordered regions is favored by the cellular system, and therefore, is maintained across mammalian evolution.

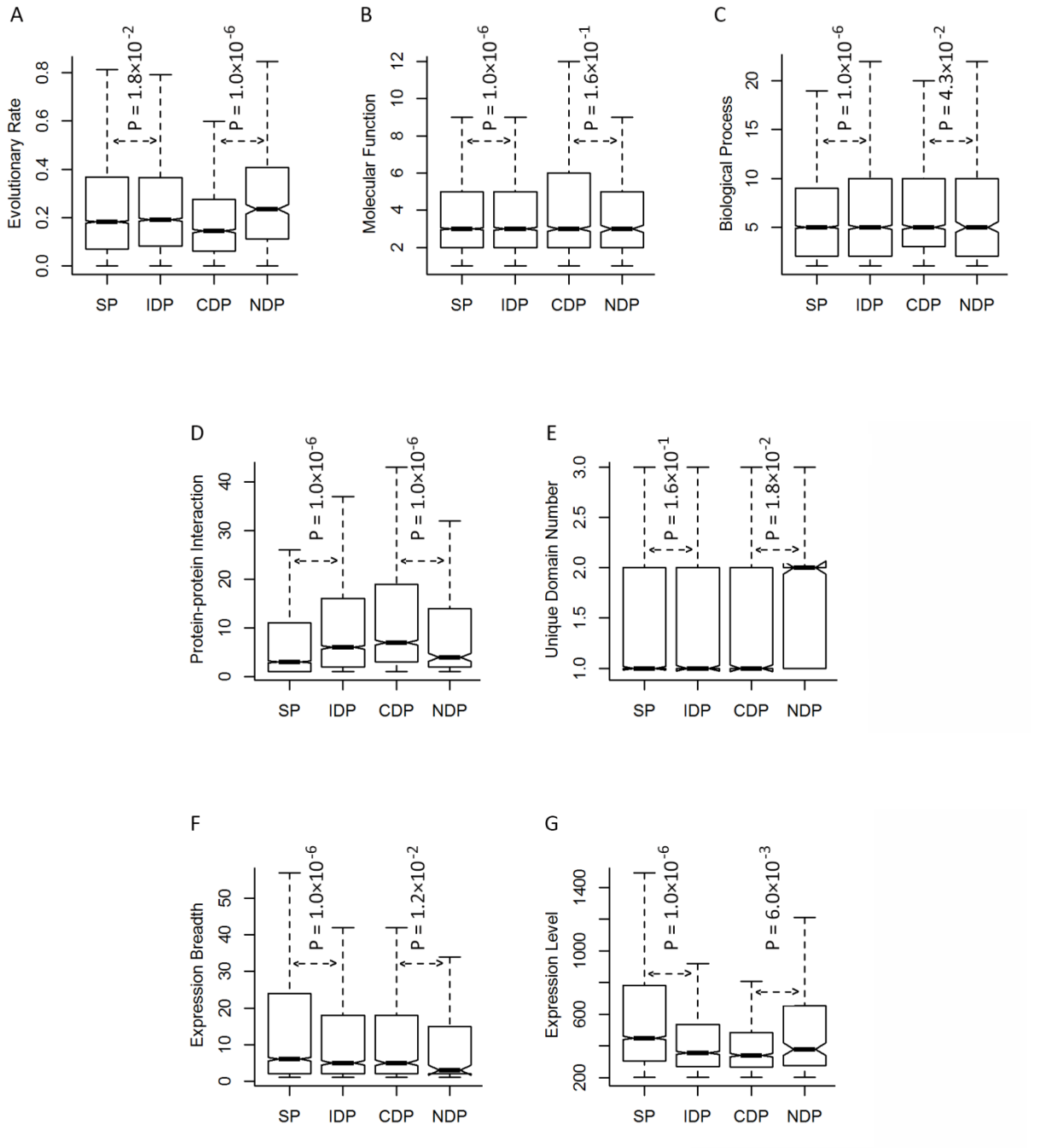


Figure 3. Boxplot showing the distribution of biological features: A. Evolutionary rate, B. Molecular Fucntions, C. Biological Processes, D. Protein-protein interaction, E. Unique domain number, F. Expression breadth, G. Expression level between the groups of intrinsically disordered (IDPs) and well-structured (SP) proteins, and conserved disordered (CDPs) and non-conserved disordered (NDPs) proteins. P-values indicate the level of significance in the difference of the distribution of each of the features between the groups.

3.5 Influence of protein domains on the conservation of intrinsically disordered regions

It is believed that a protein interacts with other proteins through distinct functional or structural units, called domains (Vogel et al., 2004). In this section, we examined the influence of protein domains on the conservation level of a disordered regions within a protein sequence. According to our dataset, when the entire set of human proteins are considered, the number of unique protein domains positively correlates with protein connectivity (Spearman's $\rho = 0.061$, $P = 1.6\times10^{-59}$), which is supported by the study of Kim et al (Kim et al., 2006b). However, intriguingly, we found that the differences in the distribution of UDN between the sets of IDPs versus SPs, and CDPs versus NDPs do not follow the above correlation. There is no difference in the median value of the number of unique protein domain between IDPs and SPs despite of having a sharp difference in the median value of their protein interactions (shown in Section 3.4) (Figure 3D). However, the result further suggests that the number of unique domains is relatively less in CDPs than in NDPs (median number of unique domains: 1 for CDPs and 2 for NDPs; Mann-Whitney U test, $P = 1.8\times10^{-2}$; Figure 3E). We also observed a similar distribution of UDN between CDPs and NDPs according to the results obtained using PONDR-FIT (median number of unique domains: 1 for CDPs and 2 for NDPs; Mann-Whitney U test, $P = 1.5\times10^{-2}$; Figure S1E) and ESpritz tools (median number of unique domains: 1 for CDPs and 2 for NDPs; Mann-Whitney U test, $P = 2.0\times10^{-2}$; Figure S1E). The result thus suggests that the adaptation of a fewer number of unique protein domains (i.e., variation in the type of protein domains) may not result in the emergence of a disordered region, but can be a determining factor influencing the conservation of the existing disordered regions across mammalian species. It is possible that a longer proteins frequently contain relatively more number or type of domains than a shorter proteins. In order to test if a fewer domain in CDPs is an artifact of the protein's length, we examined the difference in protein length between CDPs and NDPs. The result exhibits no remarkable difference in protein length between CDPs and NDPs (Figure S3), despite of the difference in the number of protein domains (Figure 3E). Inversely, there is no difference in the number (median) of domains (Figure 3E) between SPs and IDPs, despite of having a significant difference in their protein length. Hence, the result is independent of the protein length.

The above investigation establishes an association between the number of protein domains and conservation rate of the disordered regions. However, the result so far is not sufficient to claim the causality and its effect. Therefore, we further used conditional probability to quantify the relation between the conservation of disordered regions and number of protein domains. The result suggests that the likelihood of finding a protein with conserved disordered regions within the set of proteins having single domain is higher than the probability of finding a protein with single domain within a set of proteins having conserved disordered regions (p[CDPs given protein having single domains] = 0.66; p[protein having single domains given CDPs] = 0.48; Table S2 in Supplementary file 2). Therefore, it suggests that a protein having a single domain often favors the evolutionary conservation of disordered regions across human orthologs, although, the reverse is not true (Table S2 in Supplementary file 2), i.e., a proteins with conserved stretches of disordered regions may not always adapt a fewer number of domains.

In this context, the existing literature previously mentioned that the hub proteins (proteins having high connectivity), being single-interfaced (one or at most two unique domains) are more prone to adapt disordered regions compared to multi-interfaced (more than two unique domains) hub proteins (Kim et al., 2008; Singh et al., 2007). We explored if the count (single-interfaced or multi-interfaced) of domain interfaces has any effect in shaping the adaptive evolution of disordered regions. The study of Kim et al. classified proteins as SIPs and MIPs on the basis of their domain number (Kim et al., 2006a). Following their classification, we examined the distribution of SIPs and MIPs within the classes of CDPs and NDPs. The total pool of SIPs exhibited a distribution of 66.0% CDPs and 33.0% NDPs, whereas the total pool of MIPs had a distribution of 52.7% CDPs and 47.3% NDPs (Figure S4). The differences between the percentage of SIP and MIP within the classes of CDPs and NDPs are significant ($P = 1.0\times10^{-3}$) according to Fisher's Exact test. It indicates that more number of SIPs are enriched in CDPs (66.0%) compared to that of MIPs (52.7% CDPs). In contrast, NDPs (47.3%) exhibited higher enrichment in MIPs compared to the SIPs (33.0% NDPs). In addition to the result of Kim et al., we further extended that apart from adapting disordered regions (Kim et al., 2008), SIPs also conserve the disordered regions across mammals. However, an interesting question remains unexplored, i.e., why do CDPs

have significantly a lesser number of domains despite of having high protein connectivity (Section 3.4)? We tried to endeavor the principles governing such phenomenon in the discussion (Section 4).

3.6 Effects of expression level and expression breadth on the conservation of disordered regions

Gene expression is an effective measure to conclude the protein evolutionary rate (Drummond et al., 2005; Park and Choi, 2010; Subramanian and Kumar, 2004; Yang et al., 2005). We already noticed that protein evolutionary rate (d_N/d_S) differs significantly between CDPs and NDPs (Section 3.1). Hence, we assumed that gene expression may have an impact in controlling the degree of conservation of disordered regions. Expression level dominates protein evolution in unicellular eukaryotes (Drummond et al., 2006; Drummond et al., 2005; Subramanian and Kumar, 2004). In contrast, some studies argued that expression breadth, rather than expression level, determines the evolutionary rate in multicellular organisms (Park and Choi, 2010; Tuller et al., 2008). However, we considered both the dimensions of gene expression (expression breadth and expression level). According to our study, proteins evolving with conserved disordered regions (CDPs) exhibit a higher expression breadth (i.e., across many tissues) than the proteins with rapidly evolving stretches of disordered regions (NDPs) (median expression breadth: 5 for CDPs and 4 for NDPs; Mann-Whitney U test, $P = 1.2\times10^{-2}$; Figure 3F). However, the expression level of CDPs remains lower compared to that of NDPs (median expression level: 342.5 for CDPs and 373.4 for NDPs; Mann-Whitney U test, $P = 6.0\times10^{-3}$; Figure 3G). On the other hand, while comparing between the classes of IDPs and SPs, IDPs exhibit lower expression breadth and expression level compared to SPs (Figures 3F and 3G). The results are supported by the similar pattern of distribution obtained from the analyses of the groups of IDPs versus SPs, and CDPs versus NDPs using PONDR-FIT and ESpritz (Figures S1F, S1G, S2F and S2G).

In agreement with our result, it was experimentally shown that overexpression of proteins having disordered regions is extremely costly to cellular fitness (Tomala and Korona, 2013). Therefore, expressing an IDP at a high level will be a real cause of fitness decrease. It may be a reason why IDPs are strictly regulated to maintain a low expression level in order to avoid unwanted interactions (Gsponer et al., 2008). However, the impact of gene expression governing the evolutionary conservation of disordered regions within a protein

remains unexplored. It is seen that the result is partly supported by the study of Park et al. (Park and Choi, 2010), stating that expression breadth acts as a dominating factor controlling the protein evolutionary rate in mammals (Drummond et al., 2005; Pál et al., 2001). Similarly, expression breadth also subjects disordered regions to varying degree of evolutionary selection in human. The study also states that the two measures, expression breadth and expression level, are dependent, and act together on protein evolution (Park and Choi, 2010). In this context, we noticed that expression breadth strongly correlates with expression level (Spearman's $\rho = 0.907$, $P = 1.0\times10^{-6}$) while considering the entire human proteome. This result is in accordance with the investigation of Park et al. where it is shown that broadly expressed genes are likely to have a high expression level (Park and Choi, 2010). Surprisingly, we observed that the set of IDPs does not follow this usual trend. The study reported that the large expression breadth along with low expression level may favor the conservation of disordered regions in protein. The boxplot (Figure 4) shows that the difference in expression level abruptly increases with increasing expression breadth in case of NDPs and well-structured proteins (SPs) while the difference in expression level is remarkably small in case of CDPs.

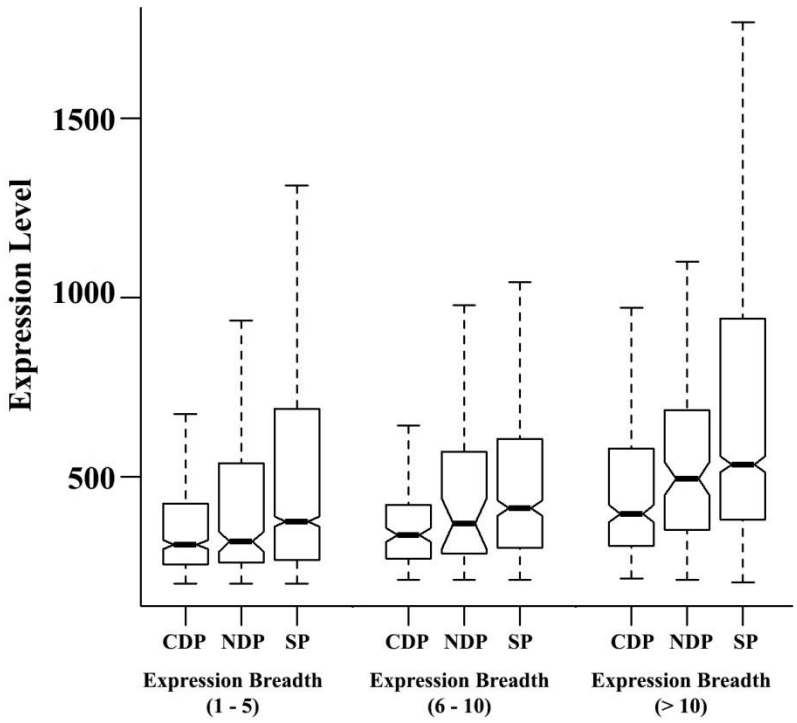


Figure 4: Boxplot showing the change in gene expression level within the groups of CDPs, NDPs and well-structured proteins (SPs) across different ranges of expression breadth.

Moreover, the instance of rapidly evolving disordered regions within NDPs compared to CDPs, goes along with the concept that the evolution of tissue specific genes is much faster than broadly expressed housekeeping genes (Zhang and Li, 2004). According to our result, the high expression level of NDPs in a limited number of tissues may indicate their tissue specific roles, whereas CDPs seem to behave more like housekeeping proteins (Banerjee and De, 2015).

3.7 Robustness of the study

In this section, we examined the robustness of the study of classifying IDPs into CDPs and NDPs by using flexible (variable) threshold rather than fixing a stringent one. For this purpose, we analyzed the influence of various features controlling the sets of CDPs and NDPs classified according to variable threshold values of D_{nor} and A_{nor}. Consequently, the outcome reveals that the trend of our result remains unchanged across the sets with varying threshold values up to 80% (Table S3 provided in Supplementary file 2). Thus, it indicates that the categorization is so far meaningful. However, if we considered a cut-off value for any of the conservation scores (D_{nor} and A_{nor}) around 70% or less, the difference in biological features between the groups of CDPs and NDPs becomes insignificant. It happens due to the huge difference in the sample size of CDPs and NDPs at these threshold values (Table S4 provided in Supplementary file 2). As a result, the threshold values produce a false positive dataset of CDPs by labeling a certain number of NDPs as “CDPs”. Moreover, we randomly shuffled the label “CDP” and “NDP” of IDPs, and repeat the analysis. Eventually, none of the results, as expected, are significant, according to Mann-Whitney U test (Table S4 provided in Supplementary file 2), despite of having an almost equal number of samples in CDPs and NDPs. The result thus ensures that the selection pressure acts differently on different stretches of disordered regions, and the genomic and proteomic features influence this selection pressure to bring out the beneficial adaptation of disordered regions.

3.8 Multiple regression analysis

So far, we have come up with several biological features that significantly control the selection pressure resulting in the evolutionary variation in intrinsically disordered regions. Although, we still pondered to what extent a particular feature independently guides the variation in conservation rate of disordered regions. In order to address this issue, we implemented multiple linear regression analysis. A multiple linear regression model takes the form of the following equation,

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n + \varepsilon$$

where y is a continuous dependent variable, while $x_1, x_2, \ldots, x_n$ are the continuous independent variables of the regression model. The terms $\beta_0, \beta_1, \beta_2, \ldots, \beta_n$ are the regression coefficients of each independent variable, while ε stands for error. The test allows measuring the type of association (positively or negatively) between each of the independent variable ($x_1, x_2, \ldots, x_n$) upon the dependent variable (y) determined by regression coefficients β. The outcome can be analyzed as the expected change in the independent variable for a unit change in the dependent variable when the effects of other covariates remain fixed. In other words, we explored how far the biological features (independent variables) individually determine the variation in conservation (dependent variable) of both amino acid residues (A_{nor} value) and disordered behavior (D_{nor} value) of intrinsically disordered regions of IDPs. For both the values of A_{nor} and D_{nor}, we performed separate regression analysis.

The results point out that the biological features hold a significant correlation with D_{nor} and A_{nor} values (Table 1). Although, in case of regression analysis considering all these features, the statistic exhibits that the independent effect of UDN, protein connectivity and expression level are significant (Table 1). We denoted the coefficients corresponding to the regression equation for D_{nor} as β_{iDnor} and for A_{nor} as β_{iAnor} of i^{th} independent variable. Among them UDN comes out to be the most determining feature controlling the conservation score ($\beta_{Anor} = -0.210, P = 8.1 \times 10^{-7}$ and $\beta_{Dnor} = -0.176, P = 3.5 \times 10^{-5}$) following the positive influence of protein connectivity ($\beta_{Anor} = 0.119, P = 5.4 \times 10^{-3}$ and $\beta_{Dnor} = 0.098, P = 2.2 \times 10^{-2}$). However, in case of expression level, the influence on the conservation of disordered behavior is only significant ($\beta_{Dnor} = -0.101, P = 1.7 \times 10^{-2}$). It may be mentioned here that, the correlation study (Table 1) shows that some of these biological features can influence the conservation level in association with other biological features. From the regression model, we

inferred that among all the features, the number of unique protein domains is the main determining features, which independently governs (negatively) the varying degree of conservation of disordered regions within IDPs, following the positive influence of protein connectivity.

Table 1: Table showing the (I) correlation and (II) regression between each of the biological features (Independent variables) with D_{nor} and A_{nor} values along with the level of significance (P value). Here, we denoted the regression coefficients for D_{nor} as β_{iDnor} and that of A_{nor} as β_{iAnor} of i^{th} independent variable.

I. CORRELATION ANALYSIS				
Independent variables	**Spearman's rho (D_{nor})**	**P value (D_{nor})**	**Spearman's rho (A_{nor})**	**P value (A_{nor})**
Domain	-0.181	P < 2.2e-16	-0.176	P < 2.2e-16
PPI	0.196	P < 2.2e-16	0.276	P < 2.2e-16
Expression Level	-0.071	P = 0.01391	-0.031	P = 0.2863
Expression Breadth	0.205	P = 5.849e-13	0.181	P = 2.054e-10
Molecular Functions	0.127	P = 1.41e-11	0.178	P < 2.2e-16
Biological Processes	0.115	P = 2.653e-09	0.163	P < 2.2e-16
II. REGRESSION ANALYSIS				
Independent variables (i)	**β_{iDnor}**	**P value (β_{iDnor})**	**β_{iAnor}**	**P value (β_{iAnor})**
Domain	-0.176	P = 3.5e-05	-0.210	P = 8.19e-07
PPI	0.098	P = 0.0220	0.119	P = 0.00541
Expression Level	-0.101	P = 0.0169	-0.058	P = 0.16956
Expression Breadth	0.074	P = 0.0838	0.033	P = 0.42977
Molecular Functions	0.064	P = 0.1571	0.087	P = 0.05441
Biological Processes	-0.033	P = 0.4616	-0.013	P = 0.78073

4. Discussion

Several studies have pointed out a striking difference in evolutionary rates within disordered and structured stretches of IDPs (Bellay et al., 2011; Brown et al., 2010; Brown et al., 2011; Brown et al., 2002). However, understanding how do genomics and proteomics features control the differential evolution of intrinsically disordered regions within a protein, still remains unexplored. Here, we predicted that among all the possible features considered in our study, UDN of IDPs is a strong determinant that influences the conservation of disordered regions within a protein over evolutionary time. Strikingly, the domain number correlates negatively with the conservation score of disordered regions, unlike that of well-structured proteins. In case of well-structured proteins, Kim et al. (Kim et al., 2006a; Kim et al., 2006b) have concluded that multi-domain proteins experience stronger evolutionary conservation compared to single-domain proteins. This is because a multi-domain protein exhibits stable protein interactions and has an enlarged interaction interface (Higurashi et al., 2008; Kim et al., 2006a). However, the trend is different in the case of IDPs. Linear regression analysis of the biological features considered in the study shows that the degree of conservation of disordered regions responds strongly to the number of unique protein domains. There appears a strong selection pressure to constrain the evolution of disordered regions if the number of unique protein domains gets reduced. We justified that a protein necessarily needs to maintain the disordered regions if it holds a few interacting domains. This is because a protein can interact with structurally different binding targets using one and the same domain interface with the help of its flexible disordered regions (Gsponer and Babu, 2009). As a result, it reduces the use of multiple proteins in order to interact with different molecular targets and thus becomes economical for the cellular system. Any deleterious substitutions in disordered regions or the substitution from disordered to structured residues within single-interfaced IDPs will destroy the utility of disordered or unstructured regions, thereby impairing their normal functions. Thus, we inferred that a protein bearing a few interacting domains remains under a strong selection pressure to conserve their disordered regions. It will maintain the structural flexibility of the particular protein. In the case of multi-domain proteins, however, the need of disordered arm is

not so crucial because they have multiple binding sites assigned for different targets. On this ground, we suggested that the selection pressure is not so strong in conserving the stretches of disordered residues in multi-domain proteins.

IDPs have a disadvantage of getting into misinteractions while in abundance (Vavouri et al., 2009). Protein misinteraction refers to the random encounters between protein molecules which sometimes leads to nonfunctional protein–protein interactions (Yang et al., 2012). These nonspecific protein interactions can be detrimental for a cellular system, because it i) consumes a huge amount of energy for the over production of protein molecules, ii) sometimes results into lethal interactions, and iii) may damage vital cellular processes. The phenomenon is enhanced by the presence of multiple interfaces within a single protein which allows a protein to get into multiple interactions, enhancing the risk of misinteractions at the same time. On the other hand, proteins evolving with a single interface will have a less tendency to get involved in misinteractions. Hence, it may be a reason why single interfaced IDPs are evolutionarily favored. Eventually, intrinsically disordered regions within SIPs experience a strong selection pressure against random mutations, and prefer to remain conserved across mammalian species. In support of the above statement, we showed that despite of having a high degree of protein interactions, a set of single domain proteins prefers conserving their disordered regions rather than adapting a number of domains. In this context, we pointed out that the well accepted concept of positive correlation between protein connectivity and the number of unique domain interfaces (Kim et al., 2006b), does not hold good particularly for IDPs adapting conserved stretches of disordered residues. The similar unusual trend also persists between the classes of IDPs and SPs (Figures 3F, 3G and 4). We provided the evidence that if the whole set of human proteins is considered (Section 3.5), a positive correlation (Spearman's $\rho = 0.061$, $P = 1.6\times10^{-59}$) exists between the number of unique domains and protein connectivity, whereas both the features correlate negatively (Spearman's $\rho = -0.063$, $P = 3.0\times10^{-23}$) in the case of IDPs. Although, the magnitudes of the correlation coefficient values are small, the opposite sign of the values indicates that the number of domain interfaces influences the conservation of disordered regions within IDPs differently from the way it influences the class of well-structured proteins. It is assumed that the small magnitude of correlation

coefficient values may be due to the presence of a large number of data points which fail to produce a sharp linear relationship.

Beside the number of unique domains and protein connectivity, other features (expression breadth and expression level) also have a significant influence in determining the conservation rate of disordered regions. However, it is noticed that these features influence the rate of conservation in association with other biological features, but not independently. Among them expression breadth correlates positively with the conservation score of disordered regions. The reason behind such outcome is that IDPs having high expression breadth get ubiquitously expressed in a huge number of tissues and thus get involved in multiple interactions with a large number of molecular targets. Therefore, we predicted that conserved disordered regions may help these proteins to interact with a multiple targets across several tissues. This may be a vital reason for which high expression breadth constrains the evolution of disordered regions within IDPs.

According to Park et al. (Park and Choi, 2010), the highly expressed genes usually express broadly. However, CDPs do not follow the rule. CDPs exhibit relatively low expression level despite of having high expression breadth compared to both the classes of NDPs and well-structured proteins (Section 3.7 and Figure 4). In other words, we assumed that the large expression breadth and low expression level constraint the rapid evolution of disordered regions across mammalian species. High levels of expression will produce high concentrations of IDPs at a particular time, which may escalate the chances of misinteractions (Babu et al., 2011; Vavouri et al., 2009) with non-specific molecular targets. Therefore, the selection pressure against the tendency towards misinteractions will suppress the expression level of CDPs. Moreover, experimental evidence shows that overexpression of proteins having disordered regions usually comes with high fitness costs (Tomala and Korona, 2013). This can be an additional reason for the low expression level of CDPs. Consequently, we suggested that genomic and proteomic features influence the evolutionary rate of disordered regions, mainly with an aim to minimize the risk of misinteractions. Yang et al. mentioned that the purifying selection on protein surface (exposed) residues follows more to the "misinteraction avoidance" hypothesis rather than "misfolding avoidance" hypothesis (Drummond et al., 2005; Yang et al., 2012). This is logical because

disordered residues exist mostly on the exposed protein surfaces (Lin et al., 2007) and do not experience the pressure against misfolding (Uversky, 2002; Uversky et al., 2000). Hence, "misinteraction avoidance" hypothesis controlling the protein evolutionary rate supports our analysis (Yang et al., 2012).

On the other hand, multifunctionality does not constrain the variation in the conservation rate of intrinsically disordered regions to that extent (Figure 3B and 3C, and Table 1). The insignificant result may arise due to the systematic redundancy of Gene Ontology database which fails to capture the intricate functions of disordered regions as recognition sequence, short linear motif, or phosphorylation sites (Park et al., 2011). Further, functionality is considered to be the phenotypic measure of the organism's fitness obtained due to the different mode of molecular adaptations taking place at genotypic level (Koonin and Wolf, 2006). Hence, the effects of various genomic and proteomic features governing the evolutionary rate is more pronounced. Similarly, in the case of disordered regions, the role of other genomic and proteomic features influencing the selection pressure acting on the disordered regions becomes prominent than the contribution of protein functionality.

5. Conclusion

We proposed that the urge of maintaining a single interface mainly conserves the disordered regions, thereby resulting in a wide range of conservation scores (D_{nor} and A_{nor}) across IDPs. Single-domain proteins having conserved disordered segment is beneficial for molecular interactions (Cortese et al., 2008; Gunasekaran et al., 2003). For this reason, they also experience a stronger selection pressure against the high risk of misinteractions compared to the other classes of proteins. In contrast, the molecular system does not afford to preserve the disordered regions across mammals where their role is not so beneficial. However, there are still lots of questions that remain uninvestigated about the evolution of IDPs. Future study needs to focus on the inevitable phenomenon of misinteractions mediated by IDPs. Do misinteractions by IDPs give birth to new functional interactions? Is this a reason that some rapidly evolving disordered regions continuously undergo the processes of mutations and selection in the course of evolution? Understanding these questions will help knowing the trend of evolution and importance of structural disorder in biological systems.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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Category 2	D_{nor}	A_{nor}
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	100.00	100.00
CDP	99.77	100.00
CDP	99.64	100.00
CDP	99.49	100.00
CDP	99.49	100.00
CDP	99.49	100.00
CDP	99.49	100.00
CDP	99.49	100.00
CDP	98.62	100.00
CDP	98.37	100.00
CDP	98.37	100.00
CDP	98.37	100.00
CDP	98.37	100.00
CDP	98.37	100.00
CDP	98.37	100.00
CDP	96.20	100.00
CDP	96.20	100.00
CDP	96.20	100.00
CDP	96.20	100.00
CDP	96.20	100.00
CDP	96.20	100.00
CDP	96.20	100.00
CDP	96.20	100.00
CDP	96.20	100.00
CDP	96.20	100.00
CDP	100.00	99.94
CDP	99.80	99.93
CDP	100.00	99.93
CDP	100.00	99.90
CDP	100.00	99.85
CDP	100.00	99.81

Category1	Category2	Number of Proteins
IDP	CDP	1822
	NDP	2008
	OTHERS	986

CDP	97.00	99.81
CDP	99.97	99.80
CDP	98.53	99.75
CDP	100.00	99.70
CDP	97.40	99.68
CDP	99.90	99.66
CDP	98.61	99.63
CDP	99.61	99.61
CDP	99.27	99.60
CDP	99.19	99.59
CDP	99.89	99.55
CDP	100.00	99.54
CDP	100.00	99.53
CDP	97.43	99.52
CDP	98.08	99.52
CDP	100.00	99.51
CDP	99.87	99.48
CDP	99.34	99.47
CDP	100.00	99.46
CDP	98.06	99.44
CDP	99.96	99.44
CDP	99.79	99.44
CDP	99.70	99.40
CDP	99.20	99.40
CDP	99.70	99.39
CDP	99.69	99.38
CDP	98.75	99.38
CDP	99.48	99.37
CDP	99.35	99.35
CDP	99.96	99.32
CDP	99.73	99.31
CDP	98.95	99.30
CDP	99.15	99.29
CDP	99.73	99.28
CDP	97.84	99.28
CDP	97.36	99.28
CDP	99.57	99.27
CDP	98.85	99.26
CDP	98.97	99.24
CDP	99.39	99.23
CDP	99.29	99.23
CDP	99.16	99.21
CDP	98.50	99.20
CDP	98.50	99.20
CDP	99.73	99.20
CDP	96.28	99.20
CDP	97.93	99.19
CDP	98.08	99.16

CDP	99.93	99.15			
CDP	98.06	99.15			
CDP	99.50	99.15			
CDP	99.37	99.14			
CDP	98.64	99.13			
CDP	100.00	99.12			
CDP	100.00	99.12			
CDP	98.60	99.09			
CDP	98.24	99.09			
CDP	99.54	99.08			
CDP	98.94	99.05			
CDP	99.52	99.04			
CDP	99.52	99.04			
CDP	96.77	99.04			
CDP	99.72	99.02			
CDP	99.57	99.01			
CDP	98.83	99.00			
CDP	99.38	99.00			
CDP	97.66	99.00			
CDP	95.41	98.98			
CDP	98.88	98.98			
CDP	98.88	98.98			
CDP	99.55	98.94	**IDP**	**NDP**	**1458**
CDP	99.12	98.94			
CDP	96.85	98.94			
CDP	99.31	98.94			
CDP	98.77	98.93			
CDP	99.85	98.92			
CDP	98.90	98.90			
CDP	98.58	98.89			
CDP	96.64	98.88			
CDP	98.20	98.87			
CDP	98.98	98.87			
CDP	99.62	98.86			
CDP	98.86	98.86			
CDP	95.80	98.83			
CDP	99.70	98.81			
CDP	98.21	98.81			
CDP	99.28	98.81			
CDP	97.46	98.80			
CDP	99.65	98.78			
CDP	99.32	98.77			
CDP	97.57	98.77			
CDP	99.66	98.74			
CDP	97.24	98.72			
CDP	99.41	98.72			
CDP	99.24	98.72			
CDP	98.10	98.71			

CDP	99.22	98.71
CDP	99.60	98.69
CDP	98.30	98.69
CDP	99.18	98.67
CDP	96.20	98.64
CDP	96.52	98.63
CDP	99.17	98.63
CDP	98.46	98.63
CDP	99.64	98.62
CDP	98.06	98.61
CDP	99.56	98.59
CDP	99.70	98.58
CDP	98.93	98.57
CDP	98.27	98.56
CDP	98.44	98.55
CDP	99.08	98.53
CDP	98.75	98.51
CDP	97.81	98.49
CDP	98.98	98.47
CDP	100.00	98.47
CDP	98.73	98.46
CDP	99.84	98.46
CDP	99.84	98.46
CDP	99.84	98.46
CDP	99.84	98.46
CDP	99.84	98.46
CDP	99.84	98.46
CDP	99.84	98.46
CDP	99.84	98.46
CDP	96.01	98.45
CDP	98.84	98.44
CDP	99.30	98.43
CDP	98.09	98.43
CDP	99.66	98.43
CDP	98.96	98.43
CDP	98.54	98.43
CDP	99.46	98.42
CDP	98.42	98.42
CDP	99.05	98.38
CDP	99.57	98.36
CDP	98.19	98.36
CDP	98.31	98.35
CDP	99.15	98.35
CDP	99.28	98.34
CDP	99.48	98.33
CDP	98.75	98.33
CDP	99.74	98.32
CDP	98.31	98.31

CDP	99.23	98.31
CDP	98.94	98.31
CDP	97.11	98.29
CDP	99.10	98.28
CDP	97.36	98.28
CDP	98.38	98.28
CDP	99.17	98.27
CDP	98.38	98.27
CDP	96.80	98.26
CDP	98.56	98.26
CDP	99.78	98.25
CDP	99.16	98.24
CDP	99.05	98.24
CDP	94.16	98.23
CDP	96.54	98.23
CDP	99.16	98.22
CDP	99.21	98.22
CDP	97.33	98.22
CDP	95.91	98.20
CDP	95.91	98.20
CDP	99.74	98.17
CDP	98.80	98.17
CDP	97.46	98.14
CDP	99.75	98.14
CDP	99.28	98.14
CDP	97.37	98.12
CDP	99.53	98.12
CDP	97.64	98.11
CDP	99.82	98.10
CDP	99.43	98.08
CDP	97.20	98.08
CDP	97.53	98.08
CDP	97.81	98.07
CDP	99.53	98.04
CDP	96.94	98.04
CDP	99.79	98.02
CDP	99.51	98.02
CDP	97.34	98.01
CDP	99.07	97.99
CDP	99.03	97.97
CDP	95.20	97.97
CDP	97.77	97.97
CDP	99.35	97.96
CDP	99.35	97.96
CDP	99.36	97.95
CDP	99.83	97.95
CDP	97.95	97.95
CDP	97.80	97.94

CDP	99.64	97.93
CDP	96.41	97.92
CDP	99.15	97.91
CDP	95.55	97.89
CDP	100.00	97.87
CDP	99.42	97.86
CDP	98.76	97.85
CDP	97.72	97.85
CDP	98.91	97.83
CDP	99.76	97.82
CDP	99.59	97.81
CDP	97.15	97.81
CDP	94.14	97.81
CDP	98.68	97.81
CDP	95.80	97.80
CDP	99.12	97.80
CDP	99.19	97.78
CDP	98.09	97.77
CDP	96.88	97.77
CDP	95.89	97.76
CDP	99.53	97.74
CDP	98.73	97.74
CDP	97.83	97.72
CDP	96.91	97.72
CDP	98.40	97.70
CDP	99.05	97.69
CDP	96.52	97.67
CDP	94.34	97.66
CDP	98.42	97.66
CDP	94.34	97.65
CDP	98.44	97.63
CDP	99.84	97.61
CDP	95.27	97.59
CDP	98.76	97.58
CDP	97.39	97.57
CDP	97.10	97.57
CDP	98.33	97.57
CDP	98.44	97.57
CDP	99.68	97.55
CDP	100.00	97.55
CDP	96.13	97.54
CDP	98.83	97.53
CDP	100.00	97.53
CDP	99.92	97.53
CDP	99.46	97.53
CDP	98.21	97.53
CDP	99.78	97.53
CDP	99.86	97.52

CDP	99.55	97.50
CDP	99.10	97.50
CDP	98.33	97.50
CDP	98.06	97.50
CDP	95.11	97.48
CDP	99.13	97.48
CDP	98.74	97.48
CDP	96.81	97.47
CDP	99.67	97.47
CDP	97.46	97.46
CDP	97.14	97.46
CDP	98.31	97.45
CDP	99.56	97.45
CDP	95.32	97.44
CDP	98.88	97.44
CDP	99.50	97.43
CDP	98.13	97.43
CDP	98.60	97.41
CDP	98.60	97.41
CDP	98.60	97.41
CDP	98.60	97.41
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CDP	98.60	97.41
CDP	98.60	97.41
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CDP	97.40	97.40
CDP	97.81	97.40
CDP	99.65	97.40
CDP	99.57	97.39
CDP	97.53	97.37
CDP	96.56	97.37
CDP	96.85	97.37
CDP	96.85	97.37
CDP	96.91	97.36
CDP	97.60	97.36
CDP	98.05	97.36
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CDP	97.32	97.35
CDP	96.68	97.34
CDP	100.00	97.34
CDP	99.27	97.32
CDP	97.90	97.31
CDP	99.32	97.30
CDP	99.64	97.28
CDP	97.34	97.28
CDP	97.69	97.28
CDP	98.91	97.27
CDP	99.57	97.26

CDP	97.57	97.25
CDP	98.16	97.24
CDP	98.42	97.24
CDP	99.19	97.22
CDP	97.68	97.21
CDP	99.29	97.20
CDP	98.70	97.20
CDP	99.53	97.19
CDP	98.93	97.19
CDP	99.47	97.19
CDP	98.75	97.19
CDP	97.64	97.16
CDP	99.86	97.15
CDP	99.66	97.14
CDP	99.52	97.14
CDP	98.86	97.14
CDP	97.70	97.14
CDP	98.17	97.13
CDP	97.23	97.13
CDP	98.65	97.13
CDP	95.13	97.13
CDP	95.92	97.12
CDP	98.83	97.11
CDP	97.48	97.10
CDP	97.83	97.10
CDP	97.08	97.08
CDP	99.61	97.06
CDP	95.36	97.06
CDP	98.05	97.05
CDP	96.58	97.04
CDP	97.57	97.04
CDP	94.68	97.03
CDP	98.99	97.03
CDP	98.74	97.03
CDP	98.63	97.02
CDP	96.93	97.02
CDP	97.70	97.01
CDP	99.70	97.01
CDP	99.41	97.01
CDP	98.93	97.00
CDP	99.39	96.99
CDP	99.05	96.99
CDP	94.80	96.99
CDP	98.68	96.97
CDP	99.72	96.97
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CDP	94.93	96.95

CDP	99.54	96.95
CDP	96.46	96.94
CDP	97.53	96.94
CDP	97.91	96.93
CDP	98.68	96.92
CDP	97.54	96.92
CDP	98.56	96.91
CDP	99.77	96.90
CDP	95.96	96.90
CDP	98.12	96.89
CDP	99.23	96.88
CDP	96.61	96.88
CDP	99.87	96.88
CDP	99.58	96.88
CDP	99.36	96.87
CDP	99.39	96.87
CDP	98.57	96.86
CDP	98.43	96.86
CDP	95.35	96.86
CDP	97.81	96.85
CDP	99.71	96.84
CDP	99.57	96.83
CDP	98.12	96.83
CDP	96.39	96.82
CDP	98.99	96.82
CDP	98.03	96.81
CDP	99.72	96.81
CDP	98.66	96.81
CDP	97.79	96.80
CDP	98.94	96.80
CDP	97.66	96.80
CDP	96.73	96.80
CDP	99.61	96.79
CDP	96.05	96.78
CDP	99.14	96.78
CDP	99.11	96.78
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CDP	97.21	96.76
CDP	98.98	96.75
CDP	95.16	96.75
CDP	99.35	96.74
CDP	97.99	96.74
CDP	99.04	96.73
CDP	98.26	96.73
CDP	96.49	96.72
CDP	99.06	96.72
CDP	95.11	96.71
CDP	95.11	96.71

CDP	98.78	96.71
CDP	98.41	96.69
CDP	97.87	96.68
CDP	98.58	96.66
CDP	98.54	96.63
CDP	98.54	96.63
CDP	98.54	96.63
CDP	98.54	96.63
CDP	98.54	96.63
CDP	98.54	96.63
CDP	94.86	96.63
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CDP	96.79	96.61
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CDP	97.33	96.60
CDP	97.42	96.60
CDP	98.36	96.59
CDP	98.12	96.59
CDP	99.96	96.58
CDP	98.36	96.58
CDP	97.65	96.58
CDP	97.54	96.58
CDP	100.00	96.57
CDP	99.29	96.56
CDP	98.06	96.55
CDP	95.00	96.54
CDP	97.21	96.54
CDP	99.78	96.54
CDP	94.67	96.54
CDP	97.24	96.53
CDP	97.24	96.53
CDP	94.49	96.52
CDP	99.24	96.52
CDP	96.40	96.51
CDP	95.20	96.51
CDP	96.33	96.51
CDP	99.30	96.50
CDP	98.79	96.49
CDP	99.90	96.48
CDP	97.78	96.47
CDP	94.77	96.47
CDP	96.66	96.47
CDP	95.29	96.47
CDP	99.68	96.46
CDP	96.62	96.46
CDP	97.00	96.45
CDP	97.73	96.44

CDP	97.36	96.44
CDP	99.62	96.43
CDP	99.01	96.41
CDP	98.22	96.41
CDP	97.65	96.41
CDP	98.10	96.39
CDP	95.90	96.39
CDP	99.49	96.38
CDP	95.97	96.37
CDP	98.13	96.37
CDP	98.86	96.37
CDP	95.23	96.36
CDP	98.88	96.33
CDP	96.32	96.32
CDP	97.68	96.31
CDP	96.68	96.31
CDP	95.81	96.31
CDP	97.44	96.29
CDP	96.89	96.29
CDP	95.05	96.28
CDP	98.29	96.28
CDP	99.19	96.28
CDP	98.00	96.28
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CDP	95.78	96.27
CDP	99.65	96.26
CDP	99.65	96.26
CDP	99.65	96.26
CDP	99.65	96.26
CDP	99.65	96.26
CDP	99.65	96.26
CDP	99.65	96.26
CDP	99.65	96.26
CDP	95.48	96.26
CDP	99.74	96.25
CDP	98.85	96.25
CDP	96.39	96.25
CDP	97.73	96.25
CDP	96.23	96.23
CDP	98.32	96.23
CDP	98.18	96.23
CDP	94.21	96.23
CDP	95.99	96.21
CDP	98.93	96.21
CDP	99.18	96.21
CDP	96.52	96.19
CDP	97.80	96.17
CDP	99.87	96.16

CDP	96.56	96.15
CDP	97.29	96.13
CDP	99.57	96.13
CDP	95.91	96.13
CDP	99.45	96.12
CDP	94.69	96.11
CDP	95.35	96.10
CDP	99.25	96.10
CDP	98.05	96.09
CDP	96.52	96.08
CDP	96.95	96.08
CDP	98.21	96.07
CDP	94.46	96.07
CDP	97.69	96.06
CDP	98.03	96.05
CDP	97.66	96.04
CDP	98.18	96.04
CDP	98.18	96.04
CDP	94.32	96.04
CDP	96.34	96.04
CDP	99.54	96.04
CDP	99.54	96.04
CDP	98.72	96.02
CDP	98.72	96.02
CDP	99.91	96.01
CDP	97.32	96.01
CDP	96.39	96.01
CDP	99.11	96.00
CDP	94.87	95.99
CDP	98.60	95.99
CDP	99.83	95.98
CDP	98.61	95.98
CDP	98.19	95.98
CDP	99.01	95.97
CDP	98.83	95.97
CDP	99.38	95.97
CDP	98.46	95.97
CDP	96.51	95.97
CDP	98.85	95.96
CDP	98.83	95.96
CDP	99.35	95.95
CDP	94.67	95.94
CDP	99.26	95.93
CDP	100.00	95.93
CDP	94.62	95.92
CDP	95.62	95.92
CDP	98.04	95.91
CDP	94.99	95.89

CDP	96.92	95.89
CDP	95.16	95.89
CDP	98.02	95.89
CDP	99.68	95.89
CDP	95.98	95.88
CDP	97.66	95.88
CDP	99.24	95.87
CDP	95.78	95.86
CDP	99.15	95.85
CDP	96.78	95.85
CDP	99.03	95.85
CDP	98.08	95.80
CDP	98.72	95.80
CDP	98.66	95.78
CDP	98.70	95.78
CDP	96.81	95.78
CDP	96.86	95.77
CDP	95.89	95.77
CDP	95.15	95.76
CDP	94.65	95.76
CDP	98.54	95.74
CDP	94.79	95.74
CDP	96.15	95.73
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CDP	98.26	95.60
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CDP	94.58	95.58
CDP	96.27	95.58
CDP	99.74	95.57
CDP	98.46	95.56
CDP	96.94	95.55
CDP	99.47	95.55
CDP	94.65	95.55
CDP	96.75	95.55
CDP	96.61	95.54

CDP	95.54	95.54
CDP	96.95	95.53
CDP	95.88	95.53
CDP	99.08	95.52
CDP	99.18	95.52
CDP	99.88	95.51
CDP	97.65	95.50
CDP	96.23	95.50
CDP	94.90	95.49
CDP	96.96	95.48
CDP	97.60	95.47
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CDP	98.88	95.46
CDP	98.30	95.45
CDP	97.48	95.44
CDP	95.27	95.44
CDP	99.25	95.43
CDP	96.03	95.43
CDP	94.32	95.43
CDP	98.56	95.43
CDP	97.17	95.42
CDP	96.31	95.42
CDP	98.65	95.42
CDP	95.96	95.42
CDP	96.08	95.41
CDP	94.40	95.41
CDP	95.55	95.41
CDP	96.30	95.41
CDP	96.69	95.40
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CDP	96.47	95.36
CDP	96.47	95.36
CDP	96.47	95.36
CDP	96.47	95.36
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CDP	96.81	95.34
CDP	98.79	95.34
CDP	98.91	95.33
CDP	95.34	95.31
CDP	97.65	95.31
CDP	96.63	95.30
CDP	99.43	95.28

CDP	95.81	95.26
CDP	97.52	95.26
CDP	97.31	95.25
CDP	96.77	95.24
CDP	98.56	95.23
CDP	97.29	95.23
CDP	94.92	95.23
CDP	95.37	95.22
CDP	94.30	95.22
CDP	97.00	95.22
CDP	99.17	95.20
CDP	97.39	95.20
CDP	98.58	95.19
CDP	99.28	95.18
CDP	96.21	95.18
CDP	97.49	95.18
CDP	99.34	95.17
CDP	96.86	95.17
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CDP	96.94	95.15
CDP	97.31	95.14
CDP	98.59	95.14
CDP	97.87	95.14
CDP	97.95	95.14
CDP	97.43	95.13
CDP	94.31	95.12
CDP	96.83	95.12
CDP	99.23	95.10
CDP	95.81	95.10
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CDP	94.42	95.07
CDP	98.24	95.06
CDP	98.32	95.03
CDP	99.65	95.03
CDP	97.90	95.02
CDP	95.43	95.02
CDP	97.48	95.01
CDP	98.53	95.00
CDP	98.88	95.00
CDP	96.52	95.00
CDP	96.00	95.00
CDP	98.57	95.00
CDP	98.28	94.99
CDP	98.28	94.99

CDP	98.28	94.99
CDP	98.28	94.99
CDP	99.81	94.99
CDP	96.68	94.99
CDP	94.33	94.98
CDP	97.30	94.98
CDP	98.97	94.96
CDP	99.21	94.96
CDP	95.84	94.95
CDP	94.66	94.95
CDP	98.67	94.94
CDP	95.16	94.94
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CDP	96.86	94.93
CDP	99.06	94.93
CDP	96.84	94.92
CDP	96.84	94.92
CDP	97.92	94.92
CDP	98.26	94.92
CDP	98.36	94.92
CDP	98.32	94.90
CDP	96.40	94.88
CDP	95.05	94.87
CDP	95.95	94.87
CDP	99.24	94.86
CDP	99.71	94.86
CDP	97.52	94.85
CDP	95.07	94.84
CDP	98.12	94.84
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CDP	98.12	94.84
CDP	98.12	94.84
CDP	98.12	94.84
CDP	99.44	94.84
CDP	97.25	94.84
CDP	96.68	94.83
CDP	94.13	94.83
CDP	98.80	94.81
CDP	99.45	94.81
CDP	97.55	94.78
CDP	98.55	94.77
CDP	97.26	94.76
CDP	97.26	94.76
CDP	97.26	94.76

CDP	96.03	94.75
CDP	95.11	94.75
CDP	98.25	94.75
CDP	95.43	94.74
CDP	97.92	94.74
CDP	98.47	94.73
CDP	99.00	94.71
CDP	94.31	94.71
CDP	99.37	94.70
CDP	96.86	94.70
CDP	97.32	94.70
CDP	99.87	94.70
CDP	97.59	94.69
CDP	95.99	94.68
CDP	97.06	94.68
CDP	95.32	94.68
CDP	94.51	94.68
CDP	97.14	94.67
CDP	98.37	94.67
CDP	97.71	94.67
CDP	97.50	94.66
CDP	99.73	94.65
CDP	95.19	94.64
CDP	97.87	94.63
CDP	96.90	94.63
CDP	97.97	94.63
CDP	94.23	94.61
CDP	95.34	94.60
CDP	96.88	94.58
CDP	98.71	94.58
CDP	100.00	94.57
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CDP	97.49	94.56
CDP	99.00	94.56
CDP	96.26	94.55
CDP	96.63	94.54
CDP	96.83	94.54
CDP	96.83	94.54
CDP	98.18	94.54
CDP	94.48	94.53
CDP	95.94	94.52
CDP	99.61	94.52
CDP	99.61	94.52
CDP	95.30	94.51
CDP	97.65	94.50
CDP	97.28	94.50
CDP	96.92	94.50
CDP	97.77	94.48

CDP	96.00	94.48
CDP	96.54	94.47
CDP	97.03	94.47
CDP	98.80	94.46
CDP	99.54	94.45
CDP	96.46	94.45
CDP	94.65	94.44
CDP	97.56	94.44
CDP	96.28	94.44
CDP	98.78	94.44
CDP	98.49	94.43
CDP	96.69	94.43
CDP	96.86	94.43
CDP	96.79	94.42
CDP	97.11	94.42
CDP	98.36	94.42
CDP	97.72	94.42
CDP	99.76	94.42
CDP	98.80	94.41
CDP	98.76	94.41
CDP	98.95	94.39
CDP	97.56	94.38
CDP	97.57	94.37
CDP	98.35	94.37
CDP	96.90	94.36
CDP	95.26	94.36
CDP	94.32	94.36
CDP	98.96	94.35
CDP	95.28	94.35
CDP	95.85	94.35
CDP	95.09	94.33
CDP	95.43	94.32
CDP	96.03	94.31
CDP	97.01	94.31
CDP	99.79	94.30
CDP	97.78	94.28
CDP	97.73	94.28
CDP	97.73	94.28
CDP	96.03	94.28
CDP	96.58	94.28
CDP	96.44	94.27
CDP	94.70	94.27
CDP	98.22	94.26
CDP	96.72	94.26
CDP	94.30	94.26
CDP	94.46	94.25
CDP	96.51	94.24
CDP	98.95	94.23

CDP	96.89	94.22
CDP	96.89	94.22
CDP	96.89	94.22
CDP	96.89	94.22
CDP	96.89	94.22
CDP	96.89	94.22
CDP	94.10	94.21
CDP	95.96	94.21
CDP	99.30	94.21
CDP	96.20	94.20
CDP	98.34	94.18
CDP	98.53	94.18
CDP	97.78	94.17
CDP	96.76	94.17
CDP	97.93	94.14
CDP	97.44	94.14
CDP	97.96	94.14
CDP	98.91	94.11
CDP	96.18	94.11
CDP	95.95	94.09
CDP	99.00	94.08
CDP	99.38	94.08
CDP	99.41	94.08
CDP	97.52	94.08
CDP	99.17	94.07
CDP	97.10	94.05
CDP	95.43	94.04
CDP	99.50	94.03
CDP	98.10	94.03
CDP	95.34	94.02
CDP	96.39	94.02
CDP	98.00	94.01
CDP	97.31	94.00
CDP	95.34	94.00
CDP	99.40	93.99
CDP	96.88	93.97
CDP	94.71	93.97
CDP	98.24	93.97
CDP	94.68	93.97
CDP	96.60	93.95
CDP	96.75	93.95
CDP	97.21	93.93
CDP	98.04	93.93
CDP	96.67	93.91
CDP	99.49	93.90
CDP	97.74	93.90
CDP	99.40	93.90
CDP	97.16	93.89

CDP	94.25	93.89
CDP	98.18	93.88
CDP	100.00	93.87
CDP	97.64	93.87
CDP	95.09	93.86
CDP	96.62	93.85
CDP	97.12	93.85
CDP	98.48	93.85
CDP	98.59	93.85
CDP	98.48	93.84
CDP	98.88	93.83
CDP	94.66	93.83
CDP	98.36	93.83
CDP	95.23	93.82
CDP	97.72	93.82
CDP	97.72	93.82
CDP	97.95	93.81
CDP	98.46	93.80
CDP	96.85	93.80
CDP	96.17	93.79
CDP	96.41	93.79
CDP	98.86	93.79
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CDP	96.88	93.75
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CDP	96.90	93.72
CDP	94.01	93.72
CDP	98.26	93.71
CDP	96.80	93.71
CDP	94.99	93.70
CDP	98.12	93.68
CDP	95.46	93.68
CDP	96.65	93.68
CDP	96.84	93.68
CDP	98.31	93.68
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CDP	95.06	93.65
CDP	96.69	93.65
CDP	98.96	93.65
CDP	97.87	93.65
CDP	94.34	93.65
CDP	94.09	93.64

CDP	98.11	93.63
CDP	96.40	93.63
CDP	99.27	93.63
CDP	97.44	93.61
CDP	97.44	93.61
CDP	97.70	93.61
CDP	97.02	93.60
CDP	97.05	93.60
CDP	98.33	93.59
CDP	96.86	93.58
CDP	95.94	93.58
CDP	98.16	93.58
CDP	97.66	93.57
CDP	97.08	93.57
CDP	95.46	93.57
CDP	98.08	93.55
CDP	99.36	93.54
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CDP	98.54	93.50
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CDP	96.89	93.49
CDP	98.10	93.49
CDP	96.27	93.49
CDP	95.36	93.48
CDP	97.91	93.48
CDP	98.77	93.47
CDP	97.16	93.47
CDP	97.02	93.44
CDP	94.36	93.44
CDP	98.02	93.43
CDP	96.95	93.42
CDP	97.39	93.42
CDP	96.47	93.42
CDP	97.37	93.41
CDP	97.83	93.40
CDP	95.14	93.39
CDP	97.19	93.39
CDP	96.03	93.39
CDP	96.06	93.38
CDP	98.18	93.38

CDP	96.86	93.37
CDP	96.94	93.37
CDP	96.35	93.37
CDP	99.16	93.37
CDP	96.16	93.36
CDP	97.41	93.35
CDP	94.78	93.35
CDP	96.05	93.35
CDP	95.70	93.35
CDP	97.95	93.35
CDP	99.44	93.34
CDP	97.93	93.33
CDP	97.30	93.33
CDP	97.05	93.31
CDP	96.65	93.30
CDP	97.66	93.28
CDP	95.51	93.27
CDP	95.80	93.26
CDP	98.47	93.26
CDP	98.57	93.26
CDP	94.97	93.25
CDP	99.86	93.25
CDP	97.69	93.25
CDP	95.52	93.25
CDP	96.48	93.24
CDP	94.13	93.24
CDP	95.37	93.23
CDP	95.13	93.22
CDP	98.54	93.22
CDP	94.66	93.21
CDP	95.13	93.20
CDP	98.53	93.19
CDP	98.11	93.19
CDP	97.63	93.18
CDP	96.24	93.18
CDP	98.28	93.18
CDP	98.82	93.18
CDP	97.26	93.17
CDP	97.58	93.17
CDP	94.83	93.15
CDP	95.10	93.14
CDP	98.16	93.12
CDP	94.52	93.11
CDP	98.16	93.10
CDP	97.37	93.10
CDP	96.86	93.10
CDP	96.03	93.08
CDP	95.22	93.06

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CDP	97.17	92.98
CDP	97.47	92.96
CDP	95.68	92.95
CDP	94.98	92.95
CDP	94.04	92.95
CDP	98.19	92.93
CDP	97.05	92.92
CDP	96.89	92.92
CDP	95.50	92.91
CDP	97.28	92.90
CDP	97.50	92.89
CDP	99.08	92.88
CDP	96.05	92.87
CDP	97.60	92.86
CDP	95.91	92.86
CDP	98.65	92.85
CDP	95.12	92.85
CDP	95.12	92.85
CDP	100.00	92.84
CDP	97.99	92.83
CDP	99.02	92.83
CDP	99.02	92.83
CDP	98.07	92.82
CDP	97.99	92.82
CDP	97.50	92.81
CDP	94.17	92.81
CDP	98.94	92.81
CDP	95.29	92.79
CDP	97.12	92.78
CDP	95.79	92.78
CDP	97.63	92.75
CDP	96.10	92.75
CDP	98.07	92.74
CDP	96.55	92.73
CDP	100.00	92.73
CDP	95.79	92.73
CDP	95.44	92.72
CDP	97.50	92.72
CDP	96.48	92.72
CDP	95.43	92.72
CDP	98.08	92.71
CDP	98.64	92.71

CDP	97.08	92.71
CDP	96.97	92.71
CDP	98.31	92.71
CDP	98.58	92.70
CDP	96.50	92.70
CDP	96.92	92.69
CDP	95.61	92.69
CDP	96.49	92.68
CDP	96.11	92.66
CDP	96.32	92.65
CDP	97.42	92.65
CDP	95.63	92.64
CDP	97.04	92.64
CDP	97.36	92.64
CDP	97.36	92.64
CDP	95.58	92.64
CDP	97.96	92.64
CDP	98.15	92.64
CDP	98.11	92.64
CDP	95.18	92.63
CDP	95.76	92.63
CDP	97.08	92.62
CDP	97.30	92.61
CDP	97.43	92.61
CDP	98.84	92.60
CDP	98.04	92.59
CDP	94.98	92.59
CDP	97.05	92.58
CDP	98.40	92.57
CDP	99.30	92.57
CDP	96.78	92.56
CDP	95.42	92.55
CDP	98.25	92.54
CDP	99.35	92.53
CDP	95.83	92.52
CDP	98.00	92.52
CDP	98.61	92.52
CDP	94.23	92.48
CDP	95.30	92.48
CDP	96.08	92.48
CDP	99.49	92.47
CDP	96.92	92.47
CDP	99.20	92.46
CDP	97.93	92.46
CDP	97.48	92.46
CDP	97.44	92.45
CDP	94.91	92.41
CDP	95.36	92.41

CDP	96.48	92.41
CDP	95.81	92.40
CDP	96.13	92.40
CDP	95.83	92.39
CDP	96.00	92.39
CDP	97.88	92.37
CDP	97.11	92.37
CDP	95.09	92.35
CDP	95.08	92.33
CDP	97.61	92.32
CDP	96.52	92.32
CDP	96.30	92.30
CDP	95.61	92.30
CDP	99.06	92.29
CDP	99.06	92.29
CDP	99.06	92.29
CDP	99.06	92.29
CDP	99.06	92.29
CDP	99.06	92.29
CDP	99.06	92.29
CDP	99.06	92.29
CDP	99.06	92.29
CDP	96.81	92.29
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CDP	97.43	92.29
CDP	98.83	92.29
CDP	97.36	92.29
CDP	94.91	92.28
CDP	98.43	92.27
CDP	97.96	92.26
CDP	96.81	92.26
CDP	96.77	92.25
CDP	95.16	92.24
CDP	96.58	92.22
CDP	97.70	92.21
CDP	97.08	92.20
CDP	96.17	92.20
CDP	98.51	92.18
CDP	95.76	92.18
CDP	99.24	92.18
CDP	96.23	92.17
CDP	98.83	92.17
CDP	99.43	92.16
CDP	98.66	92.16
CDP	97.20	92.14
CDP	97.20	92.14
CDP	97.20	92.14
CDP	97.20	92.14

CDP	99.10	92.13
CDP	97.00	92.13
CDP	96.93	92.12
CDP	97.60	92.11
CDP	97.56	92.11
CDP	96.29	92.11
CDP	98.46	92.11
CDP	97.72	92.09
CDP	96.86	92.09
CDP	97.40	92.08
CDP	98.63	92.08
CDP	95.64	92.06
CDP	95.83	92.06
CDP	94.27	92.06
CDP	97.52	92.04
CDP	97.40	92.03
CDP	96.78	92.03
CDP	95.92	92.02
CDP	94.29	92.01
CDP	97.46	91.99
CDP	95.63	91.99
CDP	95.27	91.98
CDP	94.02	91.97
CDP	95.69	91.97
CDP	95.42	91.94
CDP	98.00	91.94
CDP	96.47	91.94
CDP	95.96	91.93
CDP	99.34	91.92
CDP	95.59	91.91
CDP	96.42	91.91
CDP	95.75	91.91
CDP	96.11	91.90
CDP	100.00	91.89
CDP	96.61	91.89
CDP	98.19	91.89
CDP	98.30	91.88
CDP	99.59	91.87
CDP	97.36	91.87
CDP	97.42	91.86
CDP	96.11	91.86
CDP	95.35	91.86
CDP	95.17	91.86
CDP	95.76	91.84
CDP	97.35	91.83
CDP	95.17	91.83
CDP	97.40	91.83
CDP	94.85	91.82

CDP	99.10	91.82
CDP	96.77	91.80
CDP	98.99	91.79
CDP	94.52	91.78
CDP	95.54	91.77
CDP	95.22	91.76
CDP	94.42	91.76
CDP	95.35	91.75
CDP	97.68	91.73
CDP	96.55	91.72
CDP	97.45	91.72
CDP	94.48	91.72
CDP	98.18	91.72
CDP	98.63	91.70
CDP	94.91	91.69
CDP	96.54	91.69
CDP	97.03	91.67
CDP	99.59	91.67
CDP	98.48	91.67
CDP	96.37	91.67
CDP	95.41	91.67
CDP	100.00	91.67
CDP	98.83	91.63
CDP	98.83	91.63
CDP	98.83	91.63
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CDP	98.83	91.63
CDP	98.83	91.63
CDP	98.83	91.63
CDP	98.83	91.63
CDP	98.36	91.63
CDP	95.56	91.62
CDP	98.13	91.62
CDP	97.39	91.58
CDP	94.72	91.58
CDP	96.61	91.57
CDP	96.61	91.57
CDP	98.80	91.57
CDP	98.17	91.56
CDP	97.66	91.56
CDP	94.13	91.55
CDP	94.28	91.54
CDP	97.30	91.54
CDP	95.47	91.54
CDP	97.07	91.54
CDP	98.66	91.53
CDP	94.67	91.53

CDP	96.85	91.53
CDP	98.85	91.51
CDP	95.45	91.50
CDP	95.08	91.50
CDP	95.41	91.50
CDP	96.36	91.50
CDP	97.28	91.50
CDP	98.13	91.48
CDP	94.01	91.45
CDP	97.56	91.45
CDP	98.68	91.45
CDP	95.26	91.45
CDP	96.60	91.43
CDP	99.58	91.43
CDP	95.26	91.43
CDP	94.61	91.42
CDP	96.16	91.42
CDP	97.49	91.42
CDP	94.49	91.41
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CDP	95.76	91.40
CDP	97.09	91.40
CDP	94.67	91.39
CDP	96.52	91.39
CDP	94.79	91.39
CDP	94.01	91.38
CDP	96.89	91.38
CDP	97.14	91.37
CDP	94.14	91.37
CDP	98.97	91.37
CDP	94.98	91.37
CDP	95.22	91.35
CDP	97.76	91.34
CDP	97.62	91.34
CDP	95.12	91.32
CDP	95.40	91.32
CDP	95.79	91.31
CDP	95.98	91.31
CDP	98.69	91.31
CDP	94.06	91.31
CDP	98.24	91.31
CDP	96.01	91.31
CDP	97.05	91.30
CDP	99.02	91.29
CDP	94.61	91.28
CDP	98.91	91.28
CDP	96.55	91.27
CDP	96.94	91.25

OTHER	**961**

CDP	95.07	91.25
CDP	95.64	91.24
CDP	98.96	91.23
CDP	97.12	91.22
CDP	95.93	91.21
CDP	98.53	91.20
CDP	98.53	91.20
CDP	98.78	91.17
CDP	96.60	91.17
CDP	96.91	91.15
CDP	98.14	91.15
CDP	94.37	91.15
CDP	94.76	91.14
CDP	94.71	91.13
CDP	95.99	91.12
CDP	96.07	91.11
CDP	97.69	91.10
CDP	96.14	91.09
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CDP	98.03	91.08
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CDP	96.60	91.05
CDP	95.21	91.05
CDP	95.05	91.04
CDP	96.28	91.03
CDP	97.91	91.02
CDP	98.23	91.02
CDP	94.93	91.01
CDP	97.75	90.99
CDP	97.89	90.99
CDP	96.39	90.99
CDP	94.07	90.98
CDP	95.00	90.98
CDP	94.70	90.98
CDP	95.72	90.97
CDP	94.77	90.97
CDP	97.96	90.96
CDP	97.96	90.96
CDP	94.20	90.96
CDP	94.91	90.96
CDP	94.13	90.95
CDP	97.17	90.95
CDP	94.24	90.95
CDP	94.98	90.94

CDP	96.02	90.93
CDP	94.85	90.93
CDP	96.03	90.93
CDP	97.07	90.93
CDP	94.94	90.93
CDP	98.53	90.91
CDP	99.51	90.90
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CDP	96.63	90.90
CDP	94.67	90.88
CDP	97.01	90.88
CDP	97.01	90.88
CDP	94.76	90.87
CDP	98.13	90.86
CDP	96.24	90.85
CDP	99.37	90.84
CDP	94.63	90.84
CDP	96.62	90.82
CDP	98.47	90.82
CDP	96.70	90.80
CDP	97.97	90.80
CDP	97.69	90.79
CDP	94.65	90.79
CDP	94.23	90.79
CDP	94.72	90.79
CDP	98.56	90.79
CDP	96.10	90.78
CDP	97.20	90.78
CDP	97.54	90.77
CDP	98.48	90.75
CDP	99.38	90.75
CDP	94.93	90.73
CDP	95.98	90.73
CDP	96.26	90.73
CDP	96.64	90.73
CDP	95.76	90.73
CDP	97.92	90.71
CDP	97.06	90.71
CDP	95.67	90.71
CDP	95.20	90.70
CDP	94.05	90.70
CDP	96.75	90.70
CDP	96.42	90.70
CDP	98.66	90.70
CDP	95.81	90.69
CDP	98.96	90.67
CDP	94.75	90.67
CDP	95.33	90.66

CDP	96.75	90.65
CDP	96.88	90.65
CDP	94.81	90.64
CDP	98.80	90.64
CDP	95.57	90.64
CDP	98.24	90.63
CDP	98.28	90.63
CDP	97.78	90.63
CDP	94.18	90.63
CDP	95.25	90.62
CDP	97.27	90.61
CDP	97.46	90.60
CDP	94.13	90.60
CDP	99.17	90.60
CDP	96.22	90.59
CDP	94.69	90.58
CDP	94.07	90.58
CDP	98.38	90.57
CDP	97.64	90.57
CDP	97.27	90.55
CDP	94.41	90.53
CDP	98.05	90.53
CDP	97.47	90.51
CDP	98.75	90.51
CDP	94.80	90.50
CDP	99.58	90.49
CDP	97.30	90.49
CDP	98.85	90.44
CDP	98.10	90.43
CDP	96.18	90.43
CDP	94.28	90.43
CDP	96.99	90.42
CDP	98.37	90.42
CDP	94.63	90.42
CDP	94.08	90.41
CDP	94.97	90.41
CDP	96.42	90.41
CDP	97.71	90.40
CDP	95.98	90.39
CDP	95.06	90.39
CDP	94.84	90.36
CDP	99.15	90.36
CDP	96.15	90.35
CDP	98.52	90.34
CDP	99.13	90.33
CDP	96.39	90.32
CDP	96.07	90.32
CDP	97.73	90.31

CDP	96.62	90.31
CDP	95.80	90.30
CDP	97.73	90.29
CDP	95.29	90.29
CDP	97.46	90.25
CDP	97.26	90.24
CDP	94.97	90.23
CDP	94.43	90.23
CDP	97.59	90.23
CDP	98.73	90.21
CDP	98.58	90.21
CDP	95.15	90.21
CDP	99.00	90.20
CDP	94.50	90.18
CDP	97.78	90.18
CDP	95.52	90.18
CDP	94.58	90.17
CDP	95.76	90.15
CDP	95.02	90.15
CDP	97.90	90.14
CDP	95.37	90.12
CDP	96.94	90.10
CDP	94.19	90.08
CDP	94.31	90.08
CDP	94.54	90.08
CDP	95.71	90.08
CDP	96.58	90.06
CDP	94.99	90.05
CDP	97.70	90.05
CDP	98.15	90.03
CDP	95.32	90.01
CDP	98.91	90.01
CDP	99.05	90.00
CDP	98.26	90.00
CDP	97.17	89.99
CDP	96.30	89.99
CDP	94.94	89.98
CDP	96.36	89.97
CDP	98.25	89.96
CDP	94.86	89.95
CDP	96.27	89.95
CDP	99.09	89.94
CDP	99.09	89.94
CDP	99.09	89.94
CDP	99.09	89.94
CDP	99.09	89.94
CDP	99.09	89.94
CDP	94.24	89.94

CDP	95.50	89.93
CDP	95.69	89.92
CDP	97.18	89.92
CDP	95.30	89.92
CDP	95.30	89.92
CDP	95.30	89.92
CDP	95.30	89.92
CDP	99.89	89.90
CDP	94.56	89.90
CDP	97.09	89.90
CDP	94.58	89.90
CDP	95.70	89.90
CDP	98.12	89.90
CDP	98.12	89.90
CDP	98.12	89.90
CDP	98.12	89.90
CDP	98.12	89.90
CDP	95.96	89.89
CDP	96.15	89.89
CDP	97.05	89.89
CDP	95.89	89.87
CDP	97.63	89.87
CDP	96.65	89.86
CDP	94.92	89.85
CDP	94.41	89.85
CDP	96.54	89.84
CDP	95.92	89.84
CDP	94.33	89.83
CDP	95.11	89.81
CDP	95.36	89.81
CDP	98.89	89.80
CDP	96.56	89.79
CDP	97.33	89.77
CDP	94.02	89.77
CDP	94.02	89.77
CDP	94.02	89.77
CDP	94.02	89.77
CDP	94.02	89.77
CDP	94.02	89.77
CDP	94.02	89.77
CDP	96.65	89.75
CDP	99.81	89.74
CDP	96.32	89.73
CDP	97.26	89.71
CDP	97.06	89.71
CDP	95.59	89.71
CDP	95.52	89.68
CDP	95.02	89.68

Category 1	Category 2	Number of proteins

CDP	98.53	89.68
CDP	97.30	89.67
CDP	97.30	89.67
CDP	95.76	89.67
CDP	95.49	89.66
CDP	97.65	89.66
CDP	96.11	89.66
CDP	97.01	89.66
CDP	96.79	89.65
CDP	94.70	89.65
CDP	99.52	89.64
CDP	94.16	89.63
CDP	94.49	89.63
CDP	97.56	89.63
CDP	94.26	89.62
CDP	95.03	89.62
CDP	96.73	89.62
CDP	97.11	89.61
CDP	94.58	89.61
CDP	94.58	89.61
CDP	97.51	89.59
CDP	96.51	89.59
CDP	96.09	89.58
CDP	97.13	89.56
CDP	98.88	89.56
CDP	98.60	89.55
CDP	98.76	89.54
CDP	94.38	89.53
CDP	94.53	89.53
CDP	96.91	89.53
CDP	96.21	89.53
CDP	94.97	89.52
CDP	95.87	89.51
CDP	95.43	89.50
CDP	97.99	89.50
CDP	94.67	89.50
CDP	95.75	89.48
CDP	98.51	89.48
CDP	94.23	89.47
CDP	94.33	89.47
CDP	94.24	89.47
CDP	96.33	89.45
CDP	94.48	89.41
CDP	97.03	89.39
CDP	99.15	89.36
CDP	95.17	89.36
CDP	95.17	89.36
CDP	94.13	89.33

CDP	99.09	89.33
CDP	97.73	89.33
CDP	95.10	89.33
CDP	96.95	89.32
CDP	95.60	89.30
CDP	95.39	89.26
CDP	98.22	89.25
CDP	96.86	89.25
CDP	95.38	89.22
CDP	96.11	89.21
CDP	97.26	89.20
CDP	94.46	89.18
CDP	96.13	89.18
CDP	97.50	89.13
CDP	98.71	89.09
CDP	98.35	89.08
CDP	97.81	89.06
CDP	97.54	89.03
CDP	95.48	89.02
CDP	97.75	89.02
CDP	97.47	89.02
CDP	97.47	89.02
CDP	97.47	89.02
CDP	96.17	89.00
CDP	99.11	89.00
CDP	96.27	88.99
CDP	95.35	88.99
CDP	95.53	88.99
CDP	96.88	88.98
CDP	97.76	88.97
CDP	96.32	88.96
CDP	94.20	88.95
CDP	99.01	88.93
CDP	96.73	88.93
CDP	96.46	88.91
CDP	94.81	88.91
CDP	98.59	88.91
CDP	94.04	88.90
CDP	95.23	88.88
CDP	97.70	88.85
CDP	95.62	88.85
CDP	95.62	88.85
CDP	95.40	88.82
CDP	94.57	88.82
CDP	94.81	88.77
CDP	94.61	88.77
CDP	95.54	88.75
CDP	98.21	88.73

CDP	97.30	88.73
CDP	96.96	88.72
CDP	95.23	88.72
CDP	97.24	88.72
CDP	96.88	88.69
CDP	97.57	88.68
CDP	98.75	88.67
CDP	94.22	88.66
CDP	94.60	88.66
CDP	94.27	88.65
CDP	98.27	88.64
CDP	94.15	88.64
CDP	97.06	88.63
CDP	96.18	88.57
CDP	96.18	88.57
CDP	96.67	88.57
CDP	97.37	88.54
CDP	95.83	88.54
CDP	94.68	88.54
CDP	96.39	88.53
CDP	96.02	88.52
CDP	95.58	88.52
CDP	95.42	88.50
CDP	94.19	88.50
CDP	94.51	88.50
CDP	94.43	88.48
CDP	94.52	88.48
CDP	96.62	88.45
CDP	96.85	88.45
CDP	94.89	88.44
CDP	95.52	88.43
CDP	95.59	88.42
CDP	97.30	88.40
CDP	97.41	88.36
CDP	97.42	88.36
CDP	98.30	88.35
CDP	97.02	88.33
CDP	94.02	88.33
CDP	96.71	88.32
CDP	98.53	88.31
CDP	94.30	88.30
CDP	94.32	88.29
CDP	95.26	88.28
CDP	94.38	88.27
CDP	94.44	88.25
CDP	99.36	88.25
CDP	96.15	88.24
CDP	99.71	88.23

CDP	95.22	88.16
CDP	95.64	88.15
CDP	97.78	88.14
CDP	97.09	88.14
CDP	94.44	88.13
CDP	94.80	88.12
CDP	95.14	88.12
CDP	94.08	88.11
CDP	95.62	88.11
CDP	96.68	88.10
CDP	96.91	88.10
CDP	94.15	88.07
CDP	94.08	88.06
CDP	94.40	88.06
CDP	94.76	88.05
CDP	98.08	88.05
CDP	94.60	88.02
CDP	95.03	88.01
CDP	94.90	88.00
CDP	96.99	88.00
CDP	98.35	87.99
CDP	97.50	87.91
CDP	97.67	87.91
CDP	94.76	87.87
CDP	95.68	87.84
CDP	98.94	87.84
CDP	98.86	87.83
CDP	94.34	87.83
CDP	97.43	87.81
CDP	95.61	87.81
CDP	96.54	87.77
CDP	94.61	87.76
CDP	95.92	87.76
CDP	95.05	87.75
CDP	94.42	87.74
CDP	98.68	87.73
CDP	96.09	87.70
CDP	97.76	87.69
CDP	96.60	87.69
CDP	96.46	87.68
CDP	96.18	87.67
CDP	95.78	87.66
CDP	95.94	87.65
CDP	97.50	87.63
CDP	95.01	87.61
CDP	95.77	87.60
CDP	95.77	87.60
CDP	96.67	87.57

CDP	97.08	87.57
CDP	95.93	87.56
CDP	95.60	87.52
CDP	98.08	87.52
CDP	95.59	87.51
CDP	95.68	87.50
CDP	94.14	87.50
CDP	95.18	87.46
CDP	96.02	87.45
CDP	96.94	87.45
CDP	94.73	87.45
CDP	96.04	87.42
CDP	96.13	87.42
CDP	97.85	87.42
CDP	96.67	87.41
CDP	98.07	87.39
CDP	95.73	87.38
CDP	94.39	87.35
CDP	98.05	87.34
CDP	98.05	87.34
CDP	94.63	87.33
CDP	96.76	87.33
CDP	96.40	87.32
CDP	94.50	87.29
CDP	94.75	87.28
CDP	94.20	87.28
CDP	94.55	87.26
CDP	95.16	87.23
CDP	94.81	87.23
CDP	94.47	87.22
CDP	96.44	87.21
CDP	96.72	87.20
CDP	96.95	87.20
CDP	97.82	87.18
CDP	94.12	87.17
CDP	97.71	87.17
CDP	96.37	87.15
CDP	95.91	87.11
CDP	94.60	87.11
CDP	94.98	87.11
CDP	95.56	87.10
CDP	94.76	87.10
CDP	98.59	87.06
CDP	96.15	87.05
CDP	96.30	87.04
CDP	96.30	87.04
CDP	96.30	87.04
CDP	97.01	87.04

CDP	97.72	87.03
CDP	96.32	87.02
OTHERS	95.83	86.98
OTHERS	95.40	86.98
OTHERS	95.74	86.98
OTHERS	96.98	86.98
OTHERS	94.42	86.96
OTHERS	96.65	86.89
OTHERS	99.07	86.88
OTHERS	96.91	86.87
OTHERS	98.19	86.86
OTHERS	94.81	86.86
OTHERS	97.74	86.86
OTHERS	94.04	86.83
OTHERS	94.01	86.82
OTHERS	95.46	86.80
OTHERS	94.41	86.80
OTHERS	94.98	86.77
OTHERS	96.58	86.76
OTHERS	96.59	86.75
OTHERS	97.14	86.72
OTHERS	95.55	86.69
OTHERS	96.82	86.64
OTHERS	94.54	86.64
OTHERS	94.87	86.62
OTHERS	94.93	86.61
OTHERS	98.38	86.61
OTHERS	95.88	86.60
OTHERS	94.76	86.59
OTHERS	94.93	86.58
OTHERS	96.57	86.56
OTHERS	96.39	86.56
OTHERS	94.60	86.55
OTHERS	96.00	86.55
OTHERS	95.14	86.54
OTHERS	95.25	86.54
OTHERS	95.65	86.53
OTHERS	95.73	86.52
OTHERS	95.71	86.52
OTHERS	97.03	86.50
OTHERS	94.13	86.48
OTHERS	94.50	86.46
OTHERS	94.75	86.45
OTHERS	97.80	86.45
OTHERS	98.30	86.41
OTHERS	94.85	86.37
OTHERS	97.90	86.34
OTHERS	94.82	86.33

OTHERS	94.63	86.33		
OTHERS	96.67	86.30		
OTHERS	95.66	86.28		
OTHERS	95.83	86.27		
OTHERS	96.76	86.26		
OTHERS	95.45	86.26		
OTHERS	96.27	86.26		
OTHERS	95.29	86.25		
OTHERS	94.11	86.21		
OTHERS	97.31	86.18		
OTHERS	97.87	86.17		
OTHERS	98.24	86.17		
OTHERS	95.39	86.16		
OTHERS	98.38	86.15		
OTHERS	95.00	86.15		
OTHERS	97.53	86.13		
OTHERS	96.64	86.13		
OTHERS	94.48	86.13		
OTHERS	99.05	86.09		
OTHERS	94.89	86.06		
OTHERS	94.97	86.05		
OTHERS	97.02	86.02		
OTHERS	96.34	86.01		
OTHERS	98.50	86.00		
OTHERS	98.50	86.00		
OTHERS	95.21	85.98		
OTHERS	97.07	85.97		
OTHERS	95.69	85.95		
OTHERS	95.53	85.92	**CDP**	**2397**
OTHERS	94.61	85.92		
OTHERS	97.27	85.91		
OTHERS	95.88	85.91		
OTHERS	96.47	85.89		
OTHERS	96.68	85.89		
OTHERS	95.31	85.86		
OTHERS	95.31	85.86		
OTHERS	95.22	85.86		
OTHERS	97.87	85.84		
OTHERS	97.24	85.81		
OTHERS	97.24	85.81		
OTHERS	95.70	85.81		
OTHERS	95.69	85.79		
OTHERS	97.75	85.77		
OTHERS	97.53	85.75		
OTHERS	96.63	85.73		
OTHERS	94.03	85.72		
OTHERS	97.83	85.71		
OTHERS	96.26	85.70		

OTHERS	98.49	85.69
OTHERS	98.04	85.69
OTHERS	94.52	85.68
OTHERS	98.31	85.67
OTHERS	95.37	85.65
OTHERS	96.58	85.64
OTHERS	94.44	85.64
OTHERS	95.58	85.64
OTHERS	94.53	85.62
OTHERS	97.94	85.60
OTHERS	96.72	85.60
OTHERS	97.03	85.59
OTHERS	96.37	85.54
OTHERS	94.46	85.51
OTHERS	94.49	85.51
OTHERS	96.06	85.50
OTHERS	97.47	85.49
OTHERS	95.63	85.48
OTHERS	95.00	85.45
OTHERS	96.22	85.44
OTHERS	99.10	85.40
OTHERS	97.20	85.38
OTHERS	97.26	85.36
OTHERS	96.26	85.32
OTHERS	98.65	85.31
OTHERS	98.12	85.29
OTHERS	95.30	85.29
OTHERS	96.00	85.29
OTHERS	96.00	85.29
OTHERS	94.51	85.27
OTHERS	97.39	85.27
OTHERS	96.78	85.24
OTHERS	95.62	85.22
OTHERS	96.70	85.21
OTHERS	95.90	85.21
OTHERS	94.39	85.20
OTHERS	95.00	85.18
OTHERS	94.37	85.13
OTHERS	95.68	85.13
OTHERS	95.38	85.12
OTHERS	95.38	85.12
OTHERS	95.44	85.09
OTHERS	95.86	85.08
OTHERS	94.46	85.07
OTHERS	95.41	85.07
OTHERS	94.07	85.02
OTHERS	95.05	85.02
OTHERS	97.59	84.97

OTHERS	98.33	84.97
OTHERS	94.48	84.94
OTHERS	98.17	84.94
OTHERS	98.40	84.94
OTHERS	94.06	84.92
OTHERS	94.46	84.91
OTHERS	95.66	84.89
OTHERS	95.62	84.88
OTHERS	95.69	84.86
OTHERS	94.36	84.86
OTHERS	96.84	84.80
OTHERS	94.73	84.77
OTHERS	94.98	84.75
OTHERS	94.88	84.74
OTHERS	94.88	84.74
OTHERS	95.96	84.74
OTHERS	95.96	84.74
OTHERS	97.08	84.73
OTHERS	98.29	84.72
OTHERS	96.17	84.69
OTHERS	98.77	84.68
OTHERS	96.41	84.65
OTHERS	94.54	84.64
OTHERS	95.74	84.63
OTHERS	94.66	84.55
OTHERS	96.45	84.54
OTHERS	96.45	84.54
OTHERS	96.45	84.54
OTHERS	96.45	84.54
OTHERS	96.45	84.54
OTHERS	94.79	84.52
OTHERS	94.04	84.52
OTHERS	94.63	84.48
OTHERS	94.70	84.46
OTHERS	98.02	84.43
OTHERS	94.84	84.43
OTHERS	97.46	84.42
OTHERS	95.29	84.42
OTHERS	95.91	84.38
OTHERS	94.38	84.36
OTHERS	94.58	84.34
OTHERS	96.74	84.33
OTHERS	98.07	84.32
OTHERS	98.07	84.32
OTHERS	98.07	84.32
OTHERS	98.07	84.32
OTHERS	98.07	84.32
OTHERS	95.51	84.30

OTHERS	95.54	84.23
OTHERS	94.95	84.22
OTHERS	95.07	84.22
OTHERS	94.35	84.21
OTHERS	94.38	84.20
OTHERS	94.16	84.18
OTHERS	94.16	84.18
OTHERS	96.05	84.18
OTHERS	97.32	84.14
OTHERS	94.89	84.09
OTHERS	96.21	84.07
OTHERS	94.55	84.06
OTHERS	96.52	84.02
OTHERS	96.52	84.02
OTHERS	95.25	83.94
OTHERS	94.02	83.91
OTHERS	95.16	83.88
OTHERS	94.35	83.87
OTHERS	94.14	83.87
OTHERS	98.22	83.84
OTHERS	94.83	83.83
OTHERS	94.32	83.81
OTHERS	95.41	83.79
OTHERS	99.35	83.77
OTHERS	95.80	83.74
OTHERS	95.00	83.72
OTHERS	96.08	83.69
OTHERS	96.77	83.69
OTHERS	94.06	83.69
OTHERS	96.33	83.68
OTHERS	96.76	83.66
OTHERS	96.03	83.64
OTHERS	96.67	83.62
OTHERS	95.53	83.61
OTHERS	97.41	83.58
OTHERS	96.01	83.53
OTHERS	94.91	83.42
OTHERS	95.67	83.33
OTHERS	96.91	83.32
OTHERS	94.94	83.28
OTHERS	95.17	83.23
OTHERS	98.25	83.16
OTHERS	96.99	83.14
OTHERS	96.52	83.12
OTHERS	94.05	83.12
OTHERS	96.39	83.10
OTHERS	96.84	83.05
OTHERS	96.92	83.05

OTHERS	94.02	83.03
OTHERS	94.99	83.03
OTHERS	95.33	83.02
OTHERS	98.59	83.01
OTHERS	96.32	83.01
OTHERS	94.92	83.01
OTHERS	97.04	82.97
OTHERS	96.58	82.95
OTHERS	95.89	82.93
OTHERS	97.66	82.93
OTHERS	94.50	82.87
OTHERS	95.57	82.82
OTHERS	96.19	82.80
OTHERS	95.49	82.76
OTHERS	95.13	82.71
OTHERS	95.19	82.71
OTHERS	94.35	82.68
OTHERS	96.37	82.67
OTHERS	95.94	82.67
OTHERS	94.32	82.67
OTHERS	95.58	82.66
OTHERS	95.97	82.65
OTHERS	96.81	82.64
OTHERS	94.61	82.63
OTHERS	95.52	82.61
OTHERS	98.83	82.55
OTHERS	94.19	82.52
OTHERS	95.70	82.52
OTHERS	94.61	82.47
OTHERS	94.80	82.45
OTHERS	94.44	82.35
OTHERS	94.07	82.34
OTHERS	94.65	82.33
OTHERS	96.27	82.29
OTHERS	94.03	82.27
OTHERS	97.15	82.22
OTHERS	97.29	82.20
OTHERS	98.13	82.19
OTHERS	94.89	82.18
OTHERS	96.68	82.18
OTHERS	95.88	82.11
OTHERS	95.54	82.08
OTHERS	94.02	82.08
OTHERS	95.49	82.08
OTHERS	96.13	82.07
OTHERS	97.23	82.04
OTHERS	96.44	81.99
OTHERS	95.83	81.96

OTHERS	96.52	81.96
OTHERS	96.20	81.91
OTHERS	96.40	81.88
OTHERS	94.79	81.85
OTHERS	94.79	81.85
OTHERS	94.54	81.83
OTHERS	95.06	81.82
OTHERS	94.82	81.78
OTHERS	95.83	81.77
OTHERS	96.40	81.74
OTHERS	94.19	81.74
OTHERS	94.87	81.72
OTHERS	94.41	81.70
OTHERS	94.03	81.65
OTHERS	94.94	81.65
OTHERS	95.66	81.64
OTHERS	95.05	81.61
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	96.10	81.60
OTHERS	95.71	81.59
OTHERS	96.07	81.55
OTHERS	94.81	81.39
OTHERS	94.31	81.35
OTHERS	97.67	81.33
OTHERS	97.67	81.33
OTHERS	96.60	81.31
OTHERS	95.99	81.26
OTHERS	94.29	81.23
OTHERS	94.31	81.21
OTHERS	94.87	81.18
OTHERS	94.25	81.17
OTHERS	95.35	81.15
OTHERS	94.78	81.04
OTHERS	94.39	81.01
OTHERS	94.25	80.95
OTHERS	94.07	80.93
OTHERS	96.70	80.92
OTHERS	94.80	80.91

OTHERS	95.26	80.84
OTHERS	94.01	80.80
OTHERS	94.01	80.80
OTHERS	97.61	80.71
OTHERS	94.29	80.71
OTHERS	95.89	80.70
OTHERS	97.34	80.67
OTHERS	94.99	80.63
OTHERS	95.55	80.59
OTHERS	96.17	80.56
OTHERS	95.23	80.53
OTHERS	95.23	80.53
OTHERS	97.86	80.51
OTHERS	96.08	80.42
OTHERS	94.03	80.36
OTHERS	94.31	80.34
OTHERS	94.07	80.28
OTHERS	94.71	80.26
OTHERS	95.54	80.24
OTHERS	94.30	80.11
OTHERS	98.46	80.09
OTHERS	94.40	80.09
OTHERS	97.14	79.97
OTHERS	95.28	79.74
OTHERS	95.05	79.74
OTHERS	94.13	79.68
OTHERS	94.23	79.60
OTHERS	95.39	79.60
OTHERS	94.37	79.54
OTHERS	97.95	79.44
OTHERS	95.27	79.34
OTHERS	94.58	79.31
OTHERS	96.68	79.22
OTHERS	94.93	79.17
OTHERS	97.03	79.14
OTHERS	94.39	79.12
OTHERS	94.33	79.04
OTHERS	94.33	79.04
OTHERS	95.27	78.99
OTHERS	94.54	78.98
OTHERS	94.18	78.87
OTHERS	98.73	78.84
OTHERS	98.60	78.74
OTHERS	94.28	78.72
OTHERS	94.62	78.69
OTHERS	96.30	78.67
OTHERS	95.33	78.66
OTHERS	94.72	78.43

OTHERS	95.68	78.40
OTHERS	94.32	78.24
OTHERS	98.26	78.22
OTHERS	94.55	78.21
OTHERS	95.82	78.13
OTHERS	95.25	78.13
OTHERS	95.82	78.10
OTHERS	95.10	78.08
OTHERS	94.03	78.03
OTHERS	94.52	78.00
OTHERS	95.91	78.00
OTHERS	96.22	77.98
OTHERS	95.48	77.96
OTHERS	94.40	77.86
OTHERS	95.60	77.70
OTHERS	94.57	77.69
OTHERS	94.98	77.67
OTHERS	95.61	77.56
OTHERS	94.73	77.43
OTHERS	95.57	77.34
OTHERS	95.55	77.33
OTHERS	95.11	77.31
OTHERS	95.88	77.30
OTHERS	94.70	77.23
OTHERS	95.61	77.20
OTHERS	96.34	77.13
OTHERS	94.54	77.11
OTHERS	95.55	77.05
OTHERS	94.13	76.17
OTHERS	95.62	76.10
OTHERS	95.30	76.06
OTHERS	95.73	75.90
OTHERS	95.19	75.89
OTHERS	95.89	75.82
OTHERS	94.54	75.39
OTHERS	95.94	75.10
OTHERS	97.24	75.07
OTHERS	94.48	74.93
OTHERS	96.78	74.76
OTHERS	94.59	74.62
OTHERS	95.56	74.59
OTHERS	94.44	74.54
OTHERS	94.65	73.86
OTHERS	94.27	73.74
OTHERS	96.03	72.62
OTHERS	94.59	72.29
OTHERS	98.58	72.13
OTHERS	98.35	72.07

OTHERS	94.20	71.61
OTHERS	96.11	69.96
OTHERS	94.75	69.68
OTHERS	94.64	69.64
OTHERS	95.16	69.24
OTHERS	96.32	69.04
OTHERS	99.14	68.39
OTHERS	94.40	67.58
OTHERS	96.31	66.50
OTHERS	97.49	63.98
OTHERS	97.24	63.22
OTHERS	94.31	47.80
OTHERS	89.74	98.40
OTHERS	89.99	97.08
OTHERS	90.82	96.94
OTHERS	91.78	96.81
OTHERS	93.35	96.57
OTHERS	91.82	96.52
OTHERS	92.79	96.51
OTHERS	91.56	96.44
OTHERS	88.06	96.39
OTHERS	91.76	96.16
OTHERS	88.58	96.01
OTHERS	93.87	95.96
OTHERS	93.75	95.94
OTHERS	92.11	95.89
OTHERS	93.44	95.85
OTHERS	93.75	95.69
OTHERS	91.60	95.52
OTHERS	90.70	95.50
OTHERS	93.15	95.43
OTHERS	93.82	95.35
OTHERS	92.34	95.32
OTHERS	91.24	95.23
OTHERS	93.80	95.09
OTHERS	91.93	95.08
OTHERS	90.99	95.03
OTHERS	91.91	94.93
OTHERS	93.43	94.91
OTHERS	93.61	94.91
OTHERS	92.49	94.83
OTHERS	90.54	94.82
OTHERS	93.90	94.77
OTHERS	84.27	94.76
OTHERS	93.57	94.74
OTHERS	93.57	94.74
OTHERS	92.41	94.73
OTHERS	90.75	94.69

OTHERS	93.61	94.69
OTHERS	92.18	94.63
OTHERS	93.41	94.63
OTHERS	92.98	94.58
OTHERS	90.13	94.54
OTHERS	92.58	94.38
OTHERS	91.96	94.36
OTHERS	93.67	94.33
OTHERS	91.48	94.24
OTHERS	91.86	94.23
OTHERS	93.37	94.16
OTHERS	92.91	94.13
OTHERS	93.31	94.12
OTHERS	92.29	94.05
OTHERS	88.32	94.03
OTHERS	89.94	93.99
OTHERS	92.76	93.96
OTHERS	92.86	93.96
OTHERS	91.67	93.94
OTHERS	93.81	93.86
OTHERS	93.11	93.85
OTHERS	93.63	93.85
OTHERS	92.27	93.84
OTHERS	89.74	93.83
OTHERS	92.34	93.78
OTHERS	93.42	93.73
OTHERS	91.79	93.70
OTHERS	93.41	93.63
OTHERS	92.61	93.62
OTHERS	92.73	93.55
OTHERS	91.77	93.53
OTHERS	93.25	93.45
OTHERS	93.83	93.44
OTHERS	93.22	93.43
OTHERS	88.09	93.40
OTHERS	91.90	93.38
OTHERS	93.61	93.37
OTHERS	93.52	93.35
OTHERS	93.20	93.33
OTHERS	91.30	93.33
OTHERS	93.28	93.28
OTHERS	86.01	93.28
OTHERS	93.99	93.20
OTHERS	93.43	93.14
OTHERS	90.97	93.12
OTHERS	92.32	93.09
OTHERS	90.27	93.07
OTHERS	93.90	93.06

OTHERS	93.75	93.02
OTHERS	90.19	92.99
OTHERS	91.80	92.97
OTHERS	88.37	92.95
OTHERS	93.36	92.94
OTHERS	93.10	92.90
OTHERS	92.61	92.89
OTHERS	86.42	92.89
OTHERS	92.46	92.86
OTHERS	92.46	92.86
OTHERS	92.46	92.86
OTHERS	92.46	92.86
OTHERS	92.46	92.86
OTHERS	92.46	92.86
OTHERS	93.98	92.81
OTHERS	91.23	92.80
OTHERS	92.20	92.78
OTHERS	90.16	92.73
OTHERS	92.53	92.70
OTHERS	89.44	92.69
OTHERS	93.54	92.69
OTHERS	92.95	92.68
OTHERS	88.00	92.67
OTHERS	88.00	92.67
OTHERS	89.31	92.64
OTHERS	93.17	92.54
OTHERS	93.63	92.52
OTHERS	93.80	92.51
OTHERS	91.15	92.50
OTHERS	91.93	92.48
OTHERS	88.83	92.45
OTHERS	93.63	92.41
OTHERS	93.69	92.40
OTHERS	93.67	92.39
OTHERS	93.11	92.38
OTHERS	92.13	92.36
OTHERS	93.05	92.34
OTHERS	81.00	92.33
OTHERS	92.04	92.28
OTHERS	88.76	92.27
OTHERS	89.03	92.26
OTHERS	93.61	92.22
OTHERS	93.41	92.22
OTHERS	86.73	92.21
OTHERS	88.50	92.20
OTHERS	93.08	92.19
OTHERS	87.50	92.19
OTHERS	90.01	92.14

OTHERS	93.02	92.10
OTHERS	93.34	92.09
OTHERS	91.48	92.08
OTHERS	92.75	92.04
OTHERS	91.18	92.04
OTHERS	93.70	92.03
OTHERS	93.31	91.93
OTHERS	92.61	91.93
OTHERS	88.24	91.93
OTHERS	92.00	91.88
OTHERS	91.95	91.83
OTHERS	92.20	91.82
OTHERS	93.58	91.80
OTHERS	93.50	91.79
OTHERS	93.08	91.78
OTHERS	93.95	91.77
OTHERS	88.57	91.70
OTHERS	91.91	91.70
OTHERS	93.24	91.70
OTHERS	89.87	91.69
OTHERS	91.63	91.69
OTHERS	87.77	91.68
OTHERS	81.37	91.67
OTHERS	93.41	91.66
OTHERS	93.88	91.64
OTHERS	91.15	91.64
OTHERS	91.23	91.61
OTHERS	90.72	91.60
OTHERS	93.84	91.58
OTHERS	91.31	91.58
OTHERS	91.00	91.56
OTHERS	87.57	91.53
OTHERS	88.88	91.43
OTHERS	93.23	91.41
OTHERS	88.47	91.39
OTHERS	87.66	91.39
OTHERS	82.03	91.36
OTHERS	82.03	91.36
OTHERS	92.37	91.34
OTHERS	93.24	91.33
OTHERS	83.48	91.31
OTHERS	91.29	91.25
OTHERS	91.62	91.24
OTHERS	92.44	91.24
OTHERS	92.24	91.24
OTHERS	90.72	91.24
OTHERS	91.50	91.18
OTHERS	91.87	91.14

OTHERS	93.33	91.13
OTHERS	93.01	91.13
OTHERS	91.79	91.13
OTHERS	82.39	91.11
OTHERS	92.17	91.11
OTHERS	86.10	91.08
OTHERS	86.10	91.08
OTHERS	92.45	91.04
OTHERS	91.12	91.03
OTHERS	84.56	91.02
OTHERS	93.60	91.02
OTHERS	93.12	90.96
OTHERS	80.63	90.94
OTHERS	87.78	90.93
OTHERS	90.60	90.93
OTHERS	90.02	90.93
OTHERS	90.33	90.92
OTHERS	87.07	90.91
OTHERS	86.82	90.90
OTHERS	93.93	90.90
OTHERS	88.81	90.88
OTHERS	88.56	90.88
OTHERS	92.47	90.86
OTHERS	91.25	90.85
OTHERS	93.44	90.85
OTHERS	89.85	90.84
OTHERS	90.82	90.82
OTHERS	86.49	90.82
OTHERS	86.49	90.82
OTHERS	91.43	90.76
OTHERS	87.01	90.75
OTHERS	93.24	90.74
OTHERS	92.43	90.74
OTHERS	91.81	90.73
OTHERS	90.89	90.72
OTHERS	85.79	90.72
OTHERS	84.82	90.71
OTHERS	87.33	90.70
OTHERS	90.59	90.67
OTHERS	91.52	90.64
OTHERS	92.92	90.64
OTHERS	93.32	90.63
OTHERS	90.21	90.63
OTHERS	92.23	90.62
OTHERS	91.98	90.61
OTHERS	93.35	90.59
OTHERS	93.26	90.58
OTHERS	93.80	90.58

OTHERS	90.68	90.57
OTHERS	92.63	90.54
OTHERS	93.77	90.53
OTHERS	89.66	90.52
OTHERS	89.76	90.51
OTHERS	93.79	90.51
OTHERS	88.72	90.51
OTHERS	91.24	90.49
OTHERS	91.79	90.49
OTHERS	82.66	90.44
OTHERS	92.87	90.42
OTHERS	93.86	90.41
OTHERS	93.33	90.41
OTHERS	92.00	90.41
OTHERS	86.94	90.41
OTHERS	91.96	90.40
OTHERS	86.67	90.40
OTHERS	89.68	90.39
OTHERS	84.31	90.35
OTHERS	92.62	90.34
OTHERS	86.54	90.33
OTHERS	89.92	90.32
OTHERS	91.97	90.28
OTHERS	93.83	90.26
OTHERS	90.58	90.25
OTHERS	91.88	90.21
OTHERS	92.31	90.21
OTHERS	93.83	90.20
OTHERS	91.59	90.20
OTHERS	93.84	90.20
OTHERS	90.33	90.19
OTHERS	83.04	90.18
OTHERS	92.04	90.16
OTHERS	93.17	90.10
OTHERS	92.99	90.08
OTHERS	91.57	90.06
OTHERS	91.57	90.06
OTHERS	92.89	90.03
OTHERS	93.90	90.00
OTHERS	90.95	90.00
OTHERS	91.73	89.97
OTHERS	91.05	89.97
OTHERS	92.12	89.96
OTHERS	93.30	89.94
OTHERS	92.31	89.94
OTHERS	92.07	89.93
OTHERS	92.02	89.92
OTHERS	92.02	89.92

OTHERS	91.47	89.92
OTHERS	91.05	89.91
OTHERS	86.07	89.89
OTHERS	91.00	89.88
OTHERS	91.72	89.88
OTHERS	88.26	89.83
OTHERS	91.09	89.83
OTHERS	90.83	89.82
OTHERS	89.65	89.79
OTHERS	92.32	89.79
OTHERS	93.18	89.77
OTHERS	88.40	89.77
OTHERS	93.55	89.77
OTHERS	90.44	89.75
OTHERS	93.16	89.74
OTHERS	86.16	89.73
OTHERS	92.68	89.70
OTHERS	84.78	89.67
OTHERS	93.21	89.66
OTHERS	90.95	89.66
OTHERS	90.95	89.66
OTHERS	91.38	89.63
OTHERS	91.88	89.63
OTHERS	93.62	89.60
OTHERS	93.62	89.60
OTHERS	93.62	89.60
OTHERS	85.98	89.55
OTHERS	93.90	89.54
OTHERS	92.40	89.52
OTHERS	93.87	89.49
OTHERS	92.48	89.49
OTHERS	92.48	89.49
OTHERS	82.04	89.49
OTHERS	90.01	89.48
OTHERS	93.79	89.46
OTHERS	92.64	89.44
OTHERS	85.08	89.43
OTHERS	80.23	89.41
OTHERS	88.02	89.41
OTHERS	93.25	89.41
OTHERS	92.66	89.40
OTHERS	91.20	89.40
OTHERS	93.93	89.39
OTHERS	93.45	89.38
OTHERS	89.17	89.37
OTHERS	88.79	89.36
OTHERS	93.01	89.36
OTHERS	93.95	89.35

OTHERS	90.98	89.32
OTHERS	83.71	89.32
OTHERS	93.50	89.32
OTHERS	91.68	89.30
OTHERS	92.95	89.29
OTHERS	93.15	89.26
OTHERS	80.18	89.20
OTHERS	92.15	89.19
OTHERS	87.65	89.19
OTHERS	93.25	89.19
OTHERS	91.23	89.18
OTHERS	89.18	89.18
OTHERS	90.89	89.16
OTHERS	93.83	89.16
OTHERS	88.89	89.15
OTHERS	93.65	89.14
OTHERS	93.04	89.12
OTHERS	93.04	89.12
OTHERS	93.04	89.12
OTHERS	93.04	89.12
OTHERS	93.04	89.12
OTHERS	93.04	89.12
OTHERS	89.92	89.11
OTHERS	90.02	89.11
OTHERS	89.00	89.10
OTHERS	89.96	89.09
OTHERS	91.48	89.07
OTHERS	83.54	89.06
OTHERS	92.20	88.99
OTHERS	92.83	88.99
OTHERS	87.16	88.99
OTHERS	93.64	88.99
OTHERS	92.37	88.98
OTHERS	92.96	88.97
OTHERS	93.36	88.95
OTHERS	93.09	88.94
OTHERS	92.20	88.92
OTHERS	84.04	88.92
OTHERS	93.45	88.89
OTHERS	93.15	88.88
OTHERS	91.11	88.88
OTHERS	93.01	88.87
OTHERS	87.10	88.87
OTHERS	92.32	88.87
OTHERS	91.78	88.87
OTHERS	93.75	88.87
OTHERS	91.55	88.87
OTHERS	83.98	88.85

OTHERS	89.91	88.85
OTHERS	93.30	88.83
OTHERS	93.17	88.80
OTHERS	89.87	88.79
OTHERS	86.87	88.77
OTHERS	91.67	88.76
OTHERS	91.78	88.73
OTHERS	91.57	88.69
OTHERS	93.39	88.69
OTHERS	92.31	88.63
OTHERS	92.93	88.61
OTHERS	92.03	88.58
OTHERS	91.34	88.58
OTHERS	91.34	88.58
OTHERS	91.34	88.58
OTHERS	92.90	88.58
OTHERS	84.49	88.57
OTHERS	78.56	88.56
OTHERS	86.68	88.55
OTHERS	87.87	88.54
OTHERS	91.29	88.52
OTHERS	88.69	88.51
OTHERS	91.22	88.51
OTHERS	91.04	88.50
OTHERS	90.71	88.47
OTHERS	89.86	88.46
OTHERS	87.91	88.46
OTHERS	92.32	88.46
OTHERS	93.09	88.45
OTHERS	83.75	88.44
OTHERS	93.52	88.44
OTHERS	92.10	88.39
OTHERS	90.67	88.36
OTHERS	88.06	88.36
OTHERS	85.90	88.36
OTHERS	93.32	88.36
OTHERS	90.50	88.35
OTHERS	92.89	88.33
OTHERS	91.29	88.31
OTHERS	89.44	88.30
OTHERS	93.97	88.29
OTHERS	89.49	88.29
OTHERS	90.54	88.27
OTHERS	93.55	88.25
OTHERS	92.73	88.24
OTHERS	91.44	88.22
OTHERS	92.58	88.21
OTHERS	93.77	88.21

OTHERS	93.05	88.20
OTHERS	81.65	88.19
OTHERS	91.54	88.18
OTHERS	93.00	88.18
OTHERS	90.86	88.17
OTHERS	93.55	88.17
OTHERS	93.00	88.17
OTHERS	89.26	88.16
OTHERS	92.09	88.16
OTHERS	91.89	88.16
OTHERS	90.44	88.15
OTHERS	90.04	88.14
OTHERS	93.14	88.13
OTHERS	89.63	88.13
OTHERS	92.89	88.11
OTHERS	93.02	88.10
OTHERS	90.31	88.10
OTHERS	93.35	88.10
OTHERS	90.65	88.07
OTHERS	93.83	88.07
OTHERS	90.06	88.05
OTHERS	93.38	88.02
OTHERS	89.29	88.01
OTHERS	84.36	88.01
OTHERS	87.67	88.01
OTHERS	92.13	88.00
OTHERS	84.45	88.00
OTHERS	79.03	87.99
OTHERS	86.85	87.98
OTHERS	88.57	87.98
OTHERS	93.21	87.96
OTHERS	90.86	87.96
OTHERS	93.48	87.94
OTHERS	91.56	87.94
OTHERS	87.07	87.93
OTHERS	87.07	87.93
OTHERS	92.69	87.93
OTHERS	89.83	87.92
OTHERS	91.76	87.90
OTHERS	90.73	87.87
OTHERS	91.70	87.86
OTHERS	74.92	87.85
OTHERS	86.84	87.83
OTHERS	91.23	87.83
OTHERS	85.19	87.82
OTHERS	92.82	87.81
OTHERS	86.29	87.80
OTHERS	89.71	87.80

OTHERS	93.06	87.78
OTHERS	92.78	87.78
OTHERS	86.08	87.77
OTHERS	82.45	87.75
OTHERS	64.61	87.74
OTHERS	88.69	87.72
OTHERS	87.39	87.72
OTHERS	87.50	87.72
OTHERS	91.43	87.70
OTHERS	78.13	87.70
OTHERS	93.54	87.68
OTHERS	93.93	87.66
OTHERS	93.54	87.64
OTHERS	92.50	87.64
OTHERS	92.05	87.63
OTHERS	88.37	87.62
OTHERS	88.37	87.62
OTHERS	86.29	87.62
OTHERS	93.34	87.61
OTHERS	91.54	87.61
OTHERS	84.73	87.59
OTHERS	88.03	87.59
OTHERS	91.52	87.59
OTHERS	89.26	87.59
OTHERS	89.05	87.58
OTHERS	92.05	87.58
OTHERS	90.79	87.58
OTHERS	90.11	87.57
OTHERS	93.93	87.56
OTHERS	93.47	87.56
OTHERS	90.43	87.55
OTHERS	93.41	87.54
OTHERS	89.64	87.50
OTHERS	90.70	87.50
OTHERS	92.97	87.48
OTHERS	92.74	87.44
OTHERS	93.33	87.43
OTHERS	84.26	87.42
OTHERS	88.99	87.41
OTHERS	92.50	87.40
OTHERS	80.66	87.39
OTHERS	91.90	87.38
OTHERS	87.93	87.37
OTHERS	88.35	87.36
OTHERS	88.42	87.36
OTHERS	91.85	87.35
OTHERS	90.93	87.34
OTHERS	92.29	87.33

OTHERS	92.05	87.32
OTHERS	91.91	87.32
OTHERS	90.16	87.30
OTHERS	88.72	87.28
OTHERS	88.96	87.28
OTHERS	84.11	87.28
OTHERS	90.02	87.28
OTHERS	83.57	87.27
OTHERS	92.86	87.27
OTHERS	93.64	87.26
OTHERS	89.63	87.26
OTHERS	92.00	87.25
OTHERS	93.04	87.24
OTHERS	91.84	87.22
OTHERS	86.49	87.16
OTHERS	90.91	87.13
OTHERS	91.68	87.11
OTHERS	87.50	87.09
OTHERS	93.36	87.07
OTHERS	90.96	87.07
OTHERS	91.80	87.06
OTHERS	93.22	87.05
OTHERS	85.01	87.05
OTHERS	92.44	87.03
OTHERS	86.55	87.03
OTHERS	87.29	87.01
OTHERS	93.25	87.00
OTHERS	90.58	87.00
NDP	89.66	86.97
NDP	89.73	86.92
NDP	93.65	86.91
NDP	92.12	86.90
NDP	92.15	86.89
NDP	93.20	86.88
NDP	92.59	86.88
NDP	92.73	86.87
NDP	90.36	86.86
NDP	91.39	86.85
NDP	92.36	86.85
NDP	90.00	86.84
NDP	84.87	86.84
NDP	91.43	86.82
NDP	89.50	86.82
NDP	86.60	86.82
NDP	92.68	86.82
NDP	92.17	86.81
NDP	90.99	86.81
NDP	90.70	86.81

NDP	92.01	86.81
NDP	85.57	86.80
NDP	85.57	86.80
NDP	90.69	86.80
NDP	88.23	86.78
NDP	92.75	86.78
NDP	88.36	86.77
NDP	91.56	86.77
NDP	92.28	86.76
NDP	93.72	86.76
NDP	88.77	86.76
NDP	80.20	86.75
NDP	90.53	86.74
NDP	89.51	86.73
NDP	91.59	86.73
NDP	90.03	86.71
NDP	92.81	86.71
NDP	92.88	86.70
NDP	89.16	86.70
NDP	92.31	86.68
NDP	92.17	86.68
NDP	93.30	86.67
NDP	93.10	86.67
NDP	90.24	86.67
NDP	84.87	86.66
NDP	90.23	86.66
NDP	93.09	86.66
NDP	93.54	86.65
NDP	91.56	86.65
NDP	89.97	86.65
NDP	91.43	86.61
NDP	87.24	86.59
NDP	93.47	86.58
NDP	90.44	86.58
NDP	91.37	86.57
NDP	87.73	86.57
NDP	93.61	86.57
NDP	89.32	86.55
NDP	93.21	86.55
NDP	92.35	86.54
NDP	77.48	86.52
NDP	93.69	86.52
NDP	91.94	86.51
NDP	92.06	86.51
NDP	86.26	86.50
NDP	79.17	86.49
NDP	79.17	86.49
NDP	79.17	86.49

NDP	79.17	86.49
NDP	79.17	86.49
NDP	79.17	86.49
NDP	79.17	86.49
NDP	89.09	86.48
NDP	84.52	86.45
NDP	88.74	86.45
NDP	88.74	86.45
NDP	90.03	86.44
NDP	87.53	86.43
NDP	93.02	86.43
NDP	89.29	86.43
NDP	87.22	86.42
NDP	90.59	86.42
NDP	91.35	86.42
NDP	86.15	86.41
NDP	87.87	86.38
NDP	93.26	86.34
NDP	92.73	86.34
NDP	93.59	86.33
NDP	86.22	86.33
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NDP	86.95	86.27
NDP	88.31	86.27
NDP	91.81	86.26
NDP	88.31	86.24
NDP	91.30	86.23
NDP	88.33	86.22
NDP	86.22	86.22
NDP	87.00	86.21
NDP	92.33	86.21
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NDP	84.81	86.12
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NDP	93.31	86.09
NDP	91.82	86.05
NDP	90.06	86.04
NDP	88.41	86.02
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NDP	87.92	86.01
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NDP	84.47	85.98

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NDP	91.70	85.95
NDP	92.14	85.95
NDP	90.48	85.94
NDP	92.57	85.93
NDP	91.29	85.92
NDP	88.58	85.92
NDP	89.92	85.92
NDP	91.10	85.90
NDP	91.78	85.89
NDP	90.76	85.88
NDP	79.64	85.88
NDP	92.99	85.86
NDP	89.86	85.83
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NDP	87.17	85.80
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NDP	91.19	85.76
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NDP	88.07	85.67
NDP	93.62	85.65
NDP	92.25	85.63
NDP	84.83	85.60
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NDP	92.07	85.52
NDP	83.72	85.51

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NDP	87.91	85.45
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NDP	84.67	85.44
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NDP	86.79	85.36
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NDP	93.04	85.36
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NDP	93.70	85.32
NDP	92.91	85.31
NDP	90.49	85.30
NDP	86.08	85.29
NDP	92.98	85.29
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NDP	93.11	85.25
NDP	90.40	85.25
NDP	92.06	85.25
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NDP	91.09	85.21
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NDP	88.75	85.21
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NDP	89.37	84.56

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NDP	91.56	83.91
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NDP	90.41	83.89
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NDP	81.22	83.71
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NDP	90.10	83.65
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NDP	87.11	83.63
NDP	91.90	83.63
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NDP	80.03	83.61
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NDP	91.10	83.59
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NDP	88.76	83.50
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NDP	92.94	83.34
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NDP	91.50	83.33
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NDP	82.60	83.05
NDP	91.56	83.05
NDP	91.18	83.04
NDP	93.79	83.03
NDP	85.41	83.03
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NDP	88.09	83.02
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NDP	87.81	82.97
NDP	87.81	82.97
NDP	87.81	82.97
NDP	87.81	82.97

NDP	87.81	82.97
NDP	87.81	82.97
NDP	91.25	82.96
NDP	91.75	82.96
NDP	82.05	82.95
NDP	93.25	82.94
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NDP	85.16	82.94
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NDP	88.14	82.86
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NDP	90.00	82.85
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NDP	86.07	82.84
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NDP	76.22	82.82
NDP	78.96	82.81
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NDP	92.56	82.74
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NDP	92.11	82.69
NDP	85.87	82.68
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NDP	90.09	82.63
NDP	91.14	82.62
NDP	92.98	82.61

NDP	87.81	82.61
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NDP	93.21	82.36
NDP	89.42	82.35
NDP	89.33	82.35
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NDP	90.66	82.26
NDP	93.23	82.26

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NDP	93.82	82.25
NDP	82.32	82.24
NDP	88.08	82.23
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NDP	89.93	82.05
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NDP	92.06	82.03
NDP	82.76	82.03
NDP	92.52	82.03
NDP	93.17	82.01
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NDP	84.74	81.97
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NDP	90.53	81.97
NDP	88.71	81.96
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NDP	78.64	81.84
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NDP	89.18	81.59
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NDP	87.92	81.18
NDP	93.28	81.18
NDP	84.98	81.18
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NDP	79.91	81.05
NDP	93.78	81.05
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NDP	89.89	81.03
NDP	89.94	81.02
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NDP	80.15	81.00
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NDP	85.22	80.98
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NDP	92.89	80.85
NDP	86.59	80.84
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NDP	93.85	80.79
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NDP	84.45	80.75
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NDP	91.34	80.74
NDP	84.63	80.73
NDP	84.63	80.73
NDP	89.85	80.73
NDP	89.51	80.73
NDP	89.07	80.73
NDP	88.18	80.71
NDP	85.49	80.71
NDP	83.28	80.70
NDP	92.94	80.69
NDP	93.60	80.68
NDP	81.21	80.64
NDP	89.16	80.64
NDP	79.86	80.61
NDP	90.96	80.61
NDP	90.74	80.60
NDP	81.76	80.60
NDP	81.76	80.60

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NDP	91.69	80.56
NDP	87.70	80.53
NDP	77.37	80.53
NDP	78.14	80.53
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NDP	88.19	80.53
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NDP	83.72	80.49
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NDP	77.91	80.48
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NDP	88.12	80.46
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NDP	90.02	80.41
NDP	91.91	80.41
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NDP	90.13	80.39
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NDP	86.78	80.33
NDP	93.79	80.33
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NDP	84.30	80.19
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NDP	90.21	80.07
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NDP	87.78	79.73
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NDP	93.18	79.72
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NDP	85.68	79.72
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NDP	71.44	78.35

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NDP	89.18	76.93
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NDP	92.31	76.92
NDP	85.36	76.91
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NDP	89.08	76.70
NDP	89.08	76.70
NDP	89.08	76.70
NDP	89.08	76.70

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NDP	89.89	76.61
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NDP	83.99	73.20
NDP	90.03	73.20

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NDP	88.66	72.61
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NDP	92.30	72.32
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NDP	83.24	72.30
NDP	81.93	72.27
NDP	89.39	72.27
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NDP	76.42	72.22
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NDP	87.28	72.20

NDP	87.28	72.20
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NDP	77.90	72.18
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NDP	84.62	72.15
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NDP	84.71	72.12
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NDP	87.17	72.11
NDP	87.17	72.11
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NDP	82.88	68.50
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NDP	85.14	68.45
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NDP	74.25	63.87
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NDP	72.87	46.60
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NDP	74.64	31.34
NDP	21.80	28.89
NDP	33.60	28.64
NDP	20.00	27.27

Supplementary Materials

Deciphering the cause of evolutionary variance within intrinsically disordered regions in human proteins

Sanghita Banerjee, Sandip Chakraborty, Rajat K. De

Contents

Extended Results using the datasets of PONDR-FIT and ESpritz

We reapeted our analyses using two other disorder prediction tools in order to assure that the trend of the results is independent of disorder prediction algorithms. Here, we have reported the results obtained using the prediction tools: i) PONDR-FIT (Figure S1), and ii) ESpritz (Figure S2) for the identification of disordered residues with a protein sequence.

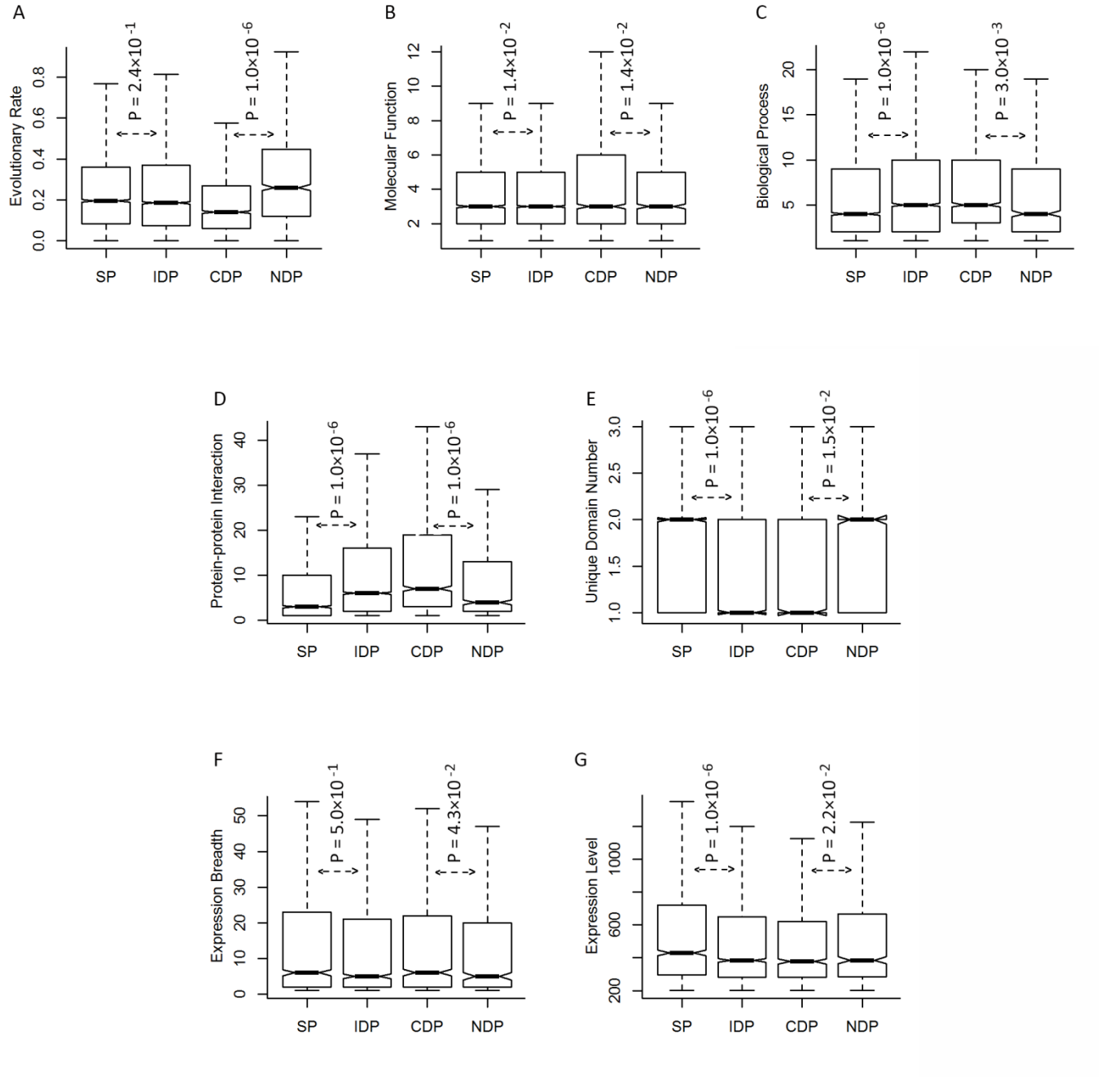

Figure S1: Boxplots showing the distribution of biological features: A. Evolutionary rate, B. Molecular Fucntions, C. Biological Processes, D. Protein-protein interaction, E. Unique domain number, F. Expression breadth, G. Expression level between the groups of intrinsically disordered (IDPs) and well-structured (SP), proteins and conserved disordered (CDPs) and non-conserved disordered (NDPs) proteins. P-values indicate the level of significance in the difference of the distribution of each of the features between the groups.

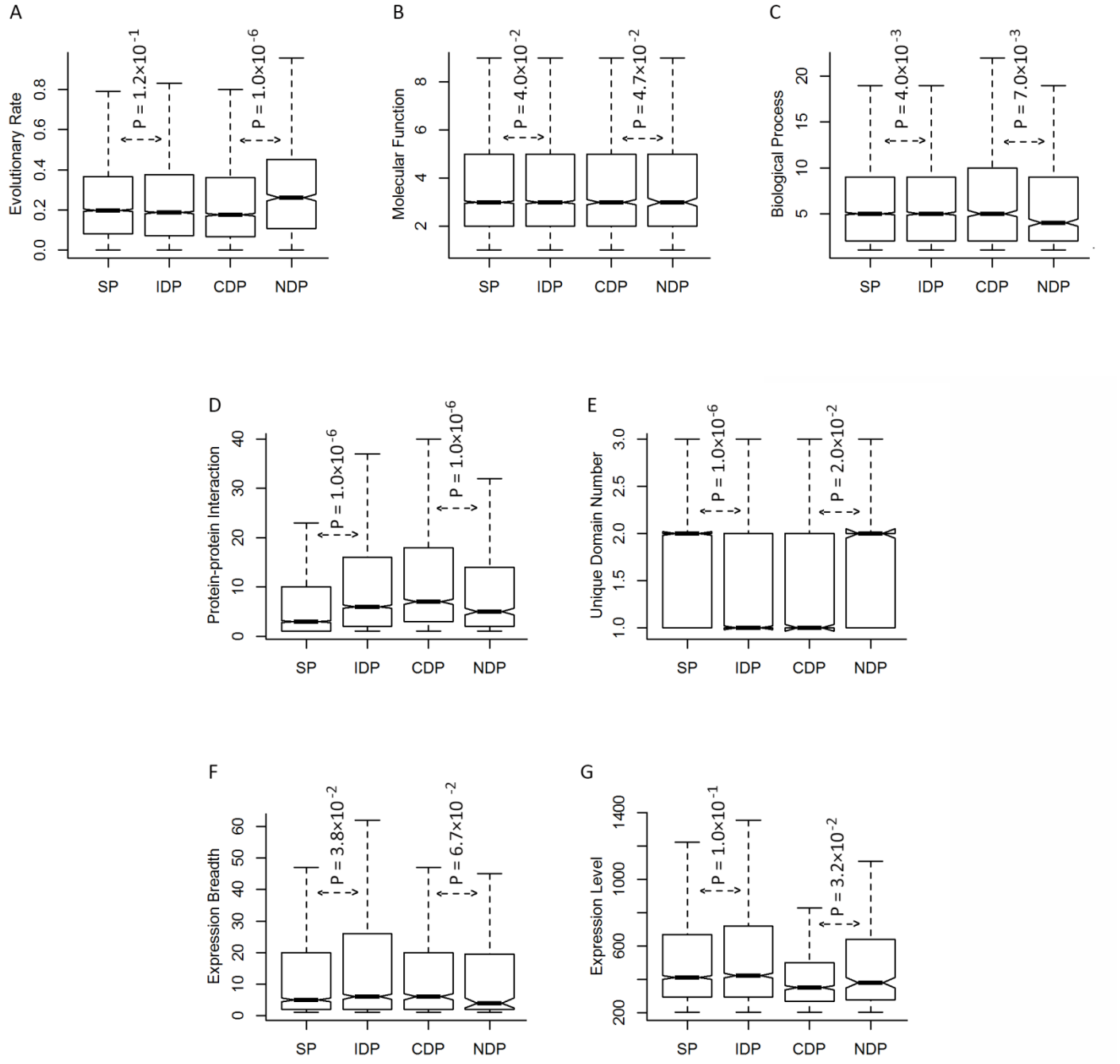

Figure S2: Boxplots showing the distribution of biological features: A. Evolutionary rate, B. Molecular Fucntions, C. Biological Processes, D. Protein-protein interaction, E. Unique domain number, F. Expression breadth, G. Expression level between the groups of intrinsically disordered (IDPs) and well-structured (SP), proteins and conserved disordered (CDPs) and non-conserved disordered (NDPs) proteins. P-values indicate the level of significance in the difference of the distribution of each of the features between the groups.

Table S1: **Conditional probability for intrinsically disordered proteins (conserved (CDPs) and non-conserved (NDPs)) and protein-protein interactions (PPI).**

Disordered Protein Category	**Protein-Protein Interactions (PPI)**			
	PPI =1, 2	**PPI = 3, 4, 5**	**PPI > 5**	**Total**
CDP	467	409	1217	2093
NDP	349	273	470	1092
Total	816	682	1687	**3185**

Case	**Event (E)**	**Condition (C)**	**Probability (E|C) = P(E∩C)/P(C)** i.e., Conditional probability of (E|C) indicates that the probability of observing an event E, given the condition C.
A	CDP	PPI > 5	The probability of finding a protein having conserved disordered regions (CDPs) among the proteins having high connectivity (PPI > 5): P (CDP| PPI > 5) = $\frac{1217}{1687} = 0.72$ The high probability value indicates that a protein having a high degree of protein connectivity is more likely to have conserved disordered segments.
	PPI > 5	CDP	The probability of finding a protein with a high degree of connectivity (PPI > 5) among the set of proteins having conserved disordered regions (CDPs): P (PPI > 5| CDP) = $\frac{1217}{2093} = 0.58$ Comparatively lower probability value (than that of the above case) indicates that the set of proteins having conserved disordered segment is less likely to have a very high protein connectivity.
B	PPI =1,2	CDP	The probability of finding a protein with a few degrees of connectivity among the set of proteins having conserved disordered regions: P (PPI =1, 2| CDP) = $\frac{467}{2093} = 0.22$ It indicates that the chance of proteins having a few interactions and adapting conserved disordered regions is lower than the probability of having highly evolvable disordered regions (≈ 0.32).

	PPI =1,2	NDP	The probability of finding a protein with a few degrees of connectivity among the set of proteins having non-conserved disordered regions: P (PPI =1, 2| NDP) = $\frac{349}{1092} = 0.32$ Higher probability value indicates that the lower degree of protein connectivity usually does not constrain the evolution of the disordered regions.
C	PPI > 5	CDP	The probability of finding a protein with a high degree of connectivity (PPI > 5) among the set of proteins having conserved disordered regions: P (PPI > 5| CDP) = $\frac{1217}{2093} = 0.58$ The probability value suggests that conserved disordered proteins (CDPs) have relatively high chance of undergoing a large number of protein interactions compared to NDPs. *(Although, the value is much lower than the first part of the case A showing the probability of finding a protein having conserved disordered regions (CDPs) among the proteins having high connectivity (PPI > 5))*
	PPI > 5	NDP	The probability of finding a protein with a high degree of connectivity (PPI > 5) among the set of proteins having non-conserved disordered regions (CDPs): P (PPI > 5| NDP) = $\frac{470}{1092} = 0.43$ The low value suggests that NDPs are less likely to have a higher number of protein connectivity compared to that of CDPs.
D	CDP	PPI =1,2	The probability of finding a protein having conserved disordered regions (CDPs) among the proteins having a few degrees of connectivity (PPI= 1, 2): P (CDP | PPI =1, 2) = $\frac{467}{816} = 0.57$ The probability that the class of proteins having a fewer number of protein interactions (PPI = 1, 2) may conserves their disordered regions, is lowest.
	CDP	PPI = 3, 4, 5	The probability of finding a protein having conserved disordered regions (CDPs) among the proteins having moderate protein connectivity (PPI= 3, 4, 5): P (CDP | PPI = 3, 4, 5) = $\frac{409}{682} = 0.59$

			The value signifies that the probability of the class of proteins having a moderate number of interactions (PPI = 3, 4, 5) may conserve their disordered regions, usually increases with increasing number of protein interactions.
	CDP	PPI > 5	The probability of finding a protein having conserved disordered regions (CDPs) among the proteins having high connectivity (PPI > 5): P (CDP | PPI > 5) = $\frac{1217}{1687} = 0.72$ The probability that the class of proteins having a high degree of interactions (PPI > 5) may conserves their disordered regions, is maximum.

Table S2: **Conditional probability for intrinsically disordered proteins (conserved (CDPs) and non-conserved (NDPs)) and unique domain number (UDN).**

Disordered Protein Category	**Unique Domain Number (UDN)**			
	UDN = 1	**UDN = 2, 3, 4**	**UDN ≥ 5**	**Total**
CDP	1075	843	51	**1969**
NDP	556	572	13	**1141**
Total	**1631**	**1415**	**64**	**3110**

Case	**Event (E)**	**Condition (C)**	**Probability (E|C) = P(E∩C)/P(C)** i.e., Conditional probability (P) of (E|C) indicates that the probability of observing an event E given the condition C.
A	UDN = 1	CDP	The probability of finding a protein having a single domain (UDN = 1) among the set of conserved disordered proteins (CDPs): P (UDN = 1| CDP) = $\frac{1075}{1969}$ = 0.54 The value suggests that the probability of a conserved disordered protein (CDP) having a single domain is lower than the probability (0.65) of a single domain protein adapting the stretches of conserved disordered regions. Instead, we have assumed that some other biological factors (other than the conservation rate of disordered regions) may influence the adaptation of a single domain in a protein.

	CDP	UDN =1	The probability of finding a protein having conserved disordered regions (CDPs) among the set of proteins having a single domain (UDN =1): P (CDP | UDN = 1) = $\frac{1075}{1631}$ = 0.65 Relatively high probability value indicates that a single domain protein is likely to adapt conserved disordered regions.
B	UDN = 1	NDP	The probability of finding a protein having a single domain (i.e., UDN =1) among the set of non-conserved disordered proteins (NDPs): P (UDN = 1| NDP) = $\frac{556}{1141}$ = 0.48 Non-conserved disordered proteins are less likely to adapt single protein domain compared to that of CDPs (≈ 0.54).
	UDN = 1	CDP	The probability of finding a single domain protein (i.e., UDN =1) among the set of conserved disordered proteins (CDPs): P (UDN = 1| CDP) = $\frac{1075}{1969}$ = 0.54 CDPs have relatively a higher probability of adapting single domains compared to that of NDPs. *(Although, the value is smaller than the probability of finding a protein having a single domain (UDN =1) among the set of conserved disordered proteins (CDPs), the second part of Case A).*

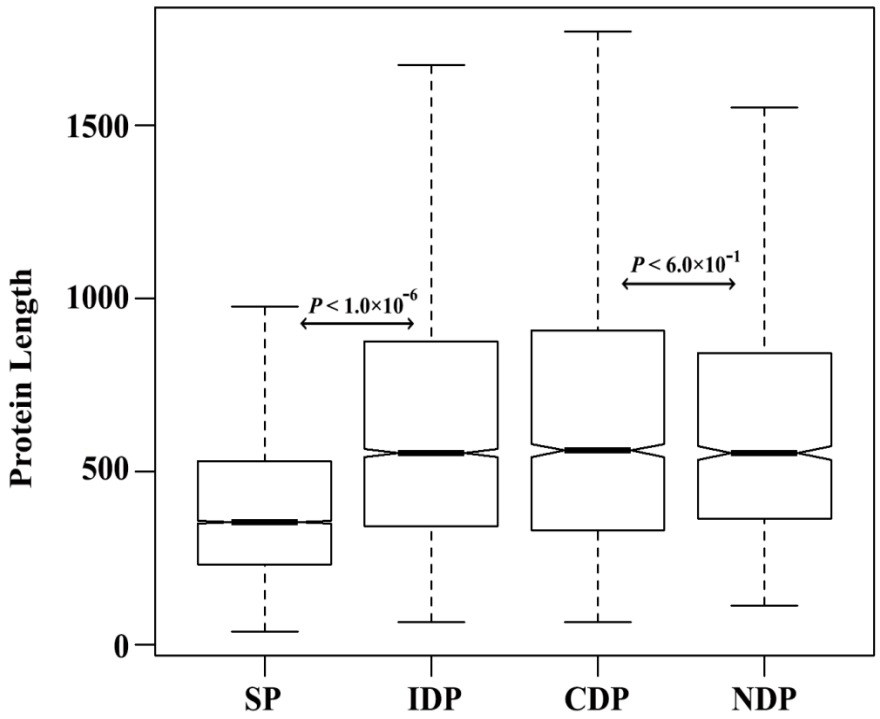

Figure S3: Boxplot showing the distribution of whole protein length between IDPs and SPs and CDPs and NDPs.

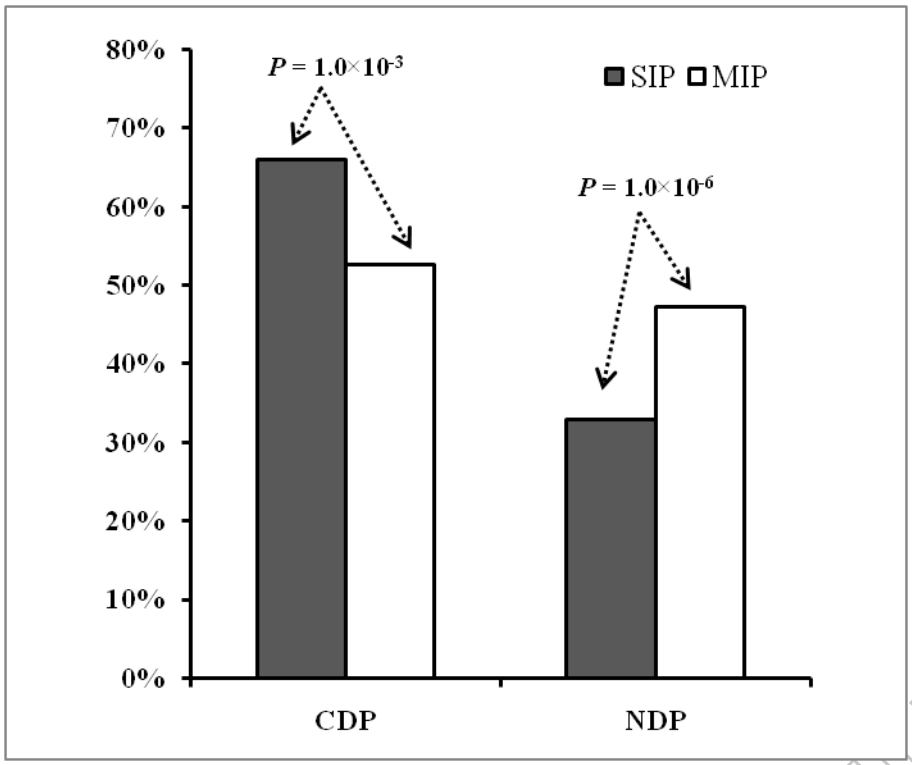

Figure S4: Bar diagram showing the distribution of conserved disordered (CDPs) and non-conserved disordered proteins (NDPs) within the sets of multi-interface (MIP) and single-interface (SIP) proteins.

Table S3: Table showing the significant effect of various features influencing the classes of conserved disordered (CDPs) and non-conserved disordered proteins (NDPs) classified according to variable threshold values of D_{nor} and A_{nor}. The median values of all the features (MF, BF, Expression level, Expression Breadth, d_N/d_S, Domain number and Protein connectivity) are given for the classes of CDPs and NDPs along with the level of significance (*P*-value).

Parameters	D_{nor} >85, A_{nor} >92	D_{nor} ≤85, A_{nor} ≤92	D_{nor} >88, A_{nor} >87	D_{nor} ≤88, A_{nor} ≤87	D_{nor} >90, A_{nor} >86	D_{nor} ≤90, A_{nor} ≤86	D_{nor} >93, A_{nor} >84	D_{nor} ≤93, A_{nor} ≤84	D_{nor} >95, A_{nor}>81	D_{nor}≤95, A_{nor}≤81
	CDP	NDP	CDP	NDP	CDP	NDP	CDP	NDP	CDP	NDP
MF	4	5	4	5	4	5	4	5	4	5
Sample number	1174	711	1963	930	2021	1138	1906	1310	1540	1099
P-value	2.0×10^{-3}		1.0×10^{-2}		6.0×10^{-3}		2.3×10^{-2}		3.4×10^{-2}	
BP	6	8	6	8	6	8	6	7	6	7
Sample number	1104	676	1844	886	1904	1077	1802	1243	1458	1045
P-value	4.0×10^{-3}		2.0×10^{-3}		1.0×10^{-3}		1.0×10^{-3}		2.6×10^{-2}	
Expression Level	346.75	383.77	345.80	348.21	345.63	359.65	344.21	360.42	348.64	374.47
Sample number	557	277	894	337	918	408	865	469	692	407
P value	5.0×10^{-3}		3.0×10^{-3}		1.5×10^{-2}		4.0×10^{-3}		1.0×10^{-3}	
Expression Breadth	6	4	6	4	6	4	6	4	6	4
Sample number	557	277	894	337	918	408	865	469	692	407
P-value	1.6×10^{-2}		1.5×10^{-2}		1.2×10^{-2}		2.0×10^{-2}		1.8×10^{-2}	
d_N/d_S	0.0007	0.1604	0.1104	0.1604	0.1232	0.1612	0.1207	0.1612	0.1207	0.1705
Sample number	1107	666	1887	886	1960	1102	1831	1277	1480	1079
P-value	1.0×10^{-6}		1.0×10^{-6}		1.0×10^{-6}		1.0×10^{-6}		1.0×10^{-6}	
Domain number	1	2	1	2	1.5	2	1.5	2	1	2
Sample number	1142	711	1876	915	1941	1106	1822	1265	1489	1066
P-value	3.2×10^{-2}		6.0×10^{-3}		6.0×10^{-3}		8.0×10^{-3}		4.0×10^{-3}	
Protein Connectivity	15	12	13	10	13	10	13	10	13	11
Sample number	1213	649	2001	856	2054	1053	1952	1208	1593	1001
P-value	1.0×10^{-6}		1.0×10^{-6}		1.0×10^{-6}		1.0×10^{-6}		1.0×10^{-6}	

Table S4: Table showing the effect of various features between the classes of conserved disordered (CDPs) and non-conserved disordered proteins (NDPs) classified according to variable threshold values of D_{nor} and A_{nor} around 70% or less. The median values of all the features (MF, BF, Expression level, Expression Breadth, d_N/d_S, Domain number and Protein connectivity) are given for the classes of CDPs and NDPs along with the level of significance (*P*-value). It has been noticed that most of the differences are not significant. Random I and Random II are the two sets, categorizing CDPs and NDPs randomly, irrespective of their conservation scores (D_{nor} and A_{nor}). However, in spite of having almost equal sample sizes, it fails to produce significant results.

	D_{nor} >53 A_{nor} >50	D_{nor} ≤53, A_{nor} ≤50	D_{nor} >68, A_{nor} >96	D_{nor} ≤68, A_{nor} ≤96	D_{nor} >73, A_{nor} >77	D_{nor} ≤73, A_{nor} ≤77	RANDOM - I		RANDOM - II	
	CDP	NDP	CDP	NDP	CDP	NDP	CDP	NDP	CDP	NDP
MF	4	11	4.5	3.5	4.0	4.5	4	5	4	4
Sample number	3963	9	488	87	3224	152	1309	1348	1313	1317
P-value	2.2×10^{-1}		2.9×10^{-4}		9.5×10^{-1}		9.6×10^{-1}		9.2×10^{-1}	
BP	7	8	6	4	7	8	7	7	7	7
Sample number	3750	8	478	81	3044	142	1237	1288	1228	1244
P value	1.6×10^{-1}		5.0×10^{-3}		3.9×10^{-1}		9.4×10^{-1}		7.0×10^{-1}	
Expression Level	349.53	1273.73	362.40	422.63	348.91	369.39	367.68	346.02	352.46	351.92
Sample number	1636	3	237	40	1358	67	529	571	525	545
P-value	5.5×10^{-1}		7.9×10^{-1}		5.7×10^{-1}		5.2×10^{-2}		6.5×10^{-1}	
Expression Breadth	5	32	6.5	4.0	5	4	5	6	5	5
Sample number	1636	3	237	40	1358	67	529	571	525	545
P-value	9.5×10^{-1}		1.3×10^{-1}		1.2×10^{-1}		9.2×10^{-1}		7.0×10^{-1}	
d_N/d_S	0.1446	0.0255	0.0420	0.1864	0.1398	0.1907	0.1404	0.1572	0.1516	0.1453
Sample number	3912	8	442	73	3204	130	1271	1351	1314	1286
P-value	5.9×10^{-1}		1.0×10^{-6}		2.0×10^{-3}		3.5×10^{-1}		3.4×10^{-1}	
Domain	2	2	1	2	2	2	2	2	2	2
Sample number	3765	10	491	86	3034	153	1221	1274	1251	1244
P-value	8.0×10^{-1}		1.2×10^{-1}		1.0×10^{-1}		5.7×10^{-1}		5.9×10^{-1}	
PPI	12	62	16.5	7.5	12	7.5	13.5	12	12	12

Sample number	**3892**	**7**	**504**	**71**	**3218**	**129**	**1291**	**1316**	**1298**	**1281**
***P*-value**	**3.5×10^{-1}**		**7.0×10^{-6}**		**3.0×10^{-3}**		**6.9×10^{-1}**		**3.0×10^{-1}**	