Multi scale modeling of relationships between protein classes and drug behavior across all diseases using the CANDO platform

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We have examined the effect of eight different protein classes (channels, GPCRs, kinases, ligases, nuclear receptors, proteases, phosphatases and transporters) on the benchmarking performance of the CANDO drug discovery and repurposing platform. The first version of the CANDO platform utilizes a matrix of predicted interactions between 48,278 proteins and 3733 human use compounds that map to 2030 indications/diseases using a hierarchical chem and bio-informatic fragment based docking with dynamics protocol. The platform uses similarity of compound-proteome interaction signatures as indicative of similar functional behavior and benchmarking accuracy is calculated across 1439 indications/diseases with more than one approved drug. The CANDO platform yields a significant correlation (0.99, p-value <0.0001) between the numbers of proteins considered and benchmarking accuracy obtained indicating the importance of multi-targeting for drug discovery. Average benchmarking accuracies range from 6.2% to 7.6% for the eight classes when the top 10 ranked compounds are considered in contrast to the range from 5.5% to 11.7% obtained for the comparison/control sets consisting of 10, 100, 1000 and 10000 single best performing proteins. These results are two orders of magnitude better than the average accuracy of 0.2% obtained when using randomly generated matrices. Different indications perform well when different classes are used but the best accuracies (11.7%) are achieved with a combination of classes consisting of the broadest distribution of protein folds. Our results illustrate the utility of the CANDO approach and the consideration of different protein classes for devising indication specific protocols for drug repurposing as well as drug discovery.

Biography

Ram Samudrala is a Professor and Chief, Division of Bioinformatics, State University of New York, Buffalo researching multi scale modeling of atomic, molecular, cellular and physiological systems with an emphasis on protein and proteome structure, function, interaction, design and evolution. His work has led to more than 115 publications in journals such as Science, Nature, *PLoS Biology*, the *Proceedings of the National Academy of Sciences* and the *Journal of the American Medical Association*. He has joined the University of Washington Faculty in 2001 (where he remains as an Affiliate Professor) after completing his Doctoral research with John Moult at the Center for Advanced Research in Biotechnology in 1997 and his Postdoctoral research with Michael Levitt (2013 Nobel in Chemistry) at Stanford University in 2000, which resulted him in making some of the best predictions at the first three community-wide assessment of protein structure prediction (CASP) experiments.

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