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Multiscale modelling of relationships between protein classes and drug behavior 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, 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 48278 proteins and 3733 human ingestible compounds (including FDA approved drugs and supplements that map to 2030 indications/diseases) using a hierarchical chem and bio-informatic fragment based docking with dynamics protocol (> one billion predicted interactions considered). 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 number of proteins considered and benchmarking accuracy obtained indicating the use of multitargeting 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 ranges of 5.5% to 11.7% obtained for the comparison/control sets consisting of 10, 100, 1000 single best performing proteins. These results are generally an order or two of magnitude better than the average accuracy of 0.2% obtained when randomly generated (fully scrambled) matrices are used. Different indications perform well when different classes are used but the best accuracies (up to 11.7% in the top 10 ranked compounds) are achieved when a combination of classes are used containing 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 Professor and Chief of the Division of Bioinformatics at SUNY Buffalo researching multiscale modelling of atomic, molecular, cellular, and physiological systems with more than 110 publications. He was on the University of Washington faculty from 2001-2014 after completing his Postdoctoral work with Michael Levitt (2013 Nobel in Chemistry), Stanford University from 1997-2000 and PhD thesis with John Moult, CARB from 1993-1997. His honors include a Searle Scholar Award (2002). He got MIT Technology Review TR100 selection (2003), Science in Medicine Lecture (2004), a NSF CAREER Award (2005), Alberta Heritage Foundation Visiting Scientist Award (2008), and a NIH Director's Pioneer Award (2010).

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