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Editorial

An Editorial Note on Proteochemometrics

Dr. Swetha Pothula

Department of Pharmaceutical Sciences,
Sciegen Pharmaceutical Inc. USA

One of the most important phases of a drug discovery campaign is the discovery of a potent inhibitor to a target driving the disease phenotype. Experimental design, make, test cycles seek to optimize initial hits to lead compounds by optimizing the protein-ligand binding affinity. However, this process is frequently slow and costly, adding to the large cost of drug discovery. Reverse transcriptase is a major drug target in highly active antiretroviral therapy (HAART) against HIV, which typically comprises two nucleoside/nucleotide analog reverse transcriptase (RT) inhibitors (NRTIs) in combination with a non-nucleoside RT inhibitor or a protease inhibitor.

Sole reliance on experimental design, make, and test cycles is costly and time consuming, providing an opportunity for computational methods to assist. Herein, we present results comparing random forest and feed-forward neural network proteochemometric models for their ability to predict pIC50 measurements for held out generic Bemis-Murcko scaffolds. Protein-ligand binding affinity is a key pharmacodynamic endpoint in drug discovery.

In addition, we assess the ability of conformal prediction to provide calibrated prediction intervals in both a retrospective and semi-prospective test using the recently released Grand Challenge 4 data set as an external test set. In total, random forest and deep neural network proteochemometric models show quality retrospective performance but suffer in the semi-prospective setting. However, the conformal predictor prediction intervals prove to be well-calibrated both retrospectively and semi-prospectively showing that they can be used to guide hit discovery and lead optimization campaigns.

Unfortunately, HIV is capable of escaping the therapy by mutating into drug-resistant variants. Computational models that correlate HIV drug susceptibilities to the virus genotype and to drug molecular properties might facilitate selection of improved combination treatment regimens. The threat to human health posed by the HIV/AIDS epidemic is increasing and represents now the third largest cause of death by infectious disease in the world. When first-line therapy fails, the treating physician needs to select a new regimen from multiple alternative possible drug combinations. Since anti-HIV drugs acting at the same target and binding site are rather similar in their molecular properties, cross-resistance is common and a new regime cannot be based on the assumption that the virus will be susceptible to the drugs remaining in the therapeutic arsenal. Therefore, resistance testing has become an important tool in management of HIV.

Such testing can be performed either by sequencing the viral genes coding for the drug targets (genotypic resistance testing), or by measuring viral activity in the presence and absence of a drug (phenotypic resistance testing). Genotypic assays are much faster and less expensive than the phenotypic ones, but sequence data provide only indirect evidence of resistance and interpretation is difficult for complex mutational combinations.

It is important to realize that in vitro susceptibility is only one of the factors to consider for drawing clinical inferences. Models have earlier also been developed to predict therapy outcome from virus genotype using clinical markers (viral load and CD4+ cell count), data on drug combinations in previously failed treatment regimens, and patient data (age, gender, mode of virus transmission, and adherence), as additional parameters in the modeling. However, these models still do not include any structural or physico-chemical data and hence cannot extrapolate to new mutations and novel drugs.

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