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An improved machine learning approach for drug combination-based drug repositioning

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Introducing a new drug to the market is time-consuming and costly. Therefore, reuse of existing drugs or drug combinations as therapeutics for diseases is identified to be much efficient and useful. This concept is known as drug repositioning/repurposing. The known drug combinations used for therapeutic effects are smaller than the total number of possible drug combinations. Hence, drug repositioning data for drug combinations naturally consists of a majority of unlabeled samples. Therefore, identifying reliable positives and reliable negatives is vital for a reliable binary classification model. With the assumption that unlabeled data is composed of both unidentified positive and negative samples, the set of unlabeled data has to be separated into positives and negatives by a reliable technique. In this study, the significance of employing Positive Unlabeled Learning (PUL) for drug combination repositioning is assessed. We integrated Drug-Target, Drug-disease, Drug-Structure, Drug-Expression and Drug-Module similarities using the Jaccard coefficient to construct the heterogeneous drug-drug similarity matrix. The proposed PUL approach has two tiers: i) determining reliable negatives by clustering the dataset, composed of known positives and unlabeled samples employing a Deep Learning-based Self Organizing Map and ii) determining reliable drug combination repositioning candidates by binary classification employing a Support Vector Machine classifier. The performance of the proposed PUL model was assessed with the frequently used Random Approach that randomly selects negatives from unlabeled samples. Significantly, there is an improvement in the Precision, Recall and F-measure by 16.14%, 18.26%, and 17.46%, respectively, for the proposed PUL approach compared to the Random Approach.We aim to publish the clinical significance of this study and analyze possible adverse drug reactions in the future.

Keywords: Drug repositioning, Deep-learning, Positive Unlabeled Learning (PUL), Support Vector Machine

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