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TITLE: Systematic evaluation of connectivity map for disease indications

ABSTRACT: Connectivity map data and associated methodologies have become a valuable tool in understanding drug mechanism of action (MOA) and discovering new indications for drugs. One of the key ideas of connectivity map (CMAP) is to measure the connectivity between disease gene expression signatures and compound-induced gene expression profiles. Despite multiple impressive anecdotal validations, only a few systematic evaluations have assessed the accuracy of this aspect of CMAP, and most of these utilize drug-to-drug matching to transfer indications across the two drugs.

Methods -To assess CMAP methodologies in a more direct setting, namely the power of classifying known drug-disease relationships, we evaluated three CMAP-based methods on their prediction performance against a curated dataset of 890 true drug-indication pairs. The disease signatures were generated using Gene Logic BioExpress™ system and the compound profiles were derived from the Connectivity Map database (CMAP, build 02, http://www.broadinstitute.org/CMAP/).

Results - The similarity scoring algorithm called eXtreme Sum (XSum) performs better than the standard Kolmogorov-Smirnov (KS) statistic in terms of the area under curve and can achieve a four-fold enrichment at 0.01 false positive rate level, with AUC = 2.2E-4, *P* value = 0.0035.

Conclusion - Connectivity map can significantly enrich true positive drug-indication pairs given an effective matching algorithm.