Drug Selection via Joint Push and Learning to Rank

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Abstract—Selecting the right drugs for the right patients is a primary goal of precision medicine. In this manuscript, we consider the problem of cancer drug selection in a learning-to-rank framework. We have formulated the cancer drug selection problem as to accurately predicting 1). the ranking positions of sensitive drugs and 2). the ranking orders among sensitive drugs in cancer cell lines based on their responses to cancer drugs. We have developed a new learning-to-rank method, denoted as pLETORg, that predicts drug ranking structures in each cell line via using drug latent vectors and cell line latent vectors. The pLETORg method learns such latent vectors through explicitly enforcing that, in the drug ranking list of each cell line, the sensitive drugs are pushed above insensitive drugs, and meanwhile the ranking orders among sensitive drugs are correct. Genomics information on cell lines is leveraged in learning the latent vectors. Our experimental results on a benchmark cell line-drug response dataset demonstrate that the new pLETORg significantly outperforms the state-of-the-art method in prioritizing new sensitive drugs.

Index Terms—Drug Selection, Learning to Rank

1 Introduction

SELECTING the right drugs for the right patients is a primary goal of precision medicine [1]. An appealing option for precision cancer drug selection is via the pan-cancer scheme [2] that examines various cancer types together. The landscape of cancer genomics reveals that various cancer types share driving mutagenesis mechanisms and corresponding molecular signaling pathways in several core cellular processes [3]. This finding has motivated the most recent clinical trials (e.g., the Molecular Analysis for Therapy Choice Trial at National Cancer Institute[1]) to identify common targets for patients of various cancer types and to prescribe same drug therapy to such patients. Such pan-cancer scheme is also well supported by the strong pan-cancer mutations [4] and copy number variation [5] patterns observed from The Cancer Genomics Atlas[2] project. The above pan-cancer evidence from theories and practices lays the foundation for joint analysis of multiple cancer cell lines and their drug responses to prioritize and select sensitive cancer drugs.

Another appealing option for precision cancer drug selection is via the popular off-label drug use [6] (i.e., the use of drugs for unapproved therapeutic indications [7]). This is due to the fact that some aggressive cancer types have very limited existing therapeutic options, while conventional drug development for those cancers, and also in general, has been extremely time-consuming, costly and risky [8]. However, a key challenge for off-label drug use is the lack of knowledge base of preclinical and clinical evidence, hence, the guidance for drug selection in practice [9].

In this manuscript, we present a new computational cancer drug selection method – joint **p**ush and **LE**arning **TO R**ank with **g**enomics regularization (pLETORg). In pLETORg, we formulate the problem of drug selection based on cell line responses as a learning-to-rank [10] problem, that is, we aim to produce accurate drug orderings (in terms of drug sensitivity) in each cell line via learning, and thus prioritize sensitive drugs in each cell line. This corresponds to the application scenario in which drugs need to be prioritized and selected to treat a given cell line/patient. Drug sensitivity here represents the capacity of drugs for reduction in cancer cell proliferation. Cell line responses to drugs reflect drug sensitivities on the cell lines, and thus, we use the concepts of drug sensitivity and cell line response in this manuscript exchangeably.

To induce correct ordering of drugs in each cell line in terms of drug sensitivity, for each involved drug and cell line, in pLETORg, we learn a latent vector and score drugs in each cell line using drug latent vectors and the corresponding cell line latent vector. We learn such latent vectors through explicitly enforcing and optimizing that, in the drug ranking list of each cell line, the sensitive drugs are pushed above insensitive drugs, and meanwhile the ranking orders among sensitive drugs are correct, where the ranking position of a drug in a cell line is determined by the drug latent vector and cell line latent vector. We simultaneously learn from all the cell lines and their drug ranking structures. In this way, the structural information of all the cell lines can be transferred across and leveraged during the learning process. We also use genomics information on cell lines to regularize the latent vectors in learning to rank. Fig. 1 demonstrates the overall scheme of the pLETORg method.

The new pLETORg is significantly different from the ex-

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1. https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match
2. https://cancergenome.nih.gov/

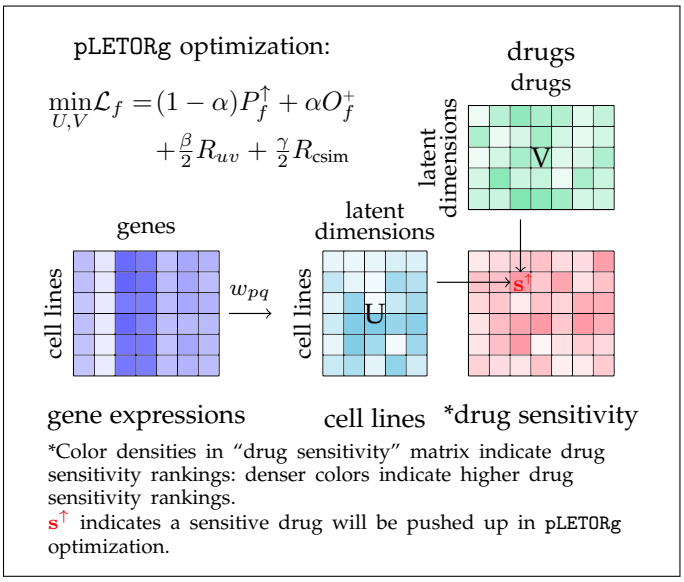


Fig. 1: pLETORg scheme overview

isting computational drug selection methods. Current computational efforts for precision cancer drug selection [11] are primarily focused on using regression methods (e.g., kernel based methods [12], [13], matrix factorization [14], [15], network-based similarity aggregation [16]) to predict drug sensitivities (e.g., in GI_{50} [3], IC_{50} [4]) numerically, and selecting drugs with optimal sensitivities in each cell line [17]. For example, in Menden *et al.* [18], cell line features (e.g., sequence variation, copy number variation) and drug features (e.g., physicochemical properties) are jointly used to train a neural network that predicts drug sensitivities in IC_{50} values. Drug selection has also been formulated as a classification problem. For example, in Stanfield *et al.* [19], cell line profiles, and drug sensitive and resistant profiles are generated from heterogeneous cell line-protein-drug interaction networks to score drugs in cell lines. The scores are compared with a threshold to classify whether the drugs are sensitive in the cell lines. Another focus of the existing methods is on effectively using genomics information on cell lines and features on drugs to improve regression [15], [12]. For example, in Ammad-ud-din *et al.* [20], a kernel is constructed on each type of drug and cell line features to measure their respective similarities, and drug sensitivity is predicted from the combination of projected drug kernels and cell line kernels.

The existing regression based methods for drug selection may suffer from the fact that the regression accuracy is largely affected by insensitive drugs, and therefore, accurate drug sensitivity regression does not necessarily lead to accurate drug selection (prioritization). This is because in regression models, in order to achieve small regression errors, the majority of drug response values in a cell line needs to be fit well. However, when insensitive drugs constitute the majority in each cell line, which is becoming common as the advanced technologies are enabling screenings over large collections of small molecules (e.g., in the Library of Integrated Network-Based Cellular Signatures (LINCS) [5]), it is very likely that the regression sacrifices its accuracies on a very few but sensitive drugs in order to achieve better accuracies on the majority insensitive drugs, and thus smaller total errors on all drugs overall. This situation is even more likely when the cell line response values on sensitive drugs follow a very different distribution, and thus appear like outliers [21], than that from insensitive drugs, which is also very often the case. Fig. 2 presents a typical distribution of cell line (LS123 from Cancer Therapeutics Response Portal (CTRP v2) [6]) responses to drugs. In Fig. 2, lower cell line response scores indicate higher drug sensitivities. It is clear in Fig. 2 that top most sensitive drugs (in red in the figure) have sensitivity values of a different distribution than the rest. When cell line responses on sensitive drugs cannot be accurately predicted by regression models, it will further lead to imprecise drug selection or prioritization (e.g., sensitive drugs may be predicted as insensitive).

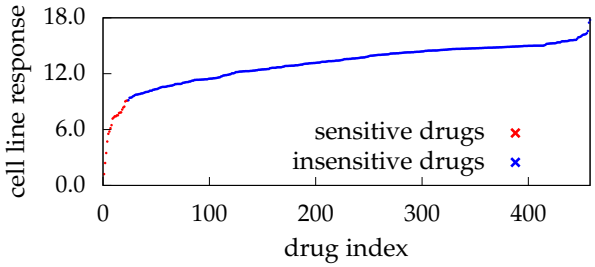


Fig. 2: Exemplar cell line response score distribution

Instead, ranking methods represent a more natural and effective alternative so as to directly prioritize and select drugs. In order to enable drug selection, in the end, a sorted/ranking order of drugs needs to be in place. Accurate predicted cell line response values on drugs can serve to sort/rank drugs in order. However, any other scores can also serve the purpose as long as they produce desired drug orders. This provides the opportunity for learning-to-rank methods for drug selection, which focus on learning the drug ranking structures directly (via using certain scores to sort drugs). Actually, regression based drug selection corresponds to point-wise learning to rank, which has been demonstrated [22] to perform suboptimally compared to pairwise and listwise ranking methods. Detailed literature review on learning to rank is available in Section 2 (additional references are available in Section S8 in the supplementary materials).

The rest of the manuscript is organized as follows. Section 2 presents the literature review on learning-to-rank methods. Section 3 presents the new pLETORg method. Section 4 presents the materials used in experiments. Section 5 presents the experimental results. Section 6 presents the conclusions.

2 Literature Review on Learning to Rank

Learning to Rank (LETOR) [23] focuses on developing machine learning methods and models that can produce accurate rankings of interested instances, rather than using

3. https://dtp.cancer.gov/databases_tools/docs/compare/compare_methodology.htm
4. https://www.ncbi.nlm.nih.gov/books/NBK91994/
5. http://www.lincsproject.org/
6. https://portals.broadinstitute.org/ctrp/

pre-defined scoring functions to sort the instances. LETOR is the key enabling technique in information retrieval [24]. Existing LETOR methods fall into three categories: 1). pointwise methods [22], which learn a score on each individual instance that will be used to sort/rank all the instances; 2). pairwise methods [25], which optimize pairwise ranking orders among all instances to induce good ranking orders among the instances; and 3) listwise methods [26], which model the full combinatorial structures of ranking lists. It has been demonstrated [22] that pairwise and listwise ranking methods outperform pointwise methods in general. This is because in pairwise and listwise methods, the ordering structures among instances are leveraged in learning, whereas in pointwise methods, no ordering information is used. Moreover, listwise methods are more computationally challenging than the others, due to the combinatorial nature of ranking lists as a whole. Thus, pairwise methods are the choice in many ranking problems, given the trade-off between ranking performance and computational demands.

The idea of using LETOR approaches to prioritize compounds has also drawn some recent attention [27], [28], [29]. For example, Agarwal *et al.* [30] developed bipartite ranking [31] to rank chemical structures for Structure-Activity-Relationship (SAR) modeling such that active compounds and inactive compounds are well separated in the ranking lists. Liu and Ning [29] developed a ranking method with bi-directional powered push strategy to prioritize selective compounds from multiple bioassays. However, LETOR has not been widely used in prioritizing drugs in computational medicine domain.

In LETOR, a particular interest is to improve the performance on the top of the ranking lists [32], [33], that is, instead of optimizing the entire ranking structures, only the top of the ranking lists will be optimized (i.e., to rank the most relevant instances on top), while the rest of the ranking lists, particularly the bottom of the ranking lists, is of little interest. An effective technique to enable good ranking performance on top in LETOR is via push [34], [35], [27]. The key idea is to explicitly push relevant instances onto top during optimization. Various optimization algorithms are developed to deal with the non-trivial objective functions when push is involved [25], [36].

3 METHODS

We propose the joint push and LEarning TO Rank with genomics regularization (pLETORg) for drug prioritization and selection. The pLETORg method learns and uses latent vectors of drugs and cell lines to score each drug in a cell line, and ranks the drugs based on their scores (Section 3.1). During the learning process, pLETORg explicitly pushes the sensitive drugs on top of the ranking lists that are produced by the prospective latent vectors (Section 3.2), and optimizes the ranking orders among sensitive drugs (Section 3.3) simultaneously. In addition, pLETORg uses genomics information on cell lines to constrain cell line latent vectors (Section 3.4). The following sections describe pLETORg in detail. The supplementary materials are available online[7].

Table 1 presents the key notations used in the manuscript. In this manuscript, drugs are indexed by i and j, and cell lines are indexed by p and q. We use d^+/d^- to indicate sensitive/insensitive drugs (sensitivity labeling will be discussed later in Section 4.1.2) in a certain cell line, for example, $d_i^+ \in \mathcal{C}_p$ or $d_i \in \mathcal{C}_p^+$ indicates that drug d_i is sensitive in cell line $\mathcal{C}_p$. Cell line is neglected when no ambiguity arises.

TABLE 1: Notations

notation	meaning
$\mathcal{C}_p$	cell line p
d_i	drug i
d^+/d^-	a sensitive/insensitive drug in a cell line
$\mathcal{C}_p^+/\mathcal{C}_p^-$	the set of sensitive/insensitive drugs in $\mathcal{C}_p$
n_p^+/n_p^-	the size of $\mathcal{C}_p^+/\mathcal{C}_p^-$
$\mathbf{u}_p/\mathbf{v}_i$	latent vector for cell line $\mathcal{C}_p$/drug d_i
m/n	the total number of cell lines/drugs

3.1 Drug Scoring

We model that the ranking of drugs in terms of their sensitivities in a cell line is determined by their latent scores in the cell line. The latent score of drug d_i in cell line $\mathcal{C}_p$, denoted as $f_p(d_i)$, is estimated as the dot product of d_i's latent vector $\mathbf{v}_i \in \mathbb{R}^{l\times 1}$ and $\mathcal{C}_p$'s latent vector $\mathbf{u}_p \in \mathbb{R}^{l\times 1}$, where l is the latent dimension, that is,

$$f_p(d_i) = f(d_i, \mathcal{C}_p) = \mathbf{u}_p^{\mathsf{T}}\mathbf{v}_i, \tag{1}$$

where $f(d, \mathcal{C})$ is the dot-product scoring function, and the latent vectors $\mathbf{u}_p$ and $\mathbf{v}_i$ will be learned. Then all the drugs are sorted based on their scores in $\mathcal{C}_p$. The most sensitive drugs in a cell line will have the highest scores and will be ranked higher than insensitive drugs. Thus, drug selection in pLETORg is to identify optimal drug and cell line latent vectors that together produce preferable cell line-specific drug scores and rankings. Note that in pLETORg, we look for scores $f_p(d_i)$ as long as they can produce correct drug rankings, but these scores are not necessarily identical to drug sensitivity values (e.g., shifted drug sensitivity values can also produce perfect drug rankings). In addition, the scoring scheme is similar to that used in some matrix factorization approaches in recommender systems research [37]. However, the latent vectors $\mathbf{u}$ and $\mathbf{v}$ will be learned via learning the top ranking structures (as will be discussed later), not through factorizing the cell line-drug matrix.

3.2 Pushing up Sensitive Drugs

To enforce the high rank of sensitive drugs, we leverage the idea of ranking with push [35]. The key idea is to quantitatively measure the ranking positions of drugs, and look for ranking models that can optimize such quantitative measurement so as to rank sensitive drugs high and insensitive drugs low. In pLETORg, we use the height of an insensitive drug d_i^- in $\mathcal{C}_p$, denoted as $h_f(d_i^-, \mathcal{C}_p)$, to measure its ranking position in $\mathcal{C}_p$ [35] as follows,

$$h_f(d_i^-, \mathcal{C}_p) = \sum_{d_j^+ \in \mathcal{C}_p^+} \mathbb{I}(f_p(d_j^+) \leq f_p(d_i^-)), \tag{2}$$

where $\mathcal{C}_p^+$ is the set of sensitive drugs in cell line $\mathcal{C}_p$, f is the drug scoring function (Equation 1), $f_p(d_j^+)$ and $f_p(d_i^-)$ are the scores of d_j^+ and d_i^- in $\mathcal{C}_p$, respectively, and $\mathbb{I}(x)$ is

7. http://cs.iupui.edu/~liujunf/projects/CCLERank/

the indicator function ($\mathbb{I}(x) = 1$ if x is true, otherwise 0). Essentially, $h_f(d_i^-, \mathcal{C}_p)$ is the number of sensitive drugs that are ranked below the insensitive drug d_i^- in cell line $\mathcal{C}_p$ by the scoring function f.

To push sensitive drugs higher in a cell line, it is to minimize the total height of all insensitive drugs in that cell line To push sensitive drugs higher in a cell line, the total height of all insensitive drugs in that cell line should be minimized (i.e., minimize the total number of sensitive drugs that are ranked below insensitive drugs). Thus, for all the cell lines, it is to minimize their total heights, denoted as $P_f^{\uparrow}$, that is,

$$P_f^{\uparrow} = \sum_{p=1}^{m} \frac{1}{n_p^+ n_p^-} \sum_{d_i^- \in \mathcal{C}_p} h_f(d_i^-, \mathcal{C}_p), \tag{3}$$

where m is the number of cell lines, and n_p^+ and n_p^- are the numbers of sensitive and insensitive drugs in cell line $\mathcal{C}_p$. The normalization by n_p^+ and n_p^- is to eliminate the effects from different cell line sizes.

3.3 Ranking among Sensitive Drugs

In addition to pushing sensitive drugs on top of insensitive drugs, we also consider the ranking orders among sensitive drugs in order to enable fine-grained prioritization among sensitive drugs. Specifically, we use $d_i \succ_R d_j$ to represent that d_i is ranked higher than d_j in the relation R. We use concordance index (CI) to measure drug ranking structures compared to the ground truth, which is defined as follows,

$$\texttt{CI}(\{d_i\}, \mathcal{C}, f) = \frac{1}{|\{d_i \succ_{\mathcal{C}} d_j\}|} \sum_{d_i \succ_{\mathcal{C}} d_j} \mathbb{I}(d_i \succ_f d_j), \tag{4}$$

where $\{d_i\}$ is the set of drugs in cell line $\mathcal{C}$, $\{d_i \succ_{\mathcal{C}} d_j\}$ is the set of ordered pairs of drugs in cell line $\mathcal{C}$ ($d_i \succ_{\mathcal{C}} d_j$ represents that d_i is more sensitive, and thus ranked higher, than d_j in $\mathcal{C}$), f is the scoring function (Equation 1) that produces an estimated drug ranking, $d_i \succ_f d_j$ represents that d_i is ranked higher than d_j by f, and $\mathbb{I}$ is the indicator function. Essentially, CI measures the ratio of correctly ordered drug pairs by f among all possible pairs. Higher CI values indicate better ranking structures.

To promote correct ranking orders among sensitive drugs in all the cell lines, we minimize the objective O_f^+, defined as the sum of $1 - \texttt{CI}$ values (i.e., the ratio of misordered drug pairs among all pairs) over the sensitive drugs of all the cell lines, as follows,

$$\begin{aligned} O_f^+ &= \sum_{p=1}^{m} [1 - \texttt{CI}(\{d_i^+\}, \mathcal{C}_p, f)] \\ &= \sum_{p=1}^{m} \frac{1}{|\{d_i^+ \succ_{\mathcal{C}_p} d_j^+\}|} \sum_{d_i^+ \succ_{\mathcal{C}_p} d_j^+} \mathbb{I}(d_i^+ \prec_f d_j^+). \end{aligned} \tag{5}$$

3.4 Overall Optimization Problem for pLETORg

Overall, we seek the cell line latent vectors and drug latent vectors that will be used in drug scoring function f (Equation 1) such that for each cell line, the sensitive drugs will be ranked on top and in right orders using the latent vectors. In pLETORg, such latent vectors are learned by solving the following optimization problem:

$$\min_{U,V} \mathcal{L}_f = (1-\alpha) P_f^{\uparrow} + \alpha O_f^+ + \frac{\beta}{2} R_{uv} + \frac{\gamma}{2} R_{\text{csim}}, \tag{6}$$

where $\mathcal{L}_f$ is the overall loss function; $P_f^{\uparrow}$ and O_f^+ are defined in Equation 3 and Equation 5, respectively; $U = [\mathbf{u}_1, \mathbf{u}_2, \cdots, \mathbf{u}_m]$ and $V = [\mathbf{v}_1, \mathbf{v}_2, \cdots, \mathbf{v}_n]$ are the latent vector matrices for cell lines and drugs, respectively ($U \in \mathbb{R}^{l \times m}$, $V \in \mathbb{R}^{l \times n}$, where l is the latent dimension); α ($\alpha \in [0, 1]$) is a weighting parameter to control the contribution from push (i.e., $P_f^{\uparrow}$) and ranking (i.e., O_f^+); β and γ are regularization parameters ($\beta \geq 0$, $\gamma \geq 0$) on the two regularizers R_{uv} and R_{csim}, respectively.

In Problem 6, R_{uv} is a regularizer on U and V to prevent overfitting, defined as

$$R_{uv} = \frac{1}{m} \|U\|_F^2 + \frac{1}{n} \|V\|_F^2, \tag{7}$$

where $\|X\|_F$ is the Frobenius norm of matrix X. R_{csim} is a regularizer on cell lines to constrain cell line latent vectors, defined as

$$R_{\text{csim}} = \frac{1}{m^2} \sum_{p=1}^{m} \sum_{q=1}^{m} w_{pq} \|\mathbf{u}_p - \mathbf{u}_q\|_2^2, \tag{8}$$

where w_{pq} is the similarity between $\mathcal{C}_p$ and $\mathcal{C}_q$ that is calculated using genomics information of the cell lines (e.g., gene expression information). The underlying assumption is that if two cell lines have similar patterns in their genomics data (i.e., large w_{pq}), they will be similar in their cell line response patterns, and thus similar latent vectors [17].

The Problem 6 involves an indicator function (in Equation 2, 4), which is not continuous or smooth. Thus, we use the logistic function as its surrogate [34], that is,

$$\mathbb{I}(x \leq y) \approx \log[1 + \exp(-(x-y))] = -\log \sigma(x-y), \tag{9}$$

where $\sigma(x)$ is a sigmoid function, that is, $\sigma(x) = \frac{1}{1+\exp(-x)}$. The optimization algorithm for pLETORg optimization is presented in Algorithm S1 in supplementary materials. We use alternating minimization with gradient descent (details in Section S2 in supplementary materials) to solve the optimization Problem 6.

Since the number of drugs pairs is quadratically larger than the number of drugs, it could be computationally expensive to use all the drug pairs during training. To solve this issue, we develop a sampling scheme. During each iteration of training, we use all the sensitive drugs in each cell line but randomly sample a same number of insensitive drugs from each respective cell line. This process is repeated for a number of times and then the average gradient is used to update U and V. This sampling scheme will significantly speed up the optimization process.

4 Materials

4.1 Dataset and Experimental Protocol

We use the cell line data and drug sensitivity data from Cancer Cell Line Encyclopedia (CCLE) [8] and Cancer Therapeutics Response Portal (CTRP v2) [9] (both accessed on 10/14/2016), respectively. CTRP provides the cell line responses to different drugs. The response is measured using

8. https://portals.broadinstitute.org/ccle/home
9. https://portals.broadinstitute.org/ctrp/

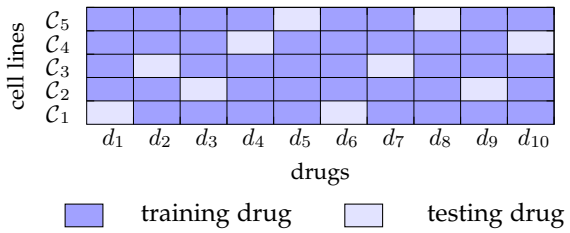


Fig. 3: Data split for 5-fold cross validation

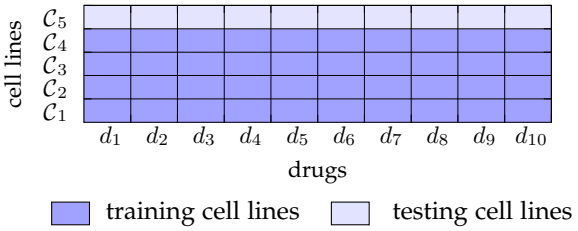


Fig. 4: Data split for testing new cell lines

TABLE 2: Dataset Description

m	n	#genes	#AUCs	#mAUCs	$\#d/\mathcal{C}$	$\#\mathcal{C}/d$
821	545	20,068	357,052	90,393	435	655

The columns of "m", "n" and "#genes" have the number of cell lines, drugs and genes in the dataset, respectively. The columns of "#AUCs" and "#mAUCs" have the total number of available response values and missing response values, respectively. The column of "$\#d/\mathcal{C}$" has the average number of available drug response values per cell line. The column of "$\#\mathcal{C}/d$" has the average number of cell lines that have response values for each drug.

area-under-concentration-response curve (AUC) sensitivity scores. Lower response (AUC) scores indicate higher drug sensitivities. CCLE provides the expression information over a set of genes for each of the cell lines. Larger expression values indicate higher gene expression levels. CCLE also provides other omics data for the cell lines (e.g., copy number variations). In this manuscript, we only use gene expression information, as it is demonstrated as the most pertinent to cell line response [17]. The use of other omics data will be explored in the future research. This dataset has large numbers of both cell lines and drugs. Table 2 presents the description of the dataset used in the experiments. Note that in the dataset, about 20% of the drug sensitivity values are missing. For the drugs which do not have response values in a cell line, we do not use the drugs in learning the corresponding cell line latent vector.

4.1.1 Experimental Setting

We had two experimental settings for the experiments.

4.1.1.1 N-Fold Cross Validation: In the first setting, we split drug sensitivity data for each cell line into a training and a testing set, and conduct 5-fold cross validation to evaluate model performance. Fig. 3 demonstrates the training-testing splits. For each cell line, its drug sensitivity data are randomly split into 5 folds. One of the 5 folds is used as testing set and the other four folds are used for training. This is done 5 times, until each of the five folds has served as testing data. The final results are the average over the 5 folds. This experimental setting corresponds to the application scenario in which additional drugs (i.e., the testing data) need to be selected for each cell line/patient.

During the data split, we ensure that for each of the drugs, there is at least one cell line in the training set that has response information for that drug. This is to avoid the situation in which drugs in the testing set do not have information during training, or the use scenario in which brand-new compounds need to be selected for further testing. The latter will be studied in future research. We also ensure that each cell line has drug sensitivities in the training set to avoid the situation of brand-new cell lines. This situation will be studied in the second experimental setting.

4.1.1.2 Leave-Out Validation: We also conduct experiments in a different setting as indicated in Fig. 4, that is, we hold out entire cell lines into the testing data so that in training data, the held-out cell lines have no drug response information at all. This corresponds to the use scenario to select sensitive drugs for new cell line/new patients. Details on how to hold out cell lines will be discussed later in Section 5.3.

4.1.2 Sensitivity Labeling Scheme

4.1.2.1 Labeling Scheme for N-Fold Cross Validation: In the 5-fold setting (Fig. 3), for each cell line, we use a certain percentile θ (e.g., θ=5) of all its response values in the training set as a threshold to determine drug sensitivity in that cell line. Thus, the sensitivity threshold is cell line specific. It is only selected from the training data of respective cell lines (i.e., testing data are not used to determine the threshold as they are considered as unknown during training). Drugs in both the training set and testing set are then labeled as sensitive in the respective cell line if the cell line has lower response values on the drugs than the threshold (lower AUC scores indicate higher sensitivity), otherwise, the drugs are labeled as insensitive. The reason why a cell-line-specific percentile threshold is used for sensitivity labeling is that there lacks a pre-defined threshold of sensitivity scores for each of the cell lines to determine sensitivity labels. Meanwhile, given the heterogeneity of cell lines, we cannot apply the same threshold for different cell lines. The idea of using sensitivity score percentile as a threshold is very similar to that in Speyer *et al.* [21], in which the outliers with low sensitivity scores are labeled as sensitive.

4.1.2.2 Labeling Scheme for Testing New Cell Lines: In the second setting with new cell lines (Fig. 4), since the new cell lines have no drug response information in training, we use a percentile threshold from the testing data (i.e., the new cell lines; the ground truth) to label sensitivities of the drugs in the new cell lines.

4.2 Baseline Methods

We use two strong baseline methods for comparison: the Bayesian Multi-Task Multi-Kernel Learning (`BMTMKL`) method and the Kernelized Rank Learning (`KRL`) method.

4.2.1 Bayesian Multi-Task Multi-Kernel Learning (`BMTMKL`)

`BMTMKL` [17], winning method for DREAM 7 challenge [10], was originally developed to rank cell lines with respect to

10. http://dreamchallenges.org/project/dream-7-nci-dream-drug-sensitivity-prediction-challenge/

a drug based on their responses to the drug. In BMTMKL, cell line ranking for each drug is considered a task. All the cell line rankings are learned simultaneously in a multi-task learning framework. Multiple kernels are constructed from multiple types of omics data for cell lines to quantify their similarities. The multi-task and multi-kernel learning is conducted within a kernelized regression with Bayesian inference for parameter estimation. Thus, BMTMKL predicts drug response values via the regression and uses the values for cell line ranking, that is, BMTMKL is a point-wise learning-to-rank method.

Note that the drug ranking problem we are tackling in this manuscript is a different problem compared to the cell line ranking problem that BMTMKL is designed to tackle. The cell line ranking problem corresponds to the application scenario in which cell lines/patients need to be selected to test a given drug. The drug ranking problem corresponds to the application scenario in which drugs need to be selected to treat a given cell line/patient. Still, BMTMKL can be used on drug ranking problems by switching the roles of "drugs" and "cell lines", and the predicted drug response values can also be used for drug ranking.

4.2.2 Kernelized Rank Learning (KRL)

KRL [13] learns a ranking structure of drugs in each cell line by approximating the sensitivity values of drugs in the cell line via a kernelized regression. The kernel matrix is constructed from the gene expression profiles of cell lines. During learning, KRL optimizes the Normalized Discounted Cumulative Gain (NDCG@k) [10], a popular metric in learning to rank, to rank the most sensitive drugs of each cell line among top k of the drug ranking list. Therefore, KRL is a list-wise learning-to-rank method.

4.3 Evaluation Metrics

We first introduce the evaluation metrics that are used in most of the experiments. Other metrics that are used in specific experiments will be introduced later when they are applied. The first metric that we use to evaluate the performance of BMTMKL and pLETORg is the average-precision at k (AP@k) [10]. It is defined as the average of precisions that are calculated at each ranking position of sensitive drugs that are ranked among top k in a ranking list, that is,

$$\text{AP@}k(\{d_i\},\mathcal{C},f)=\frac{\sum_{j=1}^{k}\text{Prec}(\{d_{\vec{1}},\cdots,d_{\vec{j}}\},\mathcal{C}^+,f)\cdot\mathbb{I}(d_{\vec{j}}\in\mathcal{C}^+)}{\sum_{j=1}^{k}\mathbb{I}(d_{\vec{j}}\in\mathcal{C}^+)}, \tag{10}$$

where $d_{\vec{j}}$ is the drug that is ranked at position j by f, $\mathbb{I}(d_{\vec{j}}\in\mathcal{C}^+)$ checks whether $d_{\vec{j}}$ is sensitive in $\mathcal{C}$ in the ground truth, and Prec is defined as

$$\text{Prec}(\{d_{\vec{1}},\cdots,d_{\vec{j}}\},\mathcal{C}^+,f)=\sum_{i=1}^{j}\mathbb{I}(d_{\vec{i}}\in\mathcal{C}^+)/j, \tag{11}$$

that is, it is calculated as the ratio of sensitive drugs among top-j ranked drugs. Thus, AP@k considers the ranking positions of sensitive drugs that are ranked among top k of a ranking list. It is a popular metric to evaluate LETOR methods. Higher AP@k values indicate that the sensitive drugs are ranked higher on average.

We define a second metric average-hit at k (AH@k) as the average number of sensitive drugs that are ranked among top k of a ranking list, that is,

$$\text{AH@}k(\{d_i\},\mathcal{C},f)=\sum_{j=1}^{k}\mathbb{I}(d_{\vec{j}}\in\mathcal{C}^+). \tag{12}$$

Higher AH@k values indicate that more sensitive drugs are ranked among top k.

We also use CI as defined in Equation 4 to evaluate the ranking structures among only sensitive drugs. In this case, we denote CI specifically as sCI (i.e., CI for sensitive drugs), and thus by default, CI evaluates the entire ranking structures of both sensitive and insensitive drugs, and sCI is only for sensitive drugs. Note that sCI (CI) and AP@k measure different aspects of a ranking list. The sCI (CI) metric measures whether the ordering structure of a ranking list is close to its ground truth, while AP@k measures whether the relevant instances (i.e., sensitive drugs in this manuscript) are ranked on top. A high AP@k does not necessarily indicate the ordering among the top-ranked drugs is correct. Similarly, a high sCI (CI) does not necessarily lead to that the most sensitive drugs being ranked on top, particularly when there are many insensitive drugs in the list. In this manuscript, both the drug sensitivity and the ordering of sensitive drugs are of concern. That is, we would like to ensure that sensitive drugs are ranked higher than insensitive drugs, and meanwhile, the sensitive drugs are well ordered in terms of their relative sensitivities (i.e., among all sensitive drugs, drugs that are more sensitive are ranked higher than those that are less sensitive).

4.4 Gene Selection and Cell Line Similarities

We use gene expression information to measure cell line similarities (i.e., w_{pq} as in Equation 8) and regularize our ranking models (i.e., $w_{pq}\|\mathbf{u}_p-\mathbf{u}_q\|_2^2$ as in Equation 8). It is well accepted that not all the genes are informative to cell line response to drugs [17], and thus we use ℓ_1 regularized linear regression to conduct feature selection over gene expression data to select informative genes with respect to each drug. It is well known that the ℓ_1 regularization will promote sparsity in the solution, in which the non-zero values will indicate useful independent variables (in our case, genes). To select informative genes, the gene expression values over all the cell lines are considered as independent variables and the response values on each drug from all the cell lines are considered as dependent variables. If a cell line has no response value on a drug, the gene expression information of that cell line is not used. A linear least-squares regression with ℓ_1 and ℓ_2 regularization (i.e., elastic net) is applied over these variables so as to select informative genes for each drug. The regularization parameters over the ℓ_1 regularizer and the ℓ_2 regularizer are identified via regularization path [38]. Fig. S1 in the supplementary materials demonstrates the regression method for gene selection. The union of all the selected genes for all the drugs will be used to calculate cell line similarities. In the end, 1,203 genes are selected. The list of the selected genes is available Section S9 in the supplementary materials. We

TABLE 3: Performance on Ranking New Drugs

sthr	method	parameters						performance					
$\theta = 2$	BMTMKL	α_b		β_b		usim	σ	AP@5	AH@5	AP@10	AH@10	sCI	CI
		1.0e-10		1.0e+10		RBF	10.0	**0.740**	**1.702**	**0.711**	**2.072**	**0.646**	**0.812**
	KRL	k		λ		usim	σ	AP@5	AH@5	AP@10	AH@10	sCI	CI
		10		1.0e-06		RBF	0.001	**0.753**	**1.784**	**0.725**	**2.137**	0.673	0.702
		10		1.0e-05		LIN	-	0.668	1.620	0.642	2.065	**0.683**	**0.745**
	pLETORg	l	α	β	γ	usim	σ	AP@5	AH@5	AP@10	AH@10	sCI	CI
		50	1.0	1.0	100.0	COS	-	0.686	1.606	0.663	1.938	**0.680**	0.770
		30	0.1	1.0	100.0	RBF	10.0	0.527	1.291	0.505	1.809	0.505	**0.805**
		10	0.0	0.1	100.0	COS	-	**0.783**	**1.856**	**0.758**	**2.159**	0.639	0.774
		10	0.0	0.1	0.0	COS	-	0.780	1.851	0.755	2.157	0.631	0.786
$\theta = 5$	BMTMKL	α_b		β_b		usim	σ	AP@5	AH@5	AP@10	AH@10	sCI	CI
		1.0e-10		1.0e+10		RBF	10.0	**0.828**	**2.736**	**0.772**	**3.761**	**0.652**	**0.812**
	KRL	k		λ		usim	σ	AP@5	AH@5	AP@10	AH@10	sCI	CI
		10		1.0e-06		RBF	0.001	**0.817**	**2.715**	**0.761**	**3.798**	0.676	0.762
		10		1.0e-04		LIN	-	0.789	2.580	0.730	3.690	**0.689**	0.756
		10		1.0e-05		RBF	0.0001	0.796	2.547	0.736	3.560	0.660	**0.768**
	pLETORg	l	α	β	γ	usim	σ	AP@5	AH@5	AP@10	AH@10	sCI	CI
		50	1.0	1.0	100.0	RBF	10.0	0.780	2.376	0.721	3.228	**0.699**	0.726
		30	0.5	0.1	100.0	COS	-	0.744	2.461	0.687	3.581	0.516	**0.810**
		50	0.0	0.1	100.0	COS	-	**0.857**	2.919	0.805	3.934	0.663	0.742
		10	0.5	1.0	100.0	RBF	10.0	0.855	**2.965**	**0.806**	**3.986**	0.658	0.804
		10	0.5	0.1	0.0	COS	-	0.855	2.965	0.806	3.985	0.658	0.804

The columns corresponding to "α_b", "β_b", "usim", and "σ" have the two hyperparameters, cell line similarity function, and parameter for RBF cell line similarity, respectively, for BMTMKL. The columns corresponding to "k", "λ", "usim", and "σ" have the two hyperparameters, cell line similarity function, and parameter for RBF cell line similarity, respectively, for KRL. The columns corresponding to "l", "α", "β", "γ", "usim", and "σ" have the latent dimension, weighting factor, latent vector regularization parameter, cell line similarity regularization parameter, cell line similarity function, and parameter for RBF cell line similarity, respectively, for pLETORg. The best performance of each method under each metric is in **bold**. The best performance of both the methods under each metric is underscored.

use cosine similarity function (COS) and radial basis function (RBF) over the selected genes (these genes are considered as cell line features) to calculate the similarities between cell lines. For KRL, we also use a linear kernel (LIN), following the experimental setting as in He *et al.* [13], to calculate cell line similarities over the selected genes.

5 Experimental Results

5.1 Ranking New Drugs

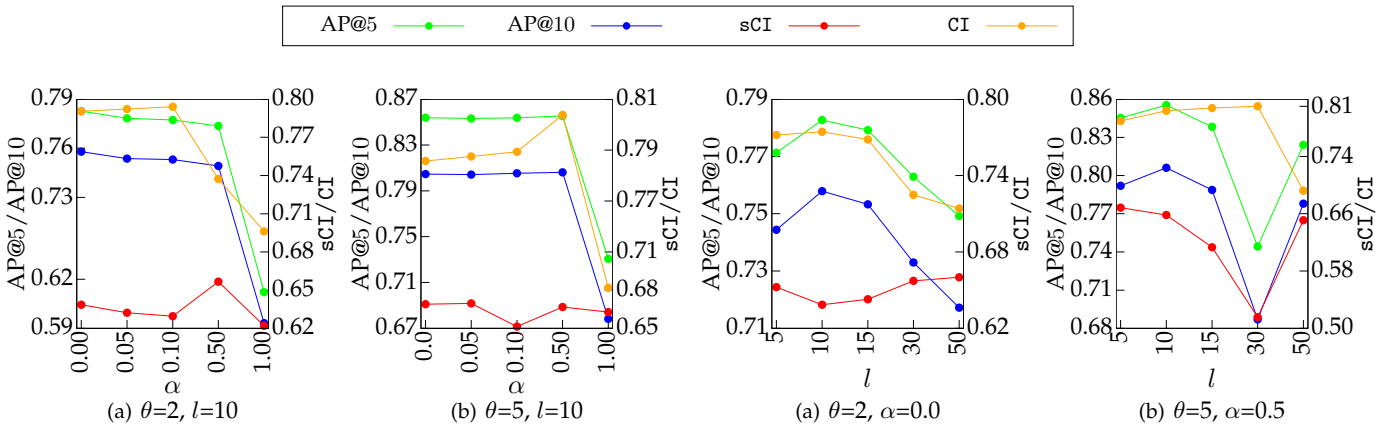
We first compare the performance of BMTMKL, KRL and pLETORg on ranking new drugs in each cell line (i.e., ranking testing drugs among themselves in each cell line). The experiments follow the protocol as indicated in Fig. 3. Note that notion of "new drugs" is with respect to each cell line, and a new drug in a cell line could be known in a different cell line.

We use 2 percentile (i.e., θ=2) and 5 percentile (i.e., θ=5) as discussed in Section 4.1.2 to label sensitivity. Although the baseline methods and pLETORg do not rely on specific labeling schemes, the small percentiles make the drug selection problem realistic. This is because in real practice, only the top few most sensitive drugs will be of great interest. However, given that the sensitive drugs are few, the drug selection problem is very non-trivial.

For the baseline methods and pLETORg we conduct a grid search for each of their parameters, and present the results that correspond to the best parameter combinations. The full set of experimental results over all parameters is available in Table S2, S3, S4, S5, S6 and S7 in the supplementary materials. Table 3 presents the overall performance.

5.1.1 Overall Comparison

5.1.1.1 2 Percentile as Sensitivity Threshold: When 2 percentile of the response values (i.e., θ=2) in training data is used as the sensitivity threshold, pLETORg achieves its best AP@5 value 0.783, and it is 5.81% higher than the best AP@5 value 0.740 of BMTMKL (p-value=3.565e-8), and 3.98% higher than the best AP@5 value 0.753 of KRL (p-value=9.400e-3). In terms of AP@10, pLETORg achieves its best value 0.758, and it is 6.61% higher than 0.711 of BMTMKL (p-value=7.994e-10) and 4.55% higher than the best AP@10 value 0.725 of KRL (p-value=6.811e-4). Meanwhile, pLETORg achieves higher AH@5 and AH@10 compared to those of BMTMKL (1.856 vs 1.702, p-value=3.379e-11; 2.159 vs 2.072, p-value=5.805e-8) and compared to those of KRL (1.856 vs 1.784, p-value=2.900e-3; 2.159 vs 2.137, p-value=5.489e-1). In particular, pLETORg achieves its best AP@k and AH@k values when α=0.0, that is, when the push term $P_f^{\uparrow}$ in Problem 6 is the only objective to optimize. The results demonstrate that pLETORg is strong in pushing more sensitive drugs on top of ranking lists and thus better prioritizes sensitive drugs for drug selection. On the contrary, BMTMKL focuses on accurately predicting the response value of each drug in each cell line. However, accurate pointwise response prediction does not guarantee that the most sensitive drugs are promoted onto the top of ranking lists in BMTMKL. KRL focuses on optimizing NDCD@k among top-k ranked drugs. However, it may heavily rely on the definition



(a) θ=2, l=10 (b) θ=5, l=10

Fig. 5: Performance of pLETORg w.r.t. the Push Parameter α

(a) θ=2, α=0.0 (b) θ=5, α=0.5

Fig. 6: Performance of pLETORg w.r.t. the Latent Dimension l

of the "gain" of a drug at a certain position, and thus larger gain may not directly lead to more sensitive drugs on top.

On the other hand, pLETORg achieves an sCI value 0.639 when it achieves its best AP@k values (i.e., when l=10, α=0.0, β=0.1 and γ=100.0 for pLETORg). Compared to the sCI value 0.646 of BMTMKL when BMTMKL achieves its best AP@k values, pLETORg does not outperform BMTMKL on sCI. However, the difference is not significant (-1.08% increase; p-value=3.117e-1). Note that when α=0.0, the ranking orders among sensitive drugs are not explicitly optimized in Problem 6. Despite this, pLETORg is able to produce ranking orders that are very competitive to those from BMTMKL. In terms of sCI, the best performance of pLETORg (0.680) and the best performance of BMTMKL (0.646) are both worse than that of KRL (0.683) (for pLETORg, -0.44% increase with p-value=5.480e-1; for BMTMKL, -5.42% increase with p-value=4.900e-3). Given the low AP@k and AH@k values of KRL, this may indicate that KRL tends to sort sensitive drugs slightly better than pLETORg and BMTMKL, but does not necessarily rank them on top. Different from KRL, pLETORg is able to prioritize sensitive drugs on top while maintaining the orders among sensitive drugs reasonably well, which is a preferred scenario in drug selection.

In addition, pLETORg achieves a CI value 0.774 together with its best AP@k values, but BMTMKL achieves a CI value 0.812 with its best AP@k values, which is significantly better (4.91% better than pLETORg, p-value=1.966e-123). As a matter of fact, the best CI value that pLETORg ever achieves (i.e., 0.805 when l=30, α=0.1, β=1.0, γ=100.0) is still significantly worse than that of BMTMKL (i.e., 0.812, p-value=4.862e-6). As BMTMKL optimizes the predicted response values, the results indicate that BMTMKL is able to reproduce the entire drug ranking structures well using the predicted values. Different from BMTMKL, pLETORg aims to push only sensitive drugs on top of the ranking structures and optimize only the ranking structures of those sensitive drugs (when $\alpha > 0$). Therefore, pLETORg is not able to well estimate the entire ranking structures for both sensitive and insensitive drugs. However, in drug selection, the top ranked drugs could be of great interest compared to those lower-ranked drugs, and therefore, the low CI performance of pLETORg can be compensated by its high sCI, AP@k and AH@k values. Compared to pLETORg and BMTMKL, KRL achieves the worst CI (0.745). Given the fact that KRL does not model the ranking relations among insensitive drugs, and considered also its high sCI values and median AP@k values, this result may indicate that KRL tends to rank some drugs that are very insensitive higher than sensitive drugs and higher than the drugs that are less insensitive.

5.1.1.2 5 Percentile as Sensitivity Threshold: When 5 percentile of the response values (i.e., θ=5) is used as the sensitivity threshold, pLETORg shows similar behaviors as in 2 percentile case. That is, in terms of AP@5, pLETORg (0.855 when l=10, α=0.5, β=0.1 and γ=100.0; 0.857 when l=50, α=0.0, β=0.1 and γ=100.0) outperforms BMTMKL (0.828) at 3.26% (p-value=2.479e-6), in terms of AP@10 at 4.40% (0.806 vs 0.772; p-value=1.511e-11), and in terms of AH@5 at 8.37% (2.965 vs 2.736; p-value=2.019e-16) and AH@10 at 5.98% (3.986 vs 3.761; p-value=2.23e-18). When pLETORg achieves its best AP@k and AH@k, in terms of sCI, pLETORg achieves similar performance as BMTMKL (0.658 vs 0.652; p-value=2.500e-1), and in terms of CI, pLETORg is significantly worse than BMTMKL (0.804 vs 0.812; p-value=3.341e-10). KRL performs similarly at θ=5 as at θ=2, that is, on average, it is worse than pLETORg at AP@k, AH@k and CI, but slightly better at sCI when both achieve their optimal AP@k and AH@k.

In particular, the AP@5 and AP@10 improvement for pLETORg at θ=2 is larger than that at θ=5, respectively (i.e., 5.81% vs 3.26% at AP@5, 6.61% vs 4.40% at AP@10). This indicates that pLETORg is good at prioritizing drugs particularly when there are a small number of sensitive drugs. Note that in Table 3, for θ=2 and θ=5, the CI values in BMTMKL are identical. This is because BMTMKL does not use labels in training, and its performance in terms of CI does not depend on labels. On the contrary, sCI depends on the labels as it only measures CI within sensitive drugs. Therefore, sCI values of BMTMKL for θ=2 and θ=5 are different. However, pLETORg relies on labels during push and ranking in order to learn the models, and thus, labels will affect its performance in both CI and sCI.

In Table 3, the optimal pLETORg results always correspond to non-zero γ values (i.e., the parameter on cell line similarity regularizer in Problem 6). This indicates that cell line similarities calculated from the gene expression information are able to help improve the ranking of drug sensitivities in pLETORg. The results in Table 3 also show that the optimal performance of pLETORg is from a relatively

small latent space with l=10. This may be due to the fact that the sampling scheme significantly reduces the size of training instances, and thus small latent vectors are sufficient to represent the learned information for drug prioritization.

5.1.2 Performance of pLETORg over Push Powers

Fig. 5 presents the best pLETORg performance on each of the four metrics with respect to different push parameter α's when l=10 (i.e., the latent dimension corresponding to the best AP@k values in Table 3). Fig. 5(a) and 5(b) show that in general as α increases (i.e., decreasing emphasis on pushing sensitive drugs on top), AP@k values decrease. When α=1.0, that is, no push takes effect, the AP@k values become lower than those when $\alpha < 1$. This demonstrates the effect of the push mechanism in prioritizing sensitive drugs in pLETORg. The figures also show that the optimal sCI values are achieved when $\alpha \in (0, 1)$, but not at α=1.0 when the ranking structure among sensitive drugs is the only focus. This is probably due to that the ranking difference between sensitive and insensitive drugs involved in the push term $P_f^{\uparrow}$ can also help improve the ranking among sensitive drugs. In addition, the figures show that the optimal CI values are achieved when $\alpha \in (0, 1)$. This is because with very small α values, sensitive drugs are strongly pushed but it does not necessarily result in good ranking structures among all sensitive and insensitive drugs. Similarly, when α is very large, the ranking structures among only sensitive drugs are highly optimized, which does not necessarily lead to good ranking structures among all drugs either. Thus, the best overall ranking structures are achieved under a combinatorial effect of both the push and the sensitive drug ranking.

5.1.3 Performance of pLETORg over Latent Dimensions

Fig. 6 presents the best pLETORg performance on each of the four metrics with respect to different latent dimension l. Fig. 6(a) and 6(b) show that in general, small latent dimensions (e.g., l in 10 to 15) are sufficient in order to achieve good results on drug ranking. We interpret each dimension in the drug latent vectors and cell line latent vectors as to represent a certain latent feature that together determine drug rankings in each cell line. Thus, the small latent dimensions indicate that the learned latent vectors are able to capture latent features that are specific to drugs and cell lines.

On the other hand, as AP@k tends to decrease as l increases, sCI tends to increase. This indicates that larger l may enable better rankings among sensitive drugs, but not necessarily pushing sensitive drugs on top. Fig. 6 also shows that CI first increases and then decreases as l becomes larger, following an opposite trend of sCI. This demonstrates that good ranking structures among all the drugs do not directly indicate good ranking structures among sensitive drugs, and vice versa. We also notice that with α=0.5, pLETORg has better AP@k as l increases from 30 to 50. This is probably because sufficiently large latent dimensions could also capture the drug sensitivity information when the sensitivity threshold is relaxed (i.e., more drugs are considered as sensitive when θ=5 than those when θ=2). Even though, pLETORg still performs better at l=10 than at l=50 with θ=5. Considering computational costs, we do not explore other even larger latent dimensions.

5.2 Ranking New and Known Drugs

We evaluate the performance of pLETORg on ranking both new drugs (i.e., testing drugs) and known drugs (i.e., training drugs) together in the experimental setting as in Fig. 3. This corresponds to the use scenario in which new drugs need to be compared with known drugs so as to select the most promising drugs among all available (i.e., both new and known) drugs. In this case, we focus on evaluating whether most of the true sensitive drugs can be prioritized.

5.2.1 Evaluation Metrics

The evaluation is based on the following two specific metrics. The first metric, denoted as AT@k, measures among the top-k most sensitive drugs of each cell line in the ground truth (including both training and testing drugs), what percentage of them are ranked still among top k in the prediction, that is,

$$\text{AT@}k(\{d_i\}, \mathcal{C}, f) = \sum_{d_j \in \text{top-}k(\mathcal{C})} \frac{\mathbb{I}(d_{\overrightarrow{j}} \in \text{top-}k(\mathcal{C}))}{k}, \quad (13)$$

where $d_{\overrightarrow{j}}$ is the drug that is ranked at position j by f, and top-$k(\mathcal{C})$ is the set of top-k most sensitive drugs in cell line $\mathcal{C}$.

The second metric, denoted as NT@k, measures among the new drugs that should be among the top-k most sensitive drugs of each cell line in the ground truth, what percentage of them are ranked actually among top k in the prediction, that is,

$$\text{NT@}k(\{d_i\}, \mathcal{C}, f) = \frac{\sum_{d_j \text{ is new}} \mathbb{I}(d_{\overrightarrow{j}} \in \text{top-}k(\mathcal{C}))}{\sum_{d_j \text{ is new}} \mathbb{I}(d_j \in \text{top-}k(\mathcal{C}))}. \quad (14)$$

The reason why AP@k and AH@k are not used in this experimental setting is that they can be easily dominated by known drugs (i.e., training data). This is because they are defined for top-k ranked drugs. It is very likely that the top-k ranked drugs, when known and new drugs are considered together, are actually known drugs since they are explicitly optimized to be on top during the training process (for pLETORg and KRL). Different from AP@k and AH@k, AT@k and NT@k are defined as particular ratios over the sensitive drugs, which are from both training and testing data in this case, and thus less biased by the training data.

5.2.2 Overall Comparison

Table 4 presents top performance of BMTMKL, KRL and pLETORg in terms of AT@k and NT@k. The full set of experimental results is available in Table S8, S9, S10, S11, S12, and S13 in the supplementary materials. The results in Table 4 show that in terms of NT@k, pLETORg is able to achieve very similar results (when l=5) as BMTMKL and KRL, in which cases, pLETORg even achieves slightly better results on AT@k than BMTMKL and KRL when both BMTMKL

TABLE 4: Performance on Ranking New and Known Drugs (%)

sthr	method	parameters						performance			
-	BMTMKL	α_b		β_b		usim	σ	AT@5	AT@10	NT@5	NT@10
		1.0e0		1.0e0		RBF	10.0	**48.03**	**54.57**	47.57	54.00
		1.0e-10		1.0e-10		RBF	10.0	47.99	54.49	**47.62**	**54.01**
$\theta = 2$	KRL	k		λ		usim	σ	AT@5	AT@10	NT@5	NT@10
		10		1.0e-06		RBF	0.01	**78.88**	**78.24**	3.43	28.51
		10		50		LIN	-	45.64	51.44	**45.99**	51.81
		10		1.0e-06		RBF	0.0001	45.63	51.88	45.55	**52.28**
	pLETORg	l	α	β	γ	usim	σ	AT@5	AT@10	NT@5	NT@10
		50	0.50	0.1	1.0	RBF	10.0	**71.38**	64.27	3.83	9.29
		50	0.10	1.0	10.0	COS	-	62.92	**65.41**	0.69	2.00
		5	0.10	0.1	100.0	RBF	10.0	49.84	58.47	**46.68**	55.60
		5	0.05	0.1	100.0	RBF	10.0	49.66	58.47	46.53	**55.71**
$\theta = 5$	KRL	k		λ		usim	σ	AT@5	AT@10	NT@5	NT@10
		10		1.0e-06		RBF	0.01	**75.97**	**75.07**	2.64	4.14
		10		1.0e-04		LIN	-	48.25	54.54	**46.42**	**54.51**
	pLETORg	l	α	β	γ	usim	σ	AT@5	AT@10	NT@5	NT@10
		50	1.00	0.1	10.0	COS	-	**79.42**	76.49	16.99	36.06
		50	0.50	0.1	100.0	COS	-	74.93	**77.36**	5.67	17.29
		5	0.50	0.1	10.0	RBF	10.0	49.84	57.97	**45.50**	**54.86**

The columns corresponding to "α_b", "β_b", "usim", and "σ" have the two hyperparameters, cell line similarity function, and parameter for RBF cell line similarity, respectively, for BMTMKL. The columns corresponding to "k", "λ", "usim", and "σ" have the two hyperparameters, cell line similarity function, and parameter for RBF cell line similarity, respectively, for KRL. The columns corresponding to "l", "α", "β", "γ", "usim", and "σ" have the latent dimension, weighting factor, latent vector regularization parameter, cell line similarity regularization parameter, cell line similarity function, and parameter for RBF cell line similarity, respectively, for pLETORg. The best performance of each method under each metric is in **bold**. The best performance of both the methods under each metric is underscored.

and KRL achieve their best NT@k. This demonstrates that pLETORg has similar power as BMTMKL and KRL in ranking new and known sensitive drugs together, and even slightly better power in prioritizing new sensitive drugs. In terms of AT@k, pLETORg is able to achieve much better results (when l=50) than BMTMKL. However, when pLETORg achieves high AT@k, the corresponding NT@k is not optimal. Since the majority of top-k most sensitive drugs among both new and known drugs will be known drugs, the good performance of pLETORg on AT@k validates that the push mechanism in pLETORg takes place during training. In addition, pLETORg outperforms KRL in terms of AT@k when θ=5, but is significantly worse than KRL when θ=2. This indicates potential overfitting of KRL in ranking sensitive drugs on top during training, particularly when sensitive training drugs are limited (θ=2) (again, sensitive training drugs will be the majority of sensitive drugs).

5.3 Ranking Drugs in New Cell Lines

In this section, we present the experimental results on ranking drugs in new cell lines. The experiments follow the experimental setting as in Fig. 4.

5.3.1 Analysis on Cell Line Similarities

New cell lines don't have any drug response information or latent vectors, and the only information that can be leveraged in order to select drugs for them is their own genomics information. Therefore, we first validate whether we can use the gene expression information for drug selection in new cell lines in pLETORg.

We first calculate the similarities of cell lines using their latent vectors learned from pLETORg (in the setting of Fig. 3) in RBF function. The correlation between such similarities and the cell line similarities calculated from gene expressions (i.e., w_{pq} as in Equation 8) using RBF function is 0.426. The correlations show that cell line gene expression similarities and their latent vector similarities are moderately correlated. We further analyze the cell lines whose gene expression similarities (using RBF function) are among 90 percentile. For each of such cell lines, we identify 10 most similar cell lines in their gene expressions. Fig. S2 in the supplementary materials shows the gene expression similarities of all such cell lines and their latent vector similarities. Fig. S2 in the supplementary materials demonstrates that for those cell lines whose gene expression similarities are high, their latent vector similarities are also significantly higher than average (the average cell line latent vector similarity is 0.682). This indicates the feasibility of using high gene expression similarities to connect new cell lines with cell lines used in pLETORg

5.3.2 Experimental Setting

Based on the analysis on cell line similarities, we split testing cell lines (i.e., new cell lines) from training cell lines (as in Fig. 4) such that each of the testing cell lines has sufficient number of similar training cell lines in terms of their gene expressions. Cell line latent vectors are learned in pLETORg only for those training cell lines, and drug latent vectors are learned for all the drugs. Note that the label scheme in this setting follows that in Section 4.1.2.2. The detailed protocol is available in Section S5 in supplementary materials.

In order to select sensitive drugs for each of the testing/new cell lines, we first generate a latent vector for the testing cell line as the weighted sum of latent vectors of its top-10 most similar (in gene expressions) training cell lines. The weights are the respective gene expression similarities.

TABLE 5: Performance on Selecting Drugs for New Cell Lines

sthr	method	AP@5								AP@10							
		50	100	150	200	250	300	350	400	50	100	150	200	250	300	350	400
$\theta = 2$	BMTMKL	0.855	0.842	0.844	0.834	0.833	0.829	0.823	0.829	0.792	**0.783**	0.783	**0.778**	0.774	0.768	0.763	0.768
	KRL	0.451	0.409	0.399	0.432	0.430	0.388	0.397	0.382	0.436	0.403	0.390	0.398	0.404	0.379	0.377	0.356
	pLETORg	**0.876**	**0.870**	**0.870**	**0.852**	**0.861**	**0.856**	**0.848**	**0.853**	**0.800**	0.770	**0.789**	0.777	**0.798**	**0.780**	**0.771**	**0.792**
		50	100	150	200	250	300	350	400	50	100	150	200	250	300	350	400
$\theta = 5$	BMTMKL	0.951	0.945	0.946	0.937	0.940	0.937	0.935	0.938	0.903	**0.908**	**0.911**	**0.907**	**0.908**	**0.906**	**0.903**	**0.906**
	KRL	0.621	0.568	0.565	0.545	0.565	0.570	0.549	0.543	0.573	0.497	0.524	0.501	0.520	0.503	0.515	0.502
	pLETORg	**0.965**	**0.958**	**0.955**	**0.949**	**0.949**	**0.949**	**0.947**	**0.947**	**0.908**	**0.908**	0.908	0.906	0.904	**0.906**	0.901	**0.906**

The columns corresponding to "AP@5" and "AP@10" have the AP@5 and AP@10 evaluation values of the corresponding methods, respectively. The columns corresponding to "50" $\cdots$ "400" have the number of new cell lines in the experiment (i.e., N_{new}). The best performance of the three methods under each metric is in **bold**.

The drugs are then scored using the latent vector of the new cell line and latent vectors of all drugs.

5.3.3 Overall Comparison

Table. 5 presents the performance of BMTMKL, KRL and pLETORg with respect to different numbers of new cell lines, denoted as N_{new}, in terms of AP@5, AP@10, respectively. We don't present the performance in sCI and CI here because in drug selection for new cell lines/patients, CI is not practically as indicative as AP@k, particularly in drug selection from a large collection of drugs. For each of the two evaluation metrics, we compare the performance of BMTMKL, KRL and pLETORg when θ=2 and θ=5. Note that as N_{new} increases (i.e., more new cell lines), the average gene expression similarities between new cell lines and training cell lines decrease according to the data split protocol.

Table. 5 shows that as N_{new} increases, the AP@5 and AP@10 values of pLETORg, KRL and pLETORg with both θ=2 and θ=5 decrease in general. This is because as more cell lines are split into testing set, on average, training cell lines and testing cell lines are less similar, and thus it is less accurate to extrapolate from training cell lines to new cell lines. Even though, pLETORg consistently outperforms BMTMKL and KRL over all N_{new} values in terms of AP@5. and performs similarly to BMTMKL and still outperforms KRL in terms of AP@10. Specifically, when 50 cell lines are held out for testing (i.e., N_{new}=50), pLETORg achieves AP@5 = 0.876/0.965 when θ = 2/5, compared to AP@5 = 0.855/0.951 of BMTMKL and AP@5 = 0.451/0.621 of KRL. When 400 cell lines are held out for testing, pLETORg achieves AP@5 = 0.853/0.947, compared to AP@5 = 0.829/0.938 of BMTMKL and AP@5 = 0.382/0.543 of KRL when θ=2/5. Particularly, with θ=2, pLETORg outperforms BMTMKL at 2.5% when N_{new}=50, and at 2.9% when N_{new}=400. This indicates that when the drug selection for new cell lines is more difficult (e.g., fewer training cell lines, fewer sensitive drugs), pLETORg outperforms BMTMKL more. Also with θ=2, when more cell lines are held out ($N_{\text{new}} \geq 250$), pLETORg outperforms BMTMKL in AP@10. For example, when N_{new}=250, pLETORg achieves AP@10 = 0.798, compared to AP@10 = 0.774 of BMTMKL. This also indicates that pLETORg outperforms pLETORg on more difficult drug selection problems. Please note that KRL performs significantly worse than pLETORg and BMTMKL in selecting drugs for new cell lines. This might be due to similar reasons as discussed in Section 5.2.2, that is, KRL tends to overfit the known (training) cell lines and is not well generalizable to new cell lines.

5.4 Analysis on Latent Vectors

5.4.1 Analysis on Drug Latent Vectors

5.4.1.1 Evaluation Measurements: We evaluate how much the learned drug latent vectors could be interpreted in differentiating sensitive drugs and insensitive drugs. To have quantitative measurements for such an evaluation, we calculate the following four types of measurement:

1) the cosine similarities of drugs using their latent vectors learned from pLETORg, denoted as COS_{L};
2) the Tanimoto coefficients [39] of drugs using their AF features [11], denoted as TAN_{AF};
3) the average ranking percentile difference for all the drug pairs over all the cell lines in the ground truth, denoted as Δr%; and
4) the average difference of responsive cell line ratios for drug pairs over all the cell lines in the ground truth, denoted as Δe%.

AF features are binary fingerprints representing whether a certain substructure is present or not in a drug. Thus, the Tanimoto coefficients over AF features measure how drugs are similar in terms of their intrinsic structures (Tanimoto coefficient has been demonstrated to be effective in comparing drug structures [39]). The measurement Δr% is calculated on all pairs of drugs over the cell lines that both of the drugs in a pair have sensitivity measurement (i.e., no missing values on either of the drugs) in the cell lines. The absolute values of the percentile ranking differences over such cell lines are then averaged into Δr%. The measurement Δe% is calculated as the percentage of cell lines in which a drug is sensitive (with θ=5). The absolute values of such ratio differences from all the drug pairs are then averaged into Δe%.

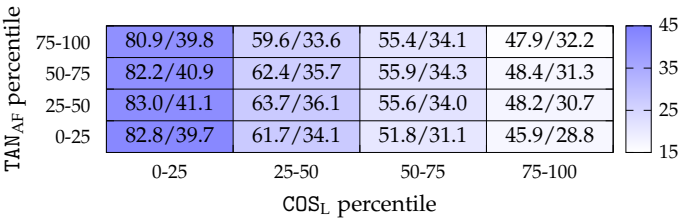


Fig. 7: Δr% in different drug pairs

5.4.1.2 Discriminant Power of Drug Latent Vectors: We group all the drug pairs based on their COS_{L} and TAN_{AF} percentile values. Fig. 7 presents the Δr% for different groups of drug pairs. In Fig. 7, the colors code the Δr%

11. http://glaros.dtc.umn.edu/gkhome/afgen/overview

values. The two values in each drug group (e.g., x/y in each cell in the figure) are the average percentile ranking of the higher-ranked drugs (i.e., x) and of the lower-ranked drugs (i.e., y) in the drug pairs, respectively. The difference of the two values in each drug group is the corresponding Δr%. Fig. 7 shows that when the drugs are less similar in their latent vectors (i.e., smaller $\texttt{COS}_\text{L}$ percentile; the left columns in Fig. 7), the drugs are ranked more differently among cell lines on average (i.e., larger Δr% values). Drugs with similar latent vectors tend to be ranked similarly (i.e., smaller Δr% values in the right columns in Fig. 7 with larger $\texttt{COS}_\text{L}$ percentiles). This indicates that the drug latent vectors learned from pLETORg are able to encode information that differentiates drug rankings in cell lines.

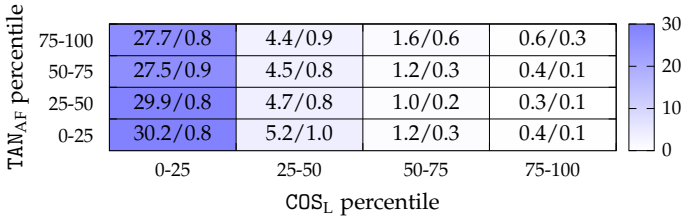


Fig. 8: Δe% in different drug pairs

Fig. 8 presents the Δe% for different groups of drug pairs. In Fig. 8, the colors code the Δe% values. The two values in each drug group (e.g., x/y) are the average responsive cell line ratio of the higher-ranked drugs (i.e., x) and of the lower-ranked drugs (i.e., y) in the drug pairs, respectively. The difference of the two values in each drug group is the corresponding Δe%. Fig. 8 shows that drugs that are very different from others in $\texttt{COS}_\text{L}$ (i.e., smaller $\texttt{COS}_\text{L}$ percentile; the left columns in Fig. 8) are sensitive in more cell lines (i.e., larger x in x/y values of the left columns). Specifically, the higher-ranked drugs (i.e., corresponding to x in x/y values in Fig. 8) in the 4 ranges of $\texttt{COS}_\text{L}$ values (in increasing order) are sensitive in 28.8%, 4.7%, 1.3% and 0.4% of the cell lines on average, respectively. This also corresponds with what Fig. 7 shows, that is, drugs that are more different from others in $\texttt{COS}_\text{L}$ tend to be ranked higher than the drugs that are more similar to others in $\texttt{COS}_\text{L}$. Specifically, in Fig. 7, the higher-ranked drugs (i.e., corresponding to x in x/y values in Fig. 7) in the 4 ranges of $\texttt{COS}_\text{L}$ values (in increasing order) are ranked at 82.2, 61.9, 54.7 and 47.6 percentile on average, respectively. These indicate that the sensitive drugs are better differentiated in drug latent vectors, and thus pLETORg is effective in deriving drug latent vectors that are specific to drug sensitivities.

5.4.1.3 Drug Latent Vectors as New Drug Features: Analysis on drug latent vectors as new drug features is available in Section S6 in the supplementary materials.

5.4.1.4 Interpretability of Drug Latent Vectors: Analysis on the interpretability of drug latent vectors is available in Section S7 in the supplementary materials.

5.4.2 Analysis on Cell Line Latent Vectors

Fig. 9 presents the correlations among three different types of cell line similarities within each of the tumor types. The three cell line similarities are calculated from gene expressions (GE) using RBF function on the 1,203 selected genes, cell line latent vectors (LV) using RBF function and drug sensitivity profiles (DS) using Spearman rank correlation coefficient. The three corresponding correlations are denoted as corr(GE, LV), corr(GE, DS) and corr(LV, DS), respectively. The numbers associated with tumor types in Fig. 9 indicate the number of cell lines of corresponding tumor types. (e.g., melanoma (51) indicates that there are 51 cell lines of melanoma). Among the 37 tumor types as originally categorized in CCLE, 28 tumor types (i.e., 75.7% of all tumor types) have their corr(LV, DS) higher than or same as corr(GE, DS), and the average percentage difference is 59.9%. For example, for 15 neuroblastoma cell lines, corr(LV, DS) is on average 191.7% higher than corr(GE, DS). For all the cell lines of various lymphoma, corr(LV, DS) is on average at least 20% higher than corr(GE, DS). This indicates that even when the correlation between gene expression and drug sensitivity is not strong, through learning cell line latent vectors, pLETORg can discover novel cell line features (i.e., cell line latent vectors) that better characterize their drug response patterns. As a matter of fact, the improvement of corr(LV, DS) over corr(GE, DS) is more significant when corr(GE, DS) is lower (i.e., the left side of the panel in Fig. 9). This indicates pLETORg may be effective for cell lines which do not have significant correlation between selected gene expression and drug sensitivity profiles. For the cell lines whose corr(GE, DS) is large (i.e., the right side of the panel in Fig. 9), corr(LV, DS) is still high in general and meanwhile corr(GE, LV) is also high. This indicates that pLETORg may be effective in retaining the useful signals from gene expression when the correlation between selected gene expression and drug sensitivity profiles is strong. For a few tumor types with relatively low corr(GE, LV) (e.g., liver, AML and esophagus), their corr(LV, DS) is actually relatively high. This may indicate the capability of pLETORg in learning new signals for cell lines by leveraging information from multiple other cell lines.

6 Discussions and Conclusions

We developed genomics-regularized joint push and learning-to-rank method pLETORg to tackle cancer drug selection for three particular application scenarios: 1). select sensitive drugs from new drugs for each known cell line; 2). select sensitive drugs from all available drugs including new and known drugs for each known cell line; and 3). select sensitive drugs from all available drugs for new cell lines. Our new method pLETORg outperforms or achieve similar performance to the state-of-the-art methods BMTMKL and KRL. Note that BMTMKL was originally developed to select cell lines for drugs. However, BMTMKL uses kernel regression and approximates drug response values to sort cell lines. Such drug response values can also be used to select drugs for cell lines, as we used in this manuscript. KRL was originally developed to select drugs for cell lines – the same goal as our pLETORg, but shows low generalization capabilities in selecting drugs for new cell lines and from new drugs.

pLETORg is a pair-wise learning-to-rank method which scores each drug in each cell line using latent vectors and ranks drugs based on the latent scores. This is fundamentally different from BMTMKL (a point-wise learning-to-rank method) and KRL (a list-wise learning-to-rank method), in

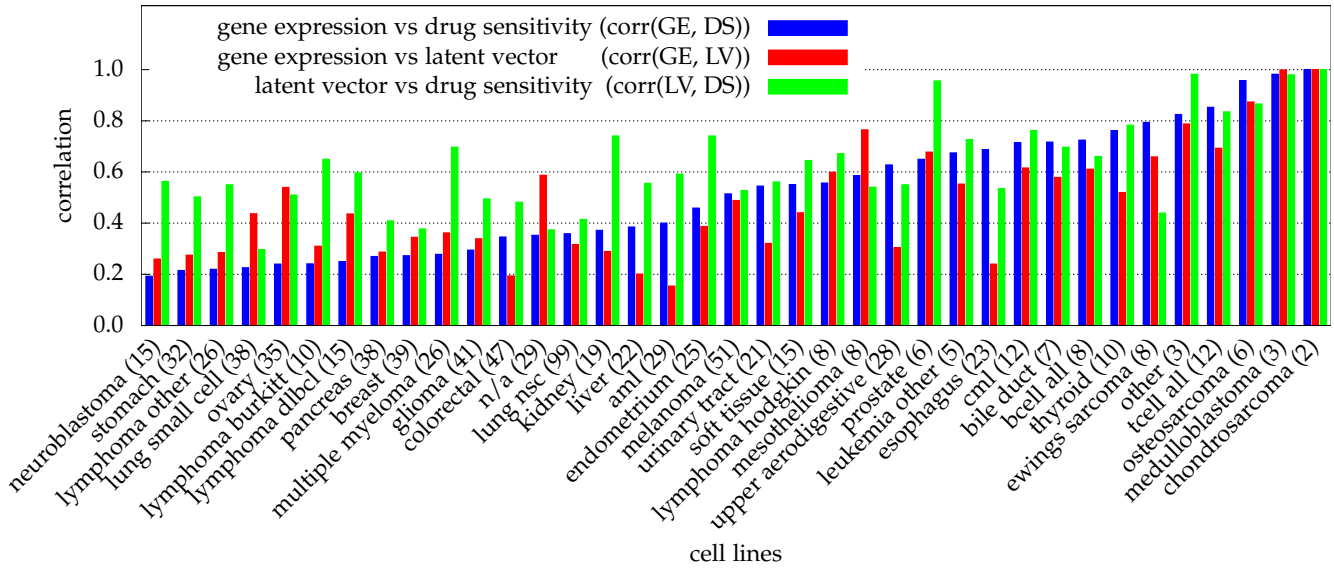


Fig. 9: Correlation among Different Cell Line Similarities

which the drug response values are approximated and used to sort drugs. The latent scores enable more flexibility to learn accurate drug ranking structures, but fall short when drug response values are also of concerns. We will investigate a combination of latent scoring and drug response value regression to leverage the advantages of both the schemes.

In pLETORg, each drug has a global latent vector which is the same in all cell lines. This might be restrictive as the learned drug latent vectors may have to compromise their performance in some cell lines in order to achieve better performance in other cell lines, and thus better overall performance. We will explore personalized drug latent vectors in the future research, that is, each drug will have different latent vectors with respect to different cell lines. In this way, the ranking performance on each cell line is expected to be further improved.

In addition, in pLETORg and BMTMKL, gene selection has been done across all tissue types/origins for all the cell lines together. However, different tissue types/origins may have different genes useful in their drug rankings. Therefore, global gene selection may end up with genes which tend to be globally indicative for assessing drug sensitivities, while locally informative gene information has been neglected. We will explore localized gene selection in the future research, by clustering cell lines based on tissues/origins and conducting gene selection over each cluster. We will also explore cell line clustering with respect to their drug ranking structures. It is expected that by localized gene selection, drug selection could be more accurate for each cell line.

The pLETORg method suffers from the lack of interpretability. It is not easy to explain what each of the drug/cell line latent dimensions represents or whether they correlate to any mechanisms of actions. This is because the latent vectors are learned only with respect to the goal of optimizing the drug ranking structures, without any potential MOA (if ever known) or causal features (if ever known) explicitly modeled. We would tackle this challenging interpretability issue in the future research, for example, by integrating known knowledge in the latent vector learning.

We will also evaluate our pLETORg method on other drug-cell line screening data, for example, NCI60 [12] and LINCS-L1000 [13] data. When the number of drugs (chemical compounds in LINCS-L1000) is large, it becomes more challenging computationally when pairs of drugs are used in learning. We will explore fast learning algorithms to learn drug latent vectors in the future research.

ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under Grant Number IIS-1566219 and IIS-1622526.

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