A computational method for drug sensitivity prediction of cancer cell lines based on various molecular information

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Abstract

Determining sensitive drugs for a patient is one of the most critical problems in precision medicine. Using genomic profiles of the tumor and drug information can help in tailoring the most efficient treatment for a patient. In this paper, we proposed a classification machine learning approach that predicts the sensitive/resistant drugs for a cell line. It can be performed by using both drug and cell line similarities, one of the cell line or drug similarities, or even not using any similarity information. This paper investigates the influence of using previously defined as well as two newly introduced similarities on predicting anti-cancer drug sensitivity. The proposed method uses max concentration thresholds for assigning drug responses to class labels. Its performance was evaluated using stratified five-fold cross-validation on cell line-drug pairs in two datasets. Assessing the predictive powers of the proposed model and three sets of methods, including state-of-the-art classification methods, state-of-the-art regression methods, and off-the-shelf classification machine learning approaches shows that the proposed method outperforms other methods. Moreover, the efficiency of the model is evaluated in tissue-specific conditions. Besides, the novel sensitive associations predicted by this model were verified by several supportive evidence in the literature and reliable database. Therefore, the proposed model can efficiently be used in predicting anti-cancer drug sensitivity. Material and implementation are available at https://github.com/fahmadimoughari/CDSML.

1 Introduction

As defined by The National Research Council, Precision medicine can be used to classify the patients into subgroups that vary in response to a medical treatment [1]. Tailoring efficient treatments based on their personalized characteristics can improve the quality of therapies, avoid extra expense, and diminish undesirable side effects [2]. Therefore, predicting the sensitivity of patients toward specific treatments is an essential issue in precision medicine. Currently, the massive collection of data prepare the ground for the development of data analysis
and computational methods such as machine learning and artificial intelligence approaches [2].

Generally, the computational methods for predicting drug response have been analyzed in two ways: 1- Classification (predicting sensitive drug-cell line pairs), 2- Regression (Predicting the value of a criterion for measuring the response of a cell line toward a drug). Numerous computational approaches have been proposed to solve the classification methods that predict anti-cancer drug sensitivity using transcriptomic features of cell lines and chemical substructures of drugs.

Zhang et al. have designed a heterogeneous network based on drug-target associations and drug sensitivity of cell lines. It also takes drug similarities, cell line similarities, and Protein-Protein Interaction (PPI) network into account. Their method, termed HNMPRD, uses an information flow-based algorithm to predict novel sensitive pairs of cell line-drug [3]. Recently, Choi et al. have designed RefDNN, a computational model based on a deep neural network and myriads of ElasticNet regressors [4]. They considered a set of reference drugs and a benchmark for classifying drugs for assessing the other drugs. They predicted drug sensitivity probabilities for a specific cell line-drug pair based upon the drug’s similarity to the reference set. RefDNN has the potentiality to be used for anti-cancer drug repositioning. One of the latest works in classifying cell line-drug pairs is DSPLMF [5]. This method uses a logistic matrix factorization with regularization terms. The regularization terms consider the drug similarity based on the chemical substructure and three types of cell line similarity based on gene expression profile, copy number variation, and mutation. Another similarity for cell lines was also calculated according to the response values of cell lines toward the drugs.

Furthermore, several computational regression approaches have been designed, which predicted the half-maximal inhibitory (IC50) of cell lines toward the drugs. In 2017, Wang et al. have suggested that the similarity of cell lines and the similarity of drugs can aid in predicting drug response values. They have proposed SRMF, a matrix factorization with regularization based on gene expression similarity of cell lines and chemical similarity of drugs [6]. They used SRMF for drug re-purposing in lung cancer cell lines. Suphavilai et al. have designed a recommender system, called CaDRReS, which benefits solely from cell line similarities [7]. They have shown that CaDRReS can extract meaningful information about drug mechanisms from the predicted drug responses. Wei et al. have introduced CDCN, which predicted drug response by inferring information from a simple network composed of cell lines and drugs [8]. CDCN yielded high-quality results despite its simple calculations. Ahmadi Moughari et al. have proposed ADRML, a framework for anti-cancer drug response prediction using manifold learning [9]. ADRML maps drug response values into a low-dimensional latent space and infers the drug response value for new cell line-drug pairs from the latent space. It takes several types of cell line similarities and drug similarities into account and uses them in the manifold learning procedure. They have shown that ADRML predicted good results correlated with drug pathway activities.

In recommending efficient remedies for a patient, it is essential to determine the drugs that a patient is sensitive to them; therefore, knowing drug response values itself may not give extra information in medical cases. Therefore, classifying cell line-drug pairs into sensitive/resistant pairs is a more fundamental and helpful problem than regressing their response values. On the other hand, a regression problem can be transferred to a classification problem via a thresholding technique.

In this work, as inspired by ADRML [9], we proposed CDSML, which applies the manifold learning method [10] for the classification problem using the maximum concentration threshold. Since predicting sensitive pairs is much more important than predicting drug response values, providing an efficient classification method can have a great impact in this field. We
show that using binary response as the input in the classification method leads to significantly higher performance of CDSML over ADRML.

Another contribution of this paper is introducing two novel and inclusive similarities for anti-cancer drugs besides using previously defined similarities. Due to incorporating the combination of various information in newly introduced drug similarities, using these similarities in other precision medicine models or related fields can be helpful. An interesting part of this paper is the assessment of the influence of each similarity type on the performance of CDSML. The proposed method uses a novel combination of standardization and normalization for transforming the similarity matrices into the ones with more desirable characteristics.

Moreover, this paper provides an extensive validation of using k-nearest neighbor strategy for imputing the missing values. Since the available datasets for cancer cell line sensitivity are not complete, there are numerous missing values. These assessments validate the rationality of using this technique to fill in the missing values.

In addition to the mentioned contributions, we extended the CDSML application in order to have the capability of handling missing values without imputation. Furthermore, the proposed method can be performed in various scenarios with or without similarity information and achieves highly reliable results in all scenarios. We provide a framework to assess the regression methods on classification mode.

The performance of CDSML in the classification problem is compared to the performance of off-the-shelf machine learning classifiers, as well as state-of-the-art classification and regression methods, all in the same setting. The tissue-specific results and literature evidence for the predicted sensitive pairs confirm CDSML performance.

2 Materials and methods

2.1 Data

Drug screening data and the transcriptomic data of the cell lines were obtained from the Genomics of Drug Sensitivity in Cancer (GDSC) [11] and Cancer Cell Line Encyclopedia (CCLE) [12]. The molar concentration of a drug needed for half inhibition of cell growth (IC50) as well as molecular information of cell lines in GDSC and CCLE, such as gene expression profiles, mutation, and copy number variation were downloaded using PharmacoGx R package [13]. The max concentration values for drugs were obtained from GDSC website http://cancerrxgene.org.

GDSC contains 439 drugs and 1124 cell lines; however, some IC50 values were not inserted in GDSC. Therefore, we purified the data using some pre-processing steps similar to several previous works [5, 9, 14, 15]. After applying data pre-processing steps, we obtained 555 cell lines and 98 drugs.

Moreover, CCLE dataset contains the information for 24 drugs. It should be noted that we require the max concentration values for drugs. Therefore, according to the previous studies [4], we restrict the CCLE dataset on the drugs that their max concentration values can be obtained from GDSC website. The final CCLE dataset, after applying pre-processing steps, contains 363 cell lines and 18 drugs.

In addition to the mentioned information, the PaDel descriptors of drugs in PubChem [16] were extracted using the rdkit package in Python [17]. The target proteins for drugs were gained from GDSC and DrugBank [18] databases as well as literature. The interaction information for proteins and drugs are obtained from STRING [19] and STITCH [20] databases.
2.2 Pre-processing

We construct three types of matrices for assessing the gathered data. The first matrix is the response matrix which contains the drug response information. The rows of the response matrix correspond to the cell lines and its columns are related to the drugs. The elements of response matrix are either the IC50 values or sensitivity labels. The second type of matrices is cell line feature matrices, in which the rows pertain to the cell lines and the columns represents different features. The last type of matrices is drug feature matrices, in which each row represents a drug and drug features are organized in the columns. After constructing these matrices, pre-processing steps were applied on them in order to impute the missing values, remove samples with significantly low information, calculate the cell line similarities and drug similarities, and make the data suitable for the proposed method. The pre-processing procedure includes the following four steps:

- **Imputing missing values**
- **Converting IC50 values into binary categories**
- **Similarity calculation**
- **Standardization and normalization**

These steps are elaborated in the following subsections.

### 2.2.1 Imputing the missing values

There are numerous missing values in the IC50 response matrix, cell line feature matrix based on copy number variation, and cell line feature matrix based on mutation profile. In order to remove the samples that have a significant lack of information, we omitted the drugs that have missing IC50 for more than half of the cell lines. Moreover, we removed the features of cell lines that have the missing values for the majority of cell lines. Afterward, we excluded the cell lines with missing entries for more than half of the columns in each of these matrices. Nevertheless, there were still some missing values in the matrices; therefore, we imputed these missing entries using a weighted mean of other entries. If we did not omit the samples with a significant lack of information and tried to impute all missing entries first, the obtained information would not be much reliable. The percentage of imputed data must be low enough to maintain the authenticity of data. For example, in the case of GDSC dataset, the raw IC50 matrix contains about 49% missing values. After removing the drugs and cell lines with a great extent of missing values, the obtained IC50 matrix contains only 2.7% missing pairs. Imputing such a limited fraction of data does not damage the data authenticity.

We used the following strategy to impute the remaining missing values, which is similar to the imputation procedure used in previous studies. [5, 14]. Let $E(c_i)$ be the gene expression profile of cell line $c_i$ and $I(c_i, d_j)$ be the IC50 value for cell lines $c_i$ against drug $d_j$. The missing value for $I(c, d)$ is imputed as the Eq 1.

$$I(c, d) = \frac{\sum_{i \in \mathcal{N}(c)} I(c_i, d) D(c, c_i)}{\sum_{j \in \mathcal{N}(d)} D(c, c_j)}$$

where $\mathcal{N}(c)$ is the set of indices for cell lines which are the $k$ nearest neighbors of the cell line $c$ with respect to the distance function $D$. We considered $k = 10$ for imputing missing values in GDSC and CCLE.

$$D(c, c_j) = \| |E(c_i) - E(c_j)|^2$$

where $\| \|_2$ is the norm-2 and $\mathcal{N}(c)$ is the set of indices for cell lines which are the $k$ nearest neighbors of the cell line $c$ with respect to the distance function $D$. We considered $k = 10$ for imputing missing values in GDSC and CCLE.
Moreover, the missing entries in copy number variation and mutation matrices are imputed similarly. Let $V(c, g)$ and $M(c, g)$ be the copy number variation and mutation status of gene $g$ in cell line $c$. The missing values for $V(c, g)$ and $M(c, g)$ are imputed according to Eqs 3 and 4, respectively.

$$V(c, g) = \frac{\sum_{i \in N(c)} V(c_i, g)D(c, c_i)}{\sum_{i \in N(c)} D(c, c_i)} \quad (3)$$

$$M(c, g) = \frac{\sum_{i \in N(c)} M(c_i, g)D(c, c_i)}{\sum_{i \in N(c)} D(c, c_i)} \quad (4)$$

It is noteworthy that gene expression profiles of cell lines are considered for calculating sample distance because the cell line feature matrix based on gene expression profiles does not contain any missing value. Therefore, the distance function $D$ can be computed for all pairs of cell lines.

### 2.2.2 Convert IC50 values into binary categories

CDSML requires discrete drug responses for classifying the cell line-drug pairs. Numerous studies have divided IC50 values into sensitive and non-sensitive classes [3–5, 14, 21]. Currently, various thresholds ($\theta$) are used to convert IC50 values into sensitive/resistance classes. In several studies, a fixed threshold is used for converting IC50 values to binary labels. For example, Brubaker et al. [22] used $\theta = 0.1$ and Chang et al. [21] used $\theta = -2$. Some studies used statistical thresholds such as drug-wise median [5, 14], mixed Gaussian distribution [3, 23], or a certain deviation from the normalized mean [24] as the threshold. While some others used reliable pharmacokinetic thresholds such as the maximum concentration of drugs ($C_{\text{max}}$) [4].

Among the various thresholds used for label assigning to drug response values, $C_{\text{max}}$ is more logical since it is based on the pharmacokinetic properties of the drug. $C_{\text{max}}$ is the maximum (peak) concentration in plasma, which is achieved by a drug. Therefore, it is evident that if a cell line requires the molar concentration of more than $C_{\text{max}}$ of a drug for half inhibition, it is resistant to the drug.

The cell lines in the GDSC database are specified as sensitive and resistant to a drug, using $C_{\text{max}}$ thresholds [11]. To clearly explain the label assignment of IC50 values, Suppose there are $m$ cell lines and $n$ drugs and $B_{m \times n}$ is a binary matrix, showing the sensitivity or resistance of cell line-drug pairs. If $B(c_i, d_j) = 1$, it denotes that cell line $c_i$ is sensitive to drug $d_j$, and resistant to it if $B(c_i, d_j) = 0$. The entries of the matrix $B$ were determined according to the following:

- If $I(c, d) < C_{\text{max}}(d)$ it is labeled sensitive, which is represented by 1.
- Otherwise, it is labeled non-sensitive, which is represented by 0

Applying $C_{\text{max}}$ threshold on the response matrix leads to labeling 59.13% of cell line-drug pairs in GDSC as sensitive pairs (i.e. 32,164 out of 54,390 pairs). Moreover, 65.1% of CCLE pairs (4,254 out of 6,534 pairs) were labeled as sensitive pairs. The remaining pairs were considered as resistant pairs.

### 2.2.3 Similarity calculation

Previous studies have frequently confirmed that similar cell lines yield similar responses to similar drugs [5–7, 25]. Therefore, the machine learning approaches can learn to predict the drug response using the similarities between cell lines and the similarities between drugs. Three types of cell line similarities and three types of drug similarities were computed for GDSC and CCLE datasets. The similarity calculation procedure is elaborated in the following.
The genomic features of cell lines are mainly characterized using gene expression profiles, copy number variation, and mutation profiles. The gene expression similarity between \(c_i\) and \(c_j\) cell lines is represented by \(SC_E(c_i, c_j)\), which is computed by Pearson Correlation Coefficient (PCC) between the gene expression profiles of the \(c_i\) and \(c_j\) (See Eq 5).

\[
SC_E = \frac{\sum_g (E(c_i, g) - \bar{E}(c_i))(E(c_j, g) - \bar{E}(c_j))}{\sqrt{(E(c_i, g) - \bar{E}(c_i))^2 \sqrt{(E(c_j, g) - \bar{E}(c_j))^2}}
\]  

(5)

where \(E(c_i, g)\) denotes the expression of gene \(g\) in cell line \(c_i\) and \(\bar{E}(c_i)\) represents the mean expressions of all genes in cell line \(c_i\).

Moreover, \(SC_V\) represent the cell line similarity based on copy number variation. Let \(V(c_i, g)\) be the copy number variation of gene \(g\) in cell line \(c_i\) and \(\bar{V}(c_i)\) mean of copy number variations of all genes for cell line \(c_i\). The similarity of cell lines corresponding to copy number variation is calculated as Eq 6.

\[
SC_V(c_i, c_j) = \frac{\sum_g (V(c_i, g) - \bar{V}(c_i))(V(c_j, g) - \bar{V}(c_j))}{\sqrt{(V(c_i, g) - \bar{V}(c_i))^2 \sqrt{(V(c_j, g) - \bar{V}(c_j))^2}}
\]  

(6)

In addition to the mentioned similarities between cell lines, another important feature in cancer cell lines is mutation profiles. Gene mutations play crucial functions roles in cancer development and progression [26]. Suppose \(M(c_i, g)\) be a binary value, showing the mutation status of gene \(g\) in cell line \(c_i\), where it equals “1” if gene \(g\) is mutated in cell line \(c_i\) and “0” if it is wild type. \(SC_M(c_i, c_j)\) represent the mutation similarity of cell lines \(c_i\) and \(c_j\) which is defined based on Jaccard Index (JI) of their mutation profiles.

\[
SC_M(c_i, c_j) = \frac{\sum_g M(c_i, g)M(c_j, g)}{\sum_g (M(c_i, g') + M(c_j, g') - \sum_g M(c_i, g')M(c_j, g'))}
\]  

(7)

One of the frequently used similarities for drugs is the similarity of chemical substructures because chemical substructure of a drug determines its functionality up to a good extent [27–29]. The chemical substructure similarity of two drugs \(d_i\) and \(d_j\) is shown by \(SD_S(d_i, d_j)\) which is calculated using the JI of PaDel descriptors of drugs \(d_i\) and \(d_j\). Let \(P(d_i, l)\) be the \(l\)th element of the PaDel descriptor for drug \(d_i\). The \(SD_S(d_i, d_j)\) value is computed as Eq 8.

\[
SD_S(d_i, d_j) = \frac{\sum_l P(d_i, l)P(d_j, l)}{\sum_l (P(d_i, l) + P(d_j, l)) - \sum_l P(d_i, l)P(d_j, l)}
\]  

(8)

Another informative similarity of drugs can be obtained based on the interaction of drugs with other chemicals and proteins. The STITCH database provides a comprehensive resource which presents the relationships between chemicals and proteins [20]. The relations in STITCH are based on various sources such as experimental evidence from ChEMBL [30] PDSP Ki database [31], Protein Data Bank (PDB) [32], pathway databases including KEGG [33], Reactome [34], and NCI nature pathway interaction database [35] as well as other databases such as DrugBank [18] and MATADOR [36]. In addition to the experimental evidences from reliable databases, it uses text mining, experimentally biochemical data, gene fusion, and genomic context prediction [20]. Hence, the network obtained from STITCH database provides an extensive insight about the drugs. The STITCH network for CCLE drugs is illustrated in Fig 1. The oval nodes in this figure represent the drugs in CCLE and other adjacent drugs, while the circle nodes indicate the neighbor proteins. The STITCH network for GDSC drugs is
presented in the S2 File (S1 Fig in S2 File). The weights of edges between nodes in STiTCH network for GDSC and CCLE drugs are presented in S1 and S2 Tables in S1 File, respectively.

We computed drug similarities based on STiTCH network \( SD_N \) according to the Eq 9, where \( N_i \) represents the immediate neighbors (both protein neighbors and chemical neighbors) of drug \( d_i \). Therefore the JI of the neighbor nodes in STiTCH network is used as the second similarity of drugs.

\[
SD_N(d_i, d_j) = \frac{|N_i \cap N_j|}{|N_i \cup N_j|}
\]  

(9)

In addition to the above drug similarities, we calculated another similarity based on PPI network of target proteins. To this aim, we obtained drug targets and considered the target
proteins for all drugs in the dataset as the target protein set. The target protein set for GDSC and CCLE are presented in S3 and S4 Tables in S1 File, respectively. Afterwards, we acquired PPI network for the target protein set from STRING database [19]. Fig 2 represents the STRING PPI network for target protein set of CCLE drugs. The STRING PPI network for GDSC drugs is presented in the S2 File (S2 Fig in S2 File). It is noteworthy that STRING database uses various types of data such as Gene ontology terms, pathways experimental evidence, and text mining features to compute the interactions between proteins. Hence, the weights of edges in STRING PPI network are the combination of various evidence. The weights of edges between nodes in STITCH network for GDSC and CCLE drugs are presented in S5 and S6 Tables in S1 File, respectively.

To compute the PPI-based similarity of drugs (SDp) we constructed a bipartite graph for each pair of drugs. To explain clearly, suppose that TPi and TPj are the sets of target proteins for drugs di and dj, respectively. Bipartite PPI graph G(i, j)PPI is constructed such that the set of nodes in one part is TPi, the set of nodes in another part is TPj and the edges are defined based on STRING PPI network. For example, assume that that TPi = {P1, P2, P3, P4} is the target proteins of drug di, while TPj = {P1, P2, P3, P4} is the target proteins of drug dj. The bipartite graph G(i, j)PPI is illustrated in Fig 3. The weights PPI edges between two parts in this graph are set by the weights of PPI in STRING network. Afterwards, we applied the maximum weighted matching algorithm [37] on this bipartite graph and consider the summation of weights of matching edges as the PPI-based similarity of drug pairs. This similarity shows the extent of accordance between the set of target proteins of two drugs. Therefore, SD(di, dj) is a high value, if the set of target proteins for di, dj match highly.

2.2.4 Standardization and normalization of similarity matrices. After computing all similarities, we standardized the similarity matrices in order to ensure that all similarity values range from 0 to 1. Since all similarities were computed based on PCC or JI, the similarity values range from -1 to 1; therefore, this standardization transforms the values in the range of [0, 1]. To clearly explain the standardization process, let S(i, j) be an entry in a similarity matrix. Its standardized value is represented by \( \hat{S}(i, j) \) and is computed according to Eq 10.

\[
\hat{S}(i, j) = \frac{S(i, j) + 1}{2}
\]

(10)

It is notable that performing standardization on similarity matrices does not change the sorting of distances between samples because this is a linear transform.

In the next step, we normalized the standardized similarity matrices using the symmetric normalized Laplacian [38]. The symmetric normalized Laplacian is a well-defined transform of the similarity matrix with several favorable algebraic and spectral characteristics such as being positive definite and diagonally dominant [39]. Moreover, its prevalence use in other problems such as spectral clustering [40] and drug target interaction prediction [41] justifies that using symmetric normalized Laplacian matrix represents the similarity of samples and shows the structural properties in a better way [42]. For each similarity matrix S, the normalized similarity matrix \( \mathcal{S} \) is obtained as Eq 11.

\[
\mathcal{S} = D^{-1/2}(D - S)D^{-1/2}
\]

(11)

In this equation, \( D \) is a diagonal matrix and \( D_{ii} = \sum_j S_{ij} \). All diagonal elements in \( D \) are non-zero. Hence, \( D^{-1/2} \) is a diagonal matrix and its entries are reverse values of the square root of elements in \( D \). It should be noted that this normalization does not affect the correlation between various types of similarity matrices. On the other hand, applying this normalization improves the model speed and leads to quicker convergence of the CDSML.
Fig 2. STRING network for drugs in CCLE.
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Fig 3. Schematic representation of the bipartite graph between the set of target proteins for a drug pair.
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2.3 Applying classification method

The classification process is inspired from ADRML method [9], but with binary response matrix \( I \), rather than IC50 value matrix \( I \). Moreover, it uses a threshold to convert obtained results into binary labels. This method has several steps, including:

1. Decompose \( B_{mxn} \) matrix into \( X_{mxk} \) and \( Y_{nxk} \) such that \( B = XY^T \)
   
   (a). Initialize \( X^{(0)} \) and \( Y^{(0)} \) randomly.
   
   (b). Compute a loss function defined as the summation of mean square error (MSE), similarity conservation terms and regularization terms.
   
   (c). Update \( X \) and \( Y \) matrices according to the Newton’s method.
   
   (d). Repeat steps 1.b and 1.c until \( X \) and \( Y \) matrices converge.

2. Decompose \( B^T \) into two latent matrices \( W \) and \( Z \) similar to step 1.

3. Compute \( \tilde{B} = \frac{1}{2}(XY^T + WZ^T) \) as the predicted sensitivity matrix.

4. Use a threshold to convert \( \tilde{B} \) into a binary matrix \( \hat{B} \).

These steps are shown in Fig 4 and explained elaborately in the following.

2.3.1 Compute loss function. To classify the cell line-drug pairs, \( B_{mxn} \) is decomposed into two latent matrices \( X_{mxk} \) (cell line latent matrix) and \( Y_{nxk} \) (drug latent matrix) with lower rank. The decomposition must satisfy the following constraints:

- Decomposition Mean Square Error (MSE): The multiplication of latent matrices \( XY^T \) must be an appropriate estimation of binary response matrix \( B \).

- Regularization: The elements of \( X \) and \( Y \) matrices should not grow excessively.

- Cell line similarity conservation: The similar cell lines must have not too far latent row vectors in \( X \) matrix.

- Drug similarity conservation: The similar drugs must have not too far latent row vectors in \( Y \) matrix.

Considering all the above constraints, the loss function is defined according to Eq 12.

\[
\text{Loss} = \frac{1}{2} \sum_{i,j} (B(i,j) - X(i)Y(j)^T)^2 + \frac{\alpha}{2} \left( \sum_i ||X(i)||^2 + \sum_j ||Y(j)||^2 \right) + \frac{\beta}{2} \left( \sum_{i,j} ||X(i) - X(j)||^2 SC(i,j) + \sum_{i,j} ||Y(i) - Y(j)||^2 SD(i,j) \right) \tag{12}
\]

where \( \alpha \) and \( \beta \) are the regularization and similarity conservation coefficients. \( X(i) \) and \( Y(i) \) denotes the \( i \)th rows in \( X \) and \( Y \) matrices, respectively. The symbol \( SC \) in Eq 12 can be substituted by \( SC_{C} \), \( SC_{C} \), or \( SC_{M} \). Two latent matrices \( X \) and \( Y \) were updated using Newton’s method to minimize the loss function iteratively. \( X^{(0)} \) and \( Y^{(0)} \) were initialized randomly and
Fig 4. The overall framework of the proposed method. The features cell lines, IC50 and $C_{max}$ values were obtained from GDSC. Besides, drug substrcures were downloaded from PubChem, STiTCH network from STITCH database, and PPI network from STRING database. The sensitivity associations between cell line-drug pairs were specified and used as the objective of manifold learning. The cell line similarities and drug similarities were calculated, standardized, and normalized. These similarities were considered as the regularization terms in manifold learning. The output of manifold learning is a predicted score matrix that assigns cell line-drug pairs into sensitive resistant classes by a threshold.

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afterwards, $X^{(k)}$ and $Y^{(k)}$ were updated using the rules defined in Eqs 13 and 14, respectively.

$$X^{(k+1)} = X^{(k)} - \nabla_{X^{(k)}} \text{Loss}$$  \hfill (13)

$$Y^{(k+1)} = Y^{(k)} - \nabla_{Y^{(k)}} \text{Loss}$$  \hfill (14)

These matrices were updated until they do not change significantly in two subsequent iterations. Specifically, when $\|X^{(k+1)} - X^{(k)}\| + \|Y^{(k+1)} - Y^{(k)}\| < 0.01$, the convergence criteria is met. The detailed formulae for updating latent matrices are described in S2 File.

2.3.2 Predicting sensitivity/resistant labels. As described above, we decomposed $B$ into two latent matrices and after convergence, the last estimated latent matrices $X^{(k)}$ and $Y^{(k)}$ were multiplied to estimate $B$:

$$\tilde{B}_1 = X^k Y^{kT}$$  \hfill (15)

Then, $B^T$ is decomposed into $W_{m \times k}$ and $Z_{n \times k}$ using the described method. This is done due to the fact that the predicted labels for samples $(c_i, d_j)$ and $(d_j, c_i)$ must be equal. After the convergence, $B^T$ is estimated using the following equation:

$$\tilde{B}_2 = W^k Z^{kT}$$  \hfill (16)

The predicted sensitivity matrix ($\tilde{B}$) was calculated as the average of $\tilde{B}_1$ and $\tilde{B}_2$. It should be noted that the estimated matrix $\tilde{B}$ is not binary valued; thus, we converted it to a binary-valued matrix $\tilde{B}$ using a threshold. So that the cell line-drug pairs were assigned to sensitive/resistant classes. The computation of best threshold is explained in Section 2.4.

2.4 Evaluation criteria

The predictive performance of models was assessed using stratified five-fold cross-validation on cell line-drug pairs. To this aim, the set of all cell line-drug pairs were partitioned randomly to five subsets of equal sizes such that the fraction of sensitive over resistant pairs was almost equal in all subsets. Four subsets were considered as the training data and the evaluation criteria were computed on the remaining subset. This procedure was iterated for each subset and the criteria were averaged over the iterations. The stratified five-fold cross-validation was repeated 30 times in order to prevent bias in partitioning the dataset. The most prevalent evaluation criteria for classification problems are defined in the following:

$$\text{Recall} = \frac{TP}{TP + FN}$$  \hfill (17)

$$\text{Precision} = \frac{TP}{TP + FP}$$  \hfill (18)

$$F1 - \text{score} = \frac{2 \times \text{Recall} \times \text{Precision}}{\text{Recall} + \text{Precision}}$$  \hfill (19)

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN}$$  \hfill (20)
Where \( TP, TN, FP \) and \( FN \) stands for true positive, true negative, false positive, and false negative, respectively. These statistics are defined in Table 1.

It should be noted that the mentioned criteria are threshold dependent. \( AUPR \) and \( AUC \) are more reliable criteria that are independent of threshold values. \( AUPR \) is the area under the plot of \( \text{Precision} \) versus \( \text{Recall} \) at various thresholds. \( AUC \) is the area under the ROC Curve which plotted \( \text{Recall} \) against \( \text{FPR} = \frac{FP}{FP + TN} \) at different threshold values.

The best threshold converting \( \hat{B} \) estimated scores to binary labels were determined using \( \text{Precision} - \text{Recall} \) curve. The threshold value related to the elbow-point in this curve is considered as the best threshold because at this threshold, there is a good balance between \( \text{Precision} \) and \( \text{Recall} \).

2.5 Variations of CDSML

The application of CDSML can be extended in order to be performed in various scenarios. The following subsections includes two variations of CDSML.

2.5.1 Performing on the response matrix with missing values. CDSML can handle the binary response matrix \( B \) without imputing missing values. To this aim, it is required to alter the Eq 12 such that it computes the loss function only for known pairs. Eq 21 is capable of handling the response matrix which contains missing values.

\[
\text{Loss}^{\text{(Missing)}} = \frac{1}{2} \sum_{i \neq \text{Missing}} (B(i,j) - X(i)Y(j)^T)^2 + \frac{\lambda}{2} \left( \sum_i ||X(i)||^2 + \sum_j ||Y(j)||^2 \right) + \frac{\beta}{2} \left( \sum_{ij} ||X(i) - X(j)||^2 SC(i,j) + \sum_{ij} ||Y(i) - Y(j)||^2 SD(i,j) \right)
\]

where \( \text{Missing} \) denotes the set of missing pairs. If we use Eq 21 instead of Eq 12, the method is able to be performed without applying the imputation step for missing IC50 values. The detailed formula for updating latent matrices in this version is explained in the S2 File. It should be noted that using these formula works also for response matrix without missing. For example, when the missing values are imputed, the set of Missing is empty; therefore, in that case the loss terms are calculated for all pairs.

2.5.2 Using double, single, or no similarity matrices. One can perform CDSML in three different scenarios based on similarity usage:

- Double similarity: using both \( SC \) and \( SD \) similarity matrices
- Single similarity: using either \( SC \) or \( SD \) similarity matrices
- No similarity: using no similarity matrix.

Table 1. The confusion table for defining classification statistics.

| Predicted labels | Real labels | Sensitive | Resistant |
|------------------|-------------|-----------|-----------|
| Sensitive        | TP          | FP        |           |
| Resistant        | FN          | TN        |           |

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To this aim, the loss function in Eq 21 must be modified. If only SC is ignored, the loss function will be changed to the Eq 22.

\[
\text{Loss}^{(SD)} = \frac{1}{2} \sum_{i,j} \left( B(i,j) - X(i)Y(j)^T \right)^2 + \frac{\alpha}{2} \left( \sum_i ||X(i)||^2 + \sum_j ||Y(j)||^2 \right) + \frac{\beta}{2} \left( \sum_{i,j} ||Y(i) - Y(j)||^2 SD(i,j) \right)
\]

(22)

If only SD is ignored, the loss function will be changed to the Eq 23.

\[
\text{Loss}^{(SC)} = \frac{1}{2} \sum_{i,j} \left( B(i,j) - X(i)Y(j)^T \right)^2 + \frac{\alpha}{2} \left( \sum_i ||X(i)||^2 + \sum_j ||Y(j)||^2 \right) + \frac{\beta}{2} \left( \sum_{i,j} ||X(i) - X(j)||^2 SC(i,j) \right)
\]

(23)

If both SC, SD are ignored, the loss function will be changed to the Eq 24.

\[
\text{Loss}^{(No~sim)} = \frac{1}{2} \sum_{i,j} \left( B(i,j) - X(i)Y(j)^T \right)^2 + \frac{\alpha}{2} \left( \sum_i ||X(i)||^2 + \sum_j ||Y(j)||^2 \right)
\]

(24)

It is notable that, in each scenario, the equations for updating latent matrices will be adjusted based on the related loss functions. The related equations for updating latent matrices in each scenario is presented in the S2 File.

It is noteworthy that both variations explained in Sections 2.5.1 and 2.5.2 can be performed simultaneously. In other words, when the user wants to perform CDSML in each of similarity scenarios, the response matrix may contain missing values or not. Because the formula used in various similarity scenarios can ignore missing values if there are any.

3 Results

In this section, we present the results of evaluating CDSML and comparing its performance with other methods.

3.1 Tuning hyper-parameters

We tuned CDSML hyper-parameters using grid search on different values of hyper-parameters on GDSC dataset using SC\(E\), SD\(S\). Then we used the same hyper-parameters for CCLE or when using other similarities. We considered \(\alpha, \beta \in \{0.125, 0.25, 0.5, 1, 1.5, 2, 2.5, \ldots, 8\}\) and \(K = K' \cdot \min(m, n)\), where \(K' \in \{0.1, 0.2, \ldots, 0.9\}\). The best values for hyper-parameters was determined based on AUC criterion because this criterion is independent from threshold value and assess the model more extensively. The best hyper-parameters for CDSML was \(\alpha = 3.5, \beta = 4.5, \) and \(K' = 0.7\).

3.2 The performance of CDSML

CDSML predicts drug sensitivity according to the cell line similarity and drug similarities. We calculated three types of cell line similarities based on gene expression, mutation profile, and copy number variation. Each of these cell line similarities can be utilized as SC in CDSML similarity conservation terms. Furthermore, we computed three types of drug similarities based on chemical substructure, STITCH network and target PPI, each of which can be considered
as SD in CDSML similarity conservation terms. We analyzed the impact of using different types of similarities on the classification performance of CDSML. Table 2 represents the CDSML performance on GDSC dataset in three scenario, namely, double similarity, single similarity, and no similarity.

We discuss about each of three scenarios in the following.

• Discussing about “No Similarity” scenario:
The results in the first row of Table 2 indicate that CDSML gained high performance even using no similarities. CDSML performance using no similarity confirmed that the matrix factorization used in CDSML is efficient itself without using other extra information. The CDSML results using no similarity outperforms most of state-of-the-art methods mentioned in the paper.

• Discussing about “Single Similarity” scenario:
Based on this table, one can conclude that using a single similarity matrix makes about 6% improvements of all criteria compared to the case of no similarities. Moreover, the performance of CDSML on various types of SC or various types of SD leads to almost equal performance, i.e. the calculated criteria for all executions on a single similarity matrix are the same. For example, using only the copy number variation similarity of cell lines leads to AUC of 0.9071 and AUPR of 0.9353, while using only the PPI similarity of drugs also leads to the same values of AUC and AUPR. Therefore, the impact of all similarity matrix on the CDSML performance is almost equal. Thus, CDSML yielded highly accurate and robust results.

• Discussing about “Double Similarity” scenario:
Moreover, by comparing the results in single and double similarity scenarios, it can be inferred that the performance of CDSML using both SC and SD make subtle improvement in comparison to the single similarity scenario.

The performance of CDSML on CCLE dataset using different scenarios including double similarity, single similarity, and no similarity are provided in S2 File. Further evaluations on CDSML were conducted using cell line similarity based on gene expression and chemical substructure similarity of drugs.

3.3 Evaluation of predicted and imputed values for missing pairs

In order to show the rationality of imputed values in response matrix using Eq 1, one can compare the predicted labels by CDSML for missing values (denoted by \( \text{Pred}_{l}^{\text{CDSML}} \)) with imputed labels using Eq 1 (denoted by \( \text{Impute}_{l}^{(\text{Eq 1})} \)). \( x \) shows that the vector consists of binary labels. \( \text{Pred}_{l}^{\text{CDSML}} \) is computed by executing CDSML on the binary response matrix with missing values (not applying imputation procedure), while considering all known pairs as training samples and all missing pairs as test samples. On other hand, \( \text{Pred}_{l}^{\text{CDSML}} \) is computed by imputing missing values using Eq 1 and then converting the imputed values \( \text{Impute}_{c}^{(\text{Eq 1})} \) (index \( C \) denotes that the vectors contain the continuous values) to the imputed labels \( \text{Impute}_{l}^{(\text{Eq 1})} \) by comparing imputed IC50 values with max concentration thresholds of drugs. Since both vectors are binary, computing \( \text{Accuracy}, \text{F1 score}, \text{Precision}, \) and \( \text{Recall} \) in addition to JI, cosine similarity, and binary cross entropy are meaningful and can give us an extensive comparison of these two vectors. \( \text{Accuracy}, \text{F1 score}, \text{Precision}, \) and \( \text{Recall} \) are computed as defined in Section 2.4. The JI, cosine similarity, and binary cross entropy of two vectors \( X, Y \) are defined in
Eqs 25–27.

\[
JI(X, Y) = \frac{\sum_i X(i)Y(i)}{\sum_i (X(i) + Y(i)) - \sum_i X(i)Y(i)} \tag{25}
\]

\[
\text{Cosine Similarity}(X, Y) = \frac{\sum_i X(i)Y(i)}{||X||_2||Y||_2} \tag{26}
\]

\[
\text{Cross Entropy}(X, Y) = -\frac{1}{n} \sum_i [X(i) \log Y(i) + (1 - X(i)) \log (1 - Y(i))] \tag{27}
\]

Note that we need to compute true positive, true negative, false positive, and false negative sample to compute the Precision and Recall. Therefore, we must consider one of \(\text{Pred}_L^{(CDSML)}\) or \(\text{Impute}_L^{(Eq 1)}\) as the ground truth labels. Note that Precision value computed by considering \(\text{Pred}_L^{(CDSML)}\) as the ground truth equals to the Recall value computed by considering \(\text{Impute}_L^{(Eq 1)}\) as the ground truth, and vice versa. All mentioned metrics lies in the range of \([0, 1]\). The higher values of these metrics (except cross entropy) are more satisfactory, while the lower values of cross entropy are more favorable.

The computed metrics by considering \(\text{Pred}_L^{(CDSML)}\) as the ground truth are shown in Table 3. According to the significantly low value of cross-entropy as well as the high value of other metrics, one can conclude that \(\text{Impute}_L^{(Eq 1)}\) and \(\text{Pred}_L^{(CDSML)}\) are considerably similar. Consequently, the imputed values for missing pairs are reasonable.
To further justify the rationality of imputed values, we compared the imputed IC50 values using Eq 1 \((\text{Impute}^{(\text{Eq}1)})\) with the predicted IC50 values by a state-of-the-art method. The method proposed by Zhang et al. predicts IC50 values uses a dual layer network which is similar to the idea used in Eq 1 [25], while having some differences. Moreover, Zhang et al. have shown that the method predicts reliable IC50 values for missing pairs by providing biological evidence for the missing IC50 values of three MEK inhibitor drugs. Thus, it is interesting to compare the IC50 values imputed using Eq 1 \((\text{Impute}^{(\text{Eq}1)})\) with the predicted IC50 values by Zhang et al. method\((\text{Pred}^{(Zhang)})\). To compare these two continuous vectors, regression criteria such as Root Mean Square Error (RMSE), Normalized Root Mean Square Error (NRMSE), and Mean Absolute Error (MAE) can be computed. RMSE, NRMSE, and MAE for two vectors \(X, Y\) are defined in Eqs 28–30.

\[
\text{RMSE}(X, Y) = \sqrt{\frac{\sum (X(i) - Y(i))^2}{n}} \tag{28}
\]

\[
\text{NRMSE}_X(X, Y) = \frac{\text{RMSE}}{\max X(i) - \min X(i)} \quad \text{NRMSE}_Y(X, Y) = \frac{\text{RMSE}}{\max Y(i) - \min Y(i)} \tag{29}
\]

\[
\text{MAE}(X, Y) = \frac{\sum |X(i) - Y(i)|}{n} \tag{30}
\]

It should be noted that RMSE, NRMSE, and MAE ranges from 0 to infinity. So, lower values of them shows that the \(X, Y\) are closer to each other. The computed metrics show that the imputed IC50 values in this paper are very close to the Zhang et al. predicted IC50 values. Additionally, the comparison of imputed values with Zhang et al. predictions in binary mode as well the comparison of CDSML predictions with Zhang et al. predictions on missing pairs are provided in the S2 File.

An interesting idea is to use Zhang et al. predicted IC50 values \((\text{Pred}^{(Zhang)})\) for filling missing values in response matrix. To this aim, we converted continuous values of \((\text{Pred}^{(Zhang)})\) into \((\text{Pred}^{(Zhang)})\) with binary entries by comparing the max concentration with \(\text{Pred}^{(Zhang)}\). In other words, we used Zhang et al. predicted labels \((\text{Pred}^{(Zhang)})\) instead of labels computed by Eq 1; i.e. \(\text{Impute}^{(\text{Eq}1)}\) for filling the missing values in the response matrix. We then performed CDSML manifold learning on the obtained response matrix. Let us denote this version as CDML-Zhang and compared its results with CDSML using a stratified 5-fold cross-validation. Table 5 shows the comparison between CDSML and CDSML-Zhang. It can be seen that the

| Method         | AUC    | AUPR   | Accuracy | F1-score | Precision | Recall  |
|----------------|--------|--------|----------|----------|-----------|---------|
| CDSML          | 0.9157 | 0.9398 | 0.8388   | 0.8715   | 0.8422    | 0.9031  |
| CDSML-Zhang    | 0.912  | 0.937  | 0.836    | 0.870    | 0.84      | 0.896   |

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evaluation criteria computed for both versions are so close to each other. However, CDSML leads to better results. These comparisons additionally validates using Eq 1 for imputing missing entries of response matrix.

To sum up all validation scenarios in this section and the related sections in S2 File, one can conclude that the results of all validations confirm that the imputed values using Eq 1 are reasonable and leads to the improvement in results.

### 3.4 Comparisons with classification methods

To compare the predictive performance of CDSML with other state-of-the-art classification methods, we used available implementations for HNMPRD [3], RefDNN [4], and DSPLMF [5]. In order to have a fair comparison, we evaluated these methods using 30 repetitions of stratified five-fold cross-validation on cell line-drug pairs for GDSC and CCLE. These methods cover a variety of classification methodology and labeling thresholds. The methodology of HNMPRD, RefDNN, and DSPLMF are based on information flow, deep neural network, and matrix factorization, respectively. Moreover, the thresholds used in HNMPRD, RefDNN, and DSPLMF to convert IC50 values to sensitive/resistance labels are mixed Gaussian distribution, \( C_{max} \), and drug-wise median, respectively.

A comparison between CDSML and other state-of-the-art methods for category classification is represented in Table 6. Considering GDSC dataset, HNMPRD obtained high Recall, but low values in other criteria. RefDNN showed satisfying performance according to all and DSPLMF obtained reasonable results according to Recall, but not high quality results with respect to other criteria. CDSML outperforms other classification methods by achieving much higher values of all criteria than other methods. It improves the results of RefDNN by almost 2% in AUC, 7% in AUPR, 2% in Accuracy, and 9% in F1 – score.

Considering CCLE dataset, HNMPRD again obtained high Recall, but low values in other criteria. RefDNN and DSPLMF revealed acceptable performance. Consequently, the CDSML performance is significantly higher than other state-of-the-art classification methods and improves the best values of AUC, AUPR, Accuracy and F1 – score by more than 10%.

To fully compare the CDSML performance with classification methods, we compared its results with six off-the-shelf classification methods covering diverse methodologies: Gaussian Naive Bayes (GBN), logistic regression (LR), random forest (RF), multi-layer perception (MLP), adaptive boosting (ADA), and K-nearest neighbor (KNN). The implementations of all these methods were conducted using the Scikit-learn python package [43]. It should be noted that the feature vector for each pair of cell line \( c \) and drug \( d \) was constructed by concatenating the \( i \)th row of SC and \( j \)th column of SD. Moreover, the \( C_{max} \) was used to label the cell line-drug pairs. The best hyper-parameter values were specified using grid search. The set of evaluated hyper-parameters and the best values of hyper-parameters for all methods are presented in Table 7. The best values of hyper-parameters were tuned using grid search and considering AUC criterion.

Table 8 provides the comparison between CDSML and off-the-shelf classification methods. On both GDSC and CCLE, all methods showed good performance in classification of anti-cancer drug sensitivity; however, the least and highest values of criteria belongs to GNB and RF, respectively. On top of them, CDSML achieved the most accurate results and outperforms other methods according to all criteria, except Precision. Nevertheless, its Precision is not too far from the best Precision.

It is noteworthy that the computed criteria for machine learning models are significantly higher than the computed criteria for state-of-the-art classification and regression methods. The tuned hyper-parameters for machine learning models turn them into efficient and potent
models that outperform other state-of-the-art methods. These findings are in agreement with the similar findings in RefDNN paper [4].

Figs 5 and 6 demonstrates the ROC curve and Precision – Recall curve for all of the classification methods on GDSC dataset, respectively. As it is shown the AUC and AUPR values for CDSML are 0.9221 and 0.943, respectively which are superior to the AUC and AUPR of other methods.

3.5 Comparison with regression methods

The prediction power of CDSML was further compared to the power of four state-of-the-art regression models: SRMF [6], CaDRReS [7], CDCN [8], and ADRML [9]. The implementation of these methods were available. We applied \( C_{\text{max}} \), threshold on the predicted IC50 values by these methods and convert them to the classification models. The performance of these models are provided in Table 9. On GDSC datset, CaDRReS achieved reasonable results. Moreover, SRMF and CDCN showed weak performance. Meanwhile, CDSML performs better than these methods with regard to all criteria. The interesting part of this evaluation is the comparison

| Method | Evaluated hyper-parameters | Best hyper-parameters |
|--------|----------------------------|-----------------------|
| GNB    | Variance smoothing:{10\(^{-12}\), 10\(^{-9}\), 10\(^{-6}\), 10\(^{-3}\), 10\(^{-1}\)} | Variance smoothing: 0.1 |
| LR     | Regularization scale:{ 0.001, 0.1, 1, 10, 100} Stop tolerance:{10\(^{-6}\), 10\(^{-4}\), 10\(^{-2}\)} | Regularization scale: 1 Stop tolerance: 10\(^{-6}\) |
| RF     | Criterion: [gini, entropy] Number of trees:{10,50,100,500,1000} | Criterion: entropy Number of trees: 100 |
| SVM    | Kernel: [linear, poly, RBF, sigmoid, precomputed] Regularization parameter: [0.01,0.1,1,10,100] | Kernel: linear Regularization parameter: 0.1 |
| MLP    | Hidden layer sizes: ([50,50,50], (50,100,50), (100,)) Activation function: [tanh, ReLU] Solver: [SGD, Adam] Learning rate: [Constant, Adaptive] Regularization term: [0.0001, 0.05] | Hidden layer sizes: (50,50,50) Activation function: ReLU Solver: Adam Learning rate: Adaptive Regularization term: 0.05 |
| ADA    | Number of estimators: [10,50,100,500,1000] Learning rate: [1,1.25,1.5,1.75,2] | Number of estimators: 50 Learning rate: 1.25 |
| KNN    | \( K \): (3,5,7,9,11,13,15,17,19,21,23,25) | \( K \): 19 |
| CDSML  | \( \alpha, \beta \in \{0.125, 0.25, 0.5, 1, 1.5, 2, 2.5, \ldots, 8\} \) \( K = k' \min(m, n), \text{where} k' \in \{0.1, 0.2, \ldots, 0.9\} \) | \( \alpha = 3.5, \beta = 4.5 \) \( k' = 0.7 \) |

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between CDSML and ADRML. According to Table 9 CDSML significantly outperforms ADRML. Since CDSML uses binary response matrix, it can be inferred that using binary response matrix as the initial input of manifold learning leads to more reliable classification of cell line-drug pairs into sensitive/resistant categories.

### Table 8. Comparison of CDSML’s performance with off-the-shelf methods’ performance on GDSC and CCLE. The assessments were done by averaging 30 repetitions of stratified five-fold cross-validation. The highest value of each criterion is shown in bold.

| Dataset | Method | AUC   | AUPR  | Accuracy | F1-score | Precision | Recall  |
|---------|--------|-------|-------|----------|----------|-----------|---------|
| GDSC    | CDSML  | 0.9157| 0.9398| 0.8388   | 0.8715   | 0.8422    | 0.9031  |
| GDSC    | GNB    | 0.8662| 0.8974| 0.7792   | 0.8033   | 0.8695    | 0.7465  |
| GDSC    | LR     | 0.9037| 0.934 | 0.8243   | 0.8524   | 0.865     | 0.8401  |
| GDSC    | RF     | 0.9163| **0.9435**| 0.8376   | 0.8653   | **0.8666**| 0.8641  |
| GDSC    | SVM    | 0.9038| 0.9343| 0.8243   | 0.8522   | 0.8663    | 0.8387  |
| GDSC    | MLP    | 0.9044| 0.9351| 0.8226   | 0.8533   | 0.8529    | 0.8562  |
| GDSC    | Ada    | 0.9039| 0.9346| 0.8268   | 0.8553   | 0.8629    | 0.848   |
| GDSC    | KNN    | 0.9091| 0.9371| 0.8341   | 0.8623   | 0.8646    | 0.86    |
| CCLE    | CDSML  | **0.9514**| **0.977**| **0.8989**| **0.9201**| **0.9485**| **0.8934**|
| CCLE    | GNB    | 0.9111| 0.9523| 0.842    | 0.8779   | 0.8914    | 0.8675  |
| CCLE    | LR     | 0.9435| 0.9651| 0.8811   | 0.9189   | 0.948     | 0.8916  |
| CCLE    | RF     | 0.9494| 0.9632| 0.8884   | 0.9193   | 0.9463    | 0.8939  |
| CCLE    | SVM    | 0.9444| 0.9694| 0.8867   | 0.9192   | 0.9478    | 0.8924  |
| CCLE    | MLP    | 0.9376| 0.9671| 0.8744   | 0.9146   | 0.9624    | 0.872   |
| CCLE    | Ada    | 0.9475| 0.9609| 0.8878   | 0.9118   | 0.9332    | 0.8924  |
| CCLE    | KNN    | 0.936 | 0.9653| 0.8788   | 0.9116   | 0.907     | 0.8843  |

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Fig 5. The ROC curve of all classification methods on GDSC dataset.

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3.6 Tissue-specific conditions

Until now, we evaluated the methods on the whole dataset, which contains 19 tissue types. Nevertheless, most oncological treatments are designed based on tissue types [44], suggesting that considering tissue type may have a large impact on drug response predictions [3, 45]. Hence, we conducted tissue-specific assessments on three major tissue types.

The number of cell lines in each tissue type is shown in Fig 7. The most major tissue types are lung NSCLC, orogenital system, and leukemia with 67, 60, and 44 cell lines, respectively. We considered these tissue types and developed the tissue-specific models. The used cell lines in the train and test set for tissue-specific models belong to the same tissue type.

Figs 8–10 illustrates the predictive performance of classification methods on three major tissues. The ranking of methods performance is similar to the methods learned on the whole dataset.

Table 9. Comparison of CDSML’s performance with state-of-the-art regression methods’ performance on GDSC and CCLE. The assessments were done by averaging 30 repetitions of stratified five-fold cross-validation. The highest value of each criterion is shown in bold.

| Dataset | Method  | AUC   | AUPR  | Accuracy | F1-score | Precision | Recall |
|---------|---------|-------|-------|----------|----------|-----------|--------|
| GDSC    | CDSML   | 0.9157| 0.9398| 0.8388   | 0.8715   | 0.8422    | 0.9031 |
| GDSC    | SRMF    | 0.4452| 0.5493| 0.712    | 0.7922   | 0.6908    | 0.9285 |
| GDSC    | CaDRReS | 0.500 | 0.5922| 0.6962   | 0.7738   | 0.6912    | 0.8788 |
| GDSC    | CDCN    | 0.4276| 0.5460| 0.7632   | 0.8164   | 0.7538    | 0.8903 |
| GDSC    | ADRML   | 0.4077| 0.5096| 0.7501   | 0.8177   | 0.7189    | 0.9481 |
| CCLE    | CDSML   | 0.9514| 0.977 | 0.8989   | 0.9201   | 0.9485    | 0.8934 |
| CCLE    | SRMF    | 0.4539| 0.6266| 0.6966   | 0.8005   | 0.6998    | 0.9351 |
| CCLE    | CaDRReS | 0.4389| 0.6732| 0.7133   | 0.8138   | 0.7048    | 0.9625 |
| CCLE    | CDCN    | 0.4262| 0.6204| 0.8608   | 0.8824   | 0.9796    | 0.8029 |
| CCLE    | ADRML   | 0.4257| 0.6229| 0.5473   | 0.6703   | 0.6373    | 0.7071 |

https://doi.org/10.1371/journal.pone.0250620.t009
**Fig 7. The number of cell lines in each tissue type.** The number shown on slices is the number of cell lines in the related tissue type. Three major tissue types are the offset slices.

https://doi.org/10.1371/journal.pone.0250620.g007

**Fig 8. The performance of methods in on NSCLC tissue.**

https://doi.org/10.1371/journal.pone.0250620.g008
dataset. All methods’ performance decline slightly due to the reduction in sample size, because the reduction in sample size limits the predicted power of models [46]. Nevertheless, CDSML outperforms other methods in three tissue-specific scenarios. The $AUC$ of CDSML were 0.9096, 0.9186, and 0.9106 on leukemia, urogenital system, and NSCLC tissues, receptively.

3.7 Case studies

As it was mentioned, some cell line-drug pairs have missing IC50 values, which were imputed in the pre-processing step. In order to conduct case studies, we considered the predictions for missing pairs and investigated their predicted novel sensitive pairs. There $B$ matrix had 7790 missing values which accounts for roughly 40% of all samples. The predicted sensitivity scores for these pairs were obtained and sorted. The list of top 2000 most sensitive and top 2000 most resistant cell line-drug pairs are provided in S7 and S8 Tables in S1 File, respectively.

The top 15 most sensitive pairs that had missing associations in the original dataset were considered for further analysis. Table 10 represents the list of top 15 ranked samples assigned as sensitive. Reliable literature and the latest version of GDSC database were probed to provide evidence for the novel sensitive associations. As it is shown in Table 10, all top 15 novel associations were verified as sensitive pairs in the final version of GDSC. In addition, there are numerous insights about these associations in the literature.

These associations mainly report sensitive cell lines for Ponatini, VX-7002, Temsirolimus, Lenalidomide, Vinorelbine, Epothilone B, Docetaxel, among which, the insights about sensitive associations of three drugs are described in the following.

Ponatinib is a tyrosine kinase inhibitor which hinders the activity of four FGFR [63]. A recent study have shown that inhibits the cell growth in cell lines of various tissues types such as colon cancer [47]. Researchers states that the multi kinase inhibitors such as Ponatinib have showed efficient activity in targeting pancreatic cancer cells [49]. In addition, its effectiveness
in the treatment of cell lines with head and neck cancer have been evaluated in several studies [47, 62].

VX-702—a P38 mitogen-activated protein kinase inhibitors—have been developed for the treatment of the inflammation diseases [64]. P38β MAPK is highly expressed in lung tissues and P38 MAPK pathways are highly activated in SCLC and breast cell lines, which leads to tumorigenesis and metastasis [48, 50]. The oral treatment with VX-702 seems to be effective in diminishing the fibrosis in SCLC and breast [50]. HuangFu et al. have shown that the

Fig 10. The performance of methods in on leukemia tissue.

https://doi.org/10.1371/journal.pone.0250620.g010

Table 10. Top 15 novel sensitive pairs and pieces of evidence for these pairs.

| Rank | Cell line name | Drug name | Cell line tissue | Sensitivity Score | Literature evidence | GDSC verification |
|------|----------------|-----------|------------------|-------------------|---------------------|------------------|
| 1    | CW-2           | Ponatinib | large intestine  | 0.9253            | [47]                | verified         |
| 2    | ZR-75-30       | VX-702    | breast           | 0.9248            | [48]                | verified         |
| 3    | YAPC           | Ponatinib | pancreas         | 0.9062            | [49]                | verified         |
| 4    | NCI-H1092      | VX-702    | SCLC             | 0.9017            | [50, 54]            | verified         |
| 5    | NCI-H1092      | Temsirolimus | SCLC             | 0.8993            | [51]                | verified         |
| 6    | CW-2           | Vinorelbine | SCLC             | 0.8929            | [52]                | verified         |
| 7    | NCI-H1563      | VX-70    | NSCLC2           | 0.8823            | [53]                | verified         |
| 8    | COR-L88        | VX-702    | SCLC             | 0.8818            | [50, 54]            | verified         |
| 9    | SHP-77         | VX-702    | SCLC             | 0.8783            | [50, 54]            | verified         |
| 10   | LB373-MEL-D    | Lenalidomide | melanoma       | 0.8758            | [55, 56, 57]        | verified         |
| 11   | COR-L88        | Temsirolimus | SCLC             | 0.8753            | [51]                | verified         |
| 12   | CP66-MEL       | VX-702    | melanoma         | 0.875             | [58]                | verified         |
| 13   | CW-2           | Epothilone B | large intestine | 0.8738            | [59]                | verified         |
| 14   | NCI-H1092      | Docetaxel | SCLC             | 0.8648            | [60, 61]            | verified         |
| 15   | SCC-9          | Ponatinib | head and neck    | 0.8619            | [47, 62]            | verified         |

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administration of VX-702 along with INFβ treatments from melanoma, stabilization of the cell response, and improvement in the treatment efficacy [58].

Lenalidomide which has tumoricidal and immunomodulatory roles, has been frequently studied for the treatment of malignant melanoma and leads to high efficiency in combination with Docarbazine [55–57].

The supportive pieces of evidence in literature and GDSC database verified that CDSML could efficiently predict drug response label associations for the cell-line drug pairs.

4 Conclusion

In this study, we proposed CDSML, a classification method for predicting anti-cancer drug sensitivity by applying manifold learning. It applies four steps of pre-processing, namely, imputing missing values, converting IC50 values to binary labels using max concentration thresholds, similarity calculations, standardization and normalization. We used an imputation procedure to fill the missing values. The similarities of drugs were computed based on the chemical substructure of drugs, STITCH network, and PPI of drug targets. We considered three types of cell line similarities based on gene expression, mutation, and copy number variation of cell lines.

We extended the CDSML application, so that it can be performed on missing values without imputation. Moreover, CDSML can be performed in three similarity settings: using no similarity information, using only one of the cell line or the drug similarities, and using both cell line and drug similarities. CDSML shows high performance in all similarity settings. Even when no similarity is used for training the model, CDSML succeeds in achieving favorable results and outperform many of state-of-the-art methods. When CDSML uses only one of the cell line or the drug similarities, it makes about 6% improvement compared to the case of not using any similarities. However, making use of both cell line and drug similarities make subtle improvement. Additionally, the performance of CDSML is robust on different types of similarities. In other words, making use of various types of similarities by CDSML leads to accurate and almost similar results.

We conducted several validations to assess the rationality of imputation procedure. To this aim, we compared the imputed values with predictions of another state-of-the-art method. In another validation, we replace the suggested implementation procedure with another method. All of validations confirmed that the suggested implementation procedure fills the missing values with reasonable values and using this procedure leads to more reliable results.

For comparison of CDSML performance, we compared its results with three sets of methods: state-of-the-art classification methods, off-the-shelf classification machine learning approaches, and state-of-the-art regression methods. The methods considered in comparisons cover diverse methodologies. In order to compare the results of CDSML with regression methods, we applied max concentration threshold on the predicted IC50 for converting them to sensitive/resistance labels. The methods were evaluated by averaging common classification criteria over 30 repetitions of stratified five-fold cross-validation. The higher performance of CDSML than other methods verifies its efficient predictive power.

We further compared CDSML performance in tissues-specific conditions, because tissue-type may influence the drug response. To this aim, we considered three major tissue types including NSCLC, urogenital system and leukemia. Then, we trained the models on each tissue type. The predictive performance of methods decline subtly on tissue-specific data due to the reduction in sample size. However, CDSML achieved better results in all tissue-specific scenarios, which suggest its capability in retrieving drug sensitivity for each tissue type.
Some of drug responses were unknown in the original dataset. The predicted sensitive associations for the Unknown pairs were considered as case studies and investigated in the latest version of GDSC along with reliable literature. All top 15 novel sensitive predicted pairs were verified in the GDSC database and several pieces of evidence support the novel associations. Therefore, the performance of CDSML in predicting anti-cancer drug sensitivity is efficient.

Some of contributions of this paper are listed below:

- The idea of CDSML was inspired from ADRML, which was a regression method and uses IC50 values for training the model. We changed ADRML in such a way that it can be used in the classification form with high efficiency. The results evidently showed that performing ADRML and just applying a threshold on the predicted IC50 values does not lead to satisfactory performance in classification area. Since suggesting efficient drugs for patients in precision medicine uses the sensitivity of patients to the anti-cancer drugs, it is more essential to predict the sensitivity or resistance label instead of the response values. Therefore, the classification problem has a higher importance than regression problem in this area. In this paper, we have shown that applying max concentration threshold on the inputs and predicting sensitive/resistant labels using manifold learning leads to more reliable sensitivity prediction.

- Moreover, it is helpful to figure out the importance of each cell line or drug similarities on the performance of the classification model. In this paper, we thoroughly investigate the effect of using no similarity, using only the cell line similarity, using only the drug similarity, and using both the drug and cell line similarities on the prediction performance.

- Numerous previous studies have proposed efficient methods for predicting drug responses using regression or classification models. It is highly efficient to set up a framework for comparing all regression and classification methods in a common setting and using fair comparison. We provide a framework to convert the regression models into classification models and compare all methods in classification mode. To this aim, we applied max concentration threshold on the predicted IC50 values in order to convert the predicted values into predicted sensitivity/resistance label.

- The proposed method in this paper has the capability of handling missing values with or without imputation strategy. Moreover, the implemented code is able to perform the proposed method using no similarity, one type of similarity, or both cell line and drug similarities. The implemented code has the capability to adopt the suitable loss function and optimization procedure based on the options that the user determined for the usage of similarity information.

- Several previous papers have used an imputation approach based on nearest neighbors to impute the missing values in response matrix or the feature matrices. The reasonability of using this procedure for imputing missing values were not fully validated in the previous studies. Here, we confirmed the reliability of using this procedure for imputing missing values using four different scenarios.

- Since the algebraic and spectral characteristics of matrices used in manifold learning influence the convergence of the model, we proposed to use the combination of standardization and normalization in this paper in order to handle the negative similarity values and transforming the similarities to more informative matrices with desirable characteristics. Using the combination of standardization and symmetric Laplacian normalization is novel.

- Furthermore, we computed two novel similarities for drugs based on the maximum matching in target PPI network obtained from STRING database and the computed Jaccard index.
in STiTCH network. These two types of similarities for drugs are fully described in the response of subsequent comments and in the revised manuscript. It should be noted that the proposed idea for computing these drug similarities leads to the calculation of highly informative and comprehensive similarities for drugs using the combination of various types of information. Since several drugs in GDSC are not FDA-approved the information about these drugs are not rich. Therefore, introducing new similarities for these anti-cancer drugs is productive. The newly introduced drug similarities may help future studies in this field and other fields related to drug discovery.

Supporting information

S1 File.
(XLSX)

S2 File.
(PDF)

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References

1. National Research Council et al. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. National Academies Press, 2011.

2. Ginsburg Geoffrey S and Phillips Kathryn A. Precision medicine: from science to value. Health Affairs, 37(5):694–701, 2018. https://doi.org/10.1377/hlthaff.2017.1624 PMID: 29733705

3. Zhang Fei, Wang Minghui, Xi Jianing, Yang Jianghong, and Li Ao. A novel heterogeneous network-based method for drug response prediction in cancer cell lines. Scientific reports, 8(1):1–9, 2018. https://doi.org/10.1038/s41598-018-21622-4 PMID: 29463808

4. Choi Jonghwan, Park Sanghyun, and Ahn Jaegoon. Rednn: a reference drug based neural network for more accurate prediction of anticancer drug resistance. Scientific reports, 10(1):1–11, 2020. https://doi.org/10.1038/s41598-020-58821-x PMID: 32024872

5. Esmadi Akram and Eslahchi Changiz. Dsplmf: A method for cancer drug sensitivity prediction using a novel regularization approach in logistic matrix factorization. Frontiers in Genetics, 11:75, 2020. https://doi.org/10.3389/fgene.2020.00075 PMID: 32174963
6. Wang Lin, Li Xiaozhong, Zhang Louxin, and Gao Qiang. Improved anticancer drug response prediction in cell lines using matrix factorization with similarity regularization. *BMC cancer*, 17(1):513, 2017. https://doi.org/10.1186/s12885-017-3500-5 PMID: 28768489

7. Suphavilai Chayaporn, Bertrand Denis, and Nagarajan Niranjan. Predicting cancer drug response using a recommender system. *Bioinformatics*, 34(22):3907–3914, 2018. https://doi.org/10.1093/bioinformatics/bty452 PMID: 29868820

8. Wei Dong, Liu Chuanying, Zheng Xiaoqi, and Li Yushuang. Comprehensive anticancer drug response prediction based on a single cell line-drug complex network model. *BMC bioinformatics*, 20(1):44, 2019. https://doi.org/10.1186/s12859-019-2608-9 PMID: 30670007

9. Moughari Fatemeh Ahmadi and Eslahchi Changiz. Adrml: anticancer drug response prediction using manifold learning. *Scientific Reports*, 10(1):1–18, 2020. https://doi.org/10.1038/s41598-020-77486-0 PMID: 33329352

10. Rohani Narjes, Eslahchi Changiz, and Katanforoush Ali. Iscmf: Integrated similarity-constrained matrix factorization for drug–drug interaction prediction. *Network Modeling Analysis in Health Informatics and Bioinformatics*, 9(1):1–8, 2020. https://doi.org/10.1007/s13721-019-0015-3

11. Garnett Mathew J, Edelman Elena J, Heidorn Sonja J, Greenman Chris D, Dastur Anahita, Lau King Wai, et al. Systematic identification of genomic markers of drug sensitivity in cancer cells. *Nature*, 483(7391):570–575, 2012. https://doi.org/10.1038/nature11005 PMID: 22460905

12. Barretina Jordi, Caponigro Giordano, Stransky Nicolas, Venkatesan Kavitha, Margolin Adam A, Kim Sungsoon, et al. The cancer cell line encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature*, 483(7391):603–607, 2012. https://doi.org/10.1038/nature11003 PMID: 22460905

13. Smirnov Petr, Safikhani Zaleah, El-Hachem Nehme, Wang Dong, She Adrian, Olsen Catharina, et al. Pharmacogx: an r package for analysis of large pharmacogenomic datasets. *Bioinformatics*, 32(8):1244–1246, 2016. https://doi.org/10.1093/bioinformatics/btv723 PMID: 26656004

14. Lu Xiaolu, Gu Hong, Wang Yang, Wang Jia, and Qin Pan. Autoencoder based feature selection method for classification of anticancer drug response. *Frontiers in genetics*, 10:233, 2019. https://doi.org/10.3389/fgene.2019.00233

15. Emdadi Akram and Eslahchi Changiz. Auto-HMM-LMF: feature selection based method for prediction of drug response via autoencoder and hidden Markov model *BMC bioinformatics*, 22(1):1–22, 2021. https://doi.org/10.1186/s12859-021-03974-3 PMID: 33509079

16. Kim Sungwhan, Chen Jie, Cheng Tiejun, Gindulyte Asta, He Jia, He Siqian, et al. Pubchem 2019 update: improved access to chemical data. *Nucleic acids research*, 47(D1):D1102–D1109, 2019. https://doi.org/10.1093/nar/gky1033 PMID: 30371825

17. Landrum Greg. Rdkit documentation. *Release*, 1:1–79, 2013.

18. Wishart David S, Feunang Yannick D, Guo An C, Lo Elvis J, Marcu Ana, Grant Jason R, et al. Drugbank 5.0: a major update to the drugbank database for 2018. *Nucleic acids research*, 46(D1):D1074–D1082, 2018. https://doi.org/10.1093/nar/gko317 PMID: 29126136

19. Szklarczyk Damian, Gable Annika L, Lyon David, Junge Alexander, Wyder Stefan, Huerta-Cepas Jaime, et al. String v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic acids research*, 47(D1):D607–D613, 2019. https://doi.org/10.1093/nar/gky1131 PMID: 30476243

20. Szklarczyk Damian, Santos Alberto, Von Mering Christian, Jensen Lars Juhi, Bork Peer, and Kuhn Michael. Stitch 5: augmenting protein–chemical interaction networks with tissue and affinity data. *Nucleic acids research*, 44(D1):D380–D384, 2016. https://doi.org/10.1093/nar/gkv1277 PMID: 26590256

21. Chang Yoosup, Park Hyejin, Yang Hyun-Jin, Lee Seungju, Lee Kwee-Yum, Kim Tae Soon, et al. Cancer drug response profile scan (cdrscan): a deep learning model that predicts drug effectiveness from cancer genomic signature. *Scientific reports*, 8(1):1–11, 2018. https://doi.org/10.1038/s41598-018-27214-6 PMID: 29891981

22. Brubaker Douglas, Difeo Analisa, Chen Yanwen, Pearl Taylor, Zhai Kaide, Bebek Gurkan, et al. Drug intervention response predictions with paradigm (dirpp) identifies drug resistant cancer cell lines and pathway mechanisms of resistance. In *Biocomputing 2014*, pages 125–135. World Scientific, 2014. PMID: 24297540

23. Iorio Francesco, Knijnenburg Theo A, Vis Daniel J, Bignell Graham R, Menden Michael P, Schubert Michael, et al. A landscape of pharmacogenomic interactions in cancer. *Cell*, 166(3):740–754, 2016. https://doi.org/10.1016/j.cell.2016.06.017 PMID: 27397505

24. Dong Zuoli, Zhang Naiqian, Li Chun, Wang Haiyun, Fang Yun, Wang Jun, et al. Anticancer drug sensitivity prediction in cell lines from baseline gene expression through recursive feature selection. *BMC cancer*, 15(1):489, 2015. https://doi.org/10.1186/s12885-015-1492-6 PMID: 26121976
25. Zhang Naiqian, Wang Haiyun, Fang Yun, Wang Jun, Zheng Xiaoli, and Shirley Liu X. Predicting anti-cancer drug responses using a dual-layer integrated cell line-drug network model. *PloS Comput Biol*, 11(9):e1004498, 2015. https://doi.org/10.1371/journal.pcbi.1004498 PMID: 26418249

26. Rohani Narjes and Eslahchi Changiz. Classifying Breast Cancer Molecular Subtypes by Using Deep Clustering Approach. *Frontiers in genetics*, 11(1):1108, 2020. https://doi.org/10.3389/fgene.2020.553587 PMID: 33324444

27. Sneath PHA. Relations between chemical structure and biological activity in peptides. *Journal of theoretical biology*, 12(2):157–195, 1966. https://doi.org/10.1016/0022-5193(66)90112-3 PMID: 4291386

28. Meyer Jesse G, Liu Shengchao, Miller Ian J, Coon Joshua J, and Gitter Anthony. Learning drug functions from chemical structures with convolutional neural networks and random forests. *Journal of chemical information and modeling*, 59(10):4438–4449, 2019. https://doi.org/10.1021/acs.jcim.9b00236 PMID: 31518132

29. McKinney James D, Richard Ann, Waller Chris, Newman Michael C, and Gerberick Frank. The practice of structure activity relationships (sar) in toxicology. *Toxicological Sciences*, 56(1):8–17, 2000. https://doi.org/10.1093/toxsci/56.1.8 PMID: 10869449

30. Patricia Bento A, Gaulton Anna, Hersey Anne, Bellis Louisa J, Chambers Jon, Davies Mark, et al. The chembl bioactivity database: an update. *Nucleic acids research*, 42(D1):D1083–D1090, 2014. https://doi.org/10.1093/nar/gkt1031 PMID: 24214965

31. Roth Bryan L, Lopez Estelle, Patel Shamil, and Kroeze Wesley K. The multiplicity of serotonin receptors: uselessly diverse molecules or an embarrassment of riches? *The Neuroscientist*, 6(4):252–262, 2000. https://doi.org/10.1177/107385840000600408

32. Rose Peter W, Přišć Andreas, Bi Chunjiao, Bluhm Wolfgang F, Christie Cole H, Dutta Shuchismita, et al. The rcsb protein data bank: views of structural biology for basic and applied research and education. *Nucleic acids research*, 43(D1):D345–D356, 2015. https://doi.org/10.1093/nar/gku1214 PMID: 25428375

33. Kaneshia Minoru, Goto Susumu, Sato Yoko, Kawashima Masayuki, Furumichi Miho, and Tanabe Mao. Data, information, knowledge and principle: back to metabolism in kegg. *Nucleic acids research*, 42(D1):D199–D205, 2014. https://doi.org/10.1093/nar/gkt1076 PMID: 24214961

34. Croft David, Mundo Antonio Fabregat, Haw Robin, Milacic Marija, Weiser Joel, Wu Guanming, et al. The reactome pathway knowledgebase. *Nucleic acids research*, 42(D1):D472–D477, 2014. https://doi.org/10.1093/nar/gkt1102 PMID: 24243840

35. Schaefer Carl F, Anthony Kira, Krupa Shiva, Buchoff Jeffrey, Day Matthew, Hannay Timo, et al. Pid: the rcsb protein data bank: views of structural biology for basic and applied research and education. *Nucleic acids research*, 43(D1):D345–D356, 2015. https://doi.org/10.1093/nar/gku1214 PMID: 25428375

36. Günther Stefan, Kuhn Michael, Dunkel Mathias, Campillos Monica, Senger Christian, Petsalaki Evangelia, et al. Supertarget and matador: resources for exploring drug-target relationships. *Nucleic acids research*, 36(suppl_1):D919–D922, 2007. https://doi.org/10.1093/nar/gkm682 PMID: 17942422

37. Papadimitriou Christos H and Steiglitz Kenneth. *Combinatorial optimization: algorithms and complexity*. Courier Corporation, 1998.

38. Xie Pinchen, Zhang Zhongzhi, and Comellas Francesc. On the spectrum of the normalized laplacian of iterated triangulations of graphs. *Applied Mathematics and Computation*, 273:1123–1129, 2016. https://doi.org/10.1016/j.amc.2015.09.057

39. Fan RK Chung and Fan Chung Graham. *Spectral graph theory*. Number 92. American Mathematical Soc., 1997.

40. Schiebering Geoffrey, Wainwright Martin J, Yu Bin, et al. The geometry of kernelized spectral clustering. *Annals of Statistics*, 43(2):819–846, 2015. https://doi.org/10.1214/14-AOS1283

41. Mongia Aanchal and Majumdar Angshul. Drug-target interaction prediction using multi graph regularized nuclear norm minimization. *PloS one*, 15(1):e0226484, 2020. https://doi.org/10.1371/journal.pone.0226484 PMID: 31945078

42. Liu Jia-Bao, Zhao Jing, Zhu Zhongxun, and Cao Jinde. On the normalized laplacian and the number of spanning trees of linear heptagonal networks. *Mathematics*, 7(4):314, 2019. https://doi.org/10.3390/math7040314

43. Pedregosa Fabian, Varoquaux Gaël, Gramfort Alexandre, Michel Vincent, Thirion Bertrand, Grisel Olivier, et al. Scikit-learn: Machine learning in python. *The Journal of Machine Learning Research*, 12:2825–2830, 2011.

44. Cohen Robert L and Settleman Jeff. From cancer genomics to precision oncology—tissue’s still an issue. *Cell*, 157(7):1509–1514, 2014. https://doi.org/10.1016/j.cell.2014.05.027 PMID: 24949964
45. Yang Jianghong, Li Ao, Li Yongqiang, Guo Xiangqian, and Wang Minghui. A novel approach for drug response prediction in cancer cell lines via network representation learning. *Bioinformatics*, 35(9):1527–1535, 2019. https://doi.org/10.1093/bioinformatics/bty848 PMID: 30304378

46. Ammad-Ud-Din Muhammad, Khan Suleiman A, Malani Dishu, Murumāgi Astrid, Kallioniemi Olli, Alottomikko Tero, et al. Drug response prediction by inferring pathway-response associations with kernalized bayesian matrix factorization. *Bioinformatics*, 32(17):i455–i463, 2016. https://doi.org/10.1093/bioinformatics/btw433 PMID: 27587662

47. Musumeci Francesca, Greco Chiara, Grossi Giancarlo, Molinari Alessio, and Schemer Silvia. Recent studies on ponatinib in cancers other than chronic myeloid leukemia. *Cancers*, 10(11):430, 2018. https://doi.org/10.3390/cancers10110430 PMID: 30423915

48. den Hollander Petra, Shah Shrutl, Zhou Xinhu, Redwood Abena, Shi-Cai Rong, Sobieski Mary, et al. Overcoming therapy resistance in stem cell-rich triple negative breast cancer through p38 map kinase inhibition, 2019.

49. Sahu Nisebita, Chan Emily, Chu Felix, Pham Thinh, Koeppen Hartmut, Forrest William, et al. Cotargeting Hollande Petra, Shah Shruti, Zhou Xinhui, Redwood Abena, Shi-Cai Rong, Sobieski Mary, et al. Overcoming therapy resistance in stem cell-rich triple negative breast cancer through p38 map kinase inhibition, 2019.

50. Matsuhashi Takashi, Date Mutsumi, Kano Miyu, Mizumaki Kie, Tennichi Momoko, Kobayashi Tatadahiro, et al. Blockade of p38 milogen-activated protein kinase inhibits murine sclerodermaent chronic graft-versus-host disease. *The American Journal of Pathology*, 187(4):841–850, 2017. https://doi.org/10.1016/j.ajpath.2018.12.016 PMID: 28189563

51. Chang Hsuen-Wen, Wu Min-Ju, Lin Zih-Miao, Wang Chueh-Yi, Cheng Shu-Yun, Lin Yen-Kuang, et al. Therapeutic effect of repurposed temsirolimus in lung adenocarcinoma model. *Frontiers in pharmacology*, 9:778, 2018. https://doi.org/10.3389/fphar.2018.00778 PMID: 30087612

52. Jia Jianghong, Li Ao, Li Yongqiang, Guo Xiangqian, and Wang Minghui. A novel approach for drug response prediction in cancer cell lines via network representation learning. *Bioinformatics*, 35(9):1527–1535, 2019. https://doi.org/10.1093/bioinformatics/bty848 PMID: 30304378

53. Hwu Wen-Jen, Knight Robert D, Patah Suda, Bassett Roland, Papadopoulos Nicholas E, Kim Kevin B, et al. Phase i safety study of lenalidomide and dacarbazine in patients with metastatic melanoma newly untreated with systemic chemotherapy. *Melanoma research*, 20(6):501–506, 2010. https://doi.org/10.1097/CJR.0b013e32833faf18 PMID: 20859231

54. Glaspy John, Atkins Michael B, Richards Jon M, Agarwala Sanjiv S, O'Day Steven, Knight Robert D, et al. Clinical activity of patupilone in patients with pretreated advanced/metastatic colon cancer: results of a phase ii randomized, double-blind, dose-escalating phase 2 study of lenalidomide in the treatment of metastatic malignant melanoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 115(22):5228–5236, 2009. https://doi.org/10.1002/cncr.24576 PMID: 19728370

55. Eisen Tim, Trefzer Uwe, Hamilton Anne, Hersey Peter, Millward Michael, Knight Robert D, et al. Results of a multicenter, randomized, double-blind, dose-evaluating phase 2/3 study of lenalidomide in the treatment of pretreated relapsed or refractory metastatic malignant melanoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 116(11):1646–1653, 2011. https://doi.org/10.1002/jcono.2011.221 PMID: 21666722

56. Hainsworth John D, Carrell Donna, Drengler Ronald L, Scroggins Carroll Jr, and Anthony Greco F. Weekly combination chemotherapy with docetaxel and gemcitabine as first-line treatment for elderly patients and patients with poor performance status who have extensive-stage small cell lung carcinoma: A minnie pearl cancer research network phase ii trial. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 100(11):2437–2441, 2004. https://doi.org/10.1002/cncr.20281
61. Smyth JF, Smith IE, Sessa C, Schoffski P, Wanders J, Franklin H, et al. Activity of docetaxel (taxotere) in small cell lung cancer. *European Journal of Cancer*, 30(8):1058–1060, 1994. https://doi.org/10.1016/0959-8049(94)90455-3

62. Rieke Damian T, Zuo Zhixiang, Endhardt Katharina, Keck Michaela, Khattri Arun, Mahmutoglu Derya, et al. Fibroblast growth factors in head and neck cancer: Genetic alterations and therapeutic targeting with ponatinib, 2012.

63. Gozgit Joseph M, Wong Matthew J, Moran Lauren, Wardwell Scott, Mohemmad Qurish K, Narasimhan Narayana I, et al. Ponatinib (ap24534), a multtargeted pan-fgfr inhibitor with activity in multiple fgfr-amplified or mutated cancer models. *Molecular cancer therapeutics*, 11(3):690–699, 2012. https://doi.org/10.1158/1535-7163.MCT-11-0450 PMID: 22238366

64. Godfrey C, Mohanlal R, Merica E, and Ette E. The pharmacokinetics (pk) and pharmacodynamics (pd) of vx-702, a novel, oral p38map kinase inhibitor, in healthy volunteers. *Clinical Pharmacology & Therapeutics*, 75(2):P52–P52, 2004. https://doi.org/10.1016/j.cpt.2003.11.197