Anti-cancer Drug Activity Prediction by Ensemble Learning

Ertan Tolan and Mehmet Tan
Department of Computer Engineering, TOBB University of Economics and Technology, Ankara, Turkey

Keywords: Cancer, Drug Activity, Ensemble Learning.

Abstract: Personalized cancer treatment is an ever-evolving approach due to complexity of cancer. As a part of personalized therapy, effectiveness of a drug on a cell line is measured. However, these experiments are backbreaking and money consuming. To surmount these difficulties, computational methods are used with the provided data sets. In the present study, we considered this as a regression problem and designed an ensemble model by combining three different regression models to reduce prediction error for each drug-cell line pair. Two major data sets were used to evaluate our method. Results of this evaluation show that predictions of ensemble method are significantly better than models *per se*. Furthermore, we report the cytotoxicty predictions of our model for the drug-cell line pairs that do not appear in the original data sets.

1 INTRODUCTION

It's a known fact that personalized cancer treatment and medicine are more effective methods than traditional therapies (Jackson and Chester, 2015). As a part of personalized treatment, experiments on tumor cells show how sensitive a tumor cell is to an anticancer drug. On deciding whether a given drug will be effective or not on the treatment of a certain cancer, experimental results on cancer cell lines are generally the starting point. However, large-scale screens of chemical compound-cell line pairs do have a significant cost due to large numbers potential drug candidates. To overcome this problem, computational models to predict drug responses are designed instead of performing wet-lab experiments for each drug response on the tumor cell.

Building models to predict drug activity has become possible due to the recent introduction of large-scale drug response screens. These databases are composed of the results of cytotoxicity experiments of a large number of chemical compounds against hundreds of cancer cell lines. The cell lines are characterized in terms of several different data types such as gene expression, DNA methylation and copy number variation data. Among these, gene expression data is considered the most informative as also confirmed by a recent DREAM challenge (Costello et al., 2014).

Models for prediction of half maximum inhibitory concentration (IC_{50}) and area under the dose-response curve (AUC) consider this either as classification or a regression problem. In comparison with binary classification (drug is sensitive or not), regression problem is explicitly harder, nevertheless it gives much more information on how drug affects tumor cell.

We define an ensemble model which combines three distinctive methods; trace-norm regularized multitask learning, kernelized Bayesian multitask learning and gradient boosting regression to predict drug responses. Since joint learning is a favorable method for response prediction of cancer drugs due to applicability of drugs as related tasks of multitask learning model , we choose two prominent and publicly available multitask learning models . Also GBR is chosen among single task learning models by considering predictive power. To build our predictive model, we use hundreds of cell lines and drug responses provided by genomics of drug sensitivity in cancer(Yang et al., 2013) and cancer therapeutics response portal(Seashore-Ludlow et al., 2015) (Rees et al., 2015) data sets.

2 RELATED WORK

To predict drug responses,(Zhang et al., 2015) developed cell line similarity network (CSN) and drug similarity network (DSN) based on similar cell lines and similar drugs have similar responses. By combining these similarity networks with a linearly weighted model they propose integrated network which outperforms single-layer models. (Bansal et al., 2014)

Tolan, E. and Tan, M.
Anti-cancer Drug Activity Prediction by Ensemble Learning.
DOI: 10.5220/0006085704310436
In *Proceedings of the 8th International Joint Conference on Knowledge Discovery, Knowledge Engineering and Knowledge Management (IC3K 2016) - Volume 1: KDIR*, pages 431-436
ISBN: 978-989-758-203-5

show computational prediction of compound-pair activity is possible by using single-compound perturbation data. Another method to develop efficient cancer therapies taking advantage of synergistic effects of different drugs is proposed by (Qin et al., 2015). (Dong et al., 2015), unlike the other methods, combine two different databases, Cancer Cell Line Encyclopedia and CGP, to build and evaluate their model.

Omissions of drug responses make data set smaller. By using kernelized bayesian multitask learning (Gonen and Margolin, 2014) off-target effects and experimental noise are eliminated and shortcomings of discarding missing values are compensated. Learning model of Gonen is highly applicable for drug response prediction and publicly available.

Feature selection is used to reduce dimension of data to purify from irrelevant features. (Zhao et al., 2013) develop their model with feature selection and multiple instance learning. (Menden et al., 2013) combine structural drug properties and genomic characterizations of cell lines to build their model. Also (Cortés-Ciriano et al., 2015) use combination of the chemical information of compounds and cell line profiling data as input. By associating multivariate interaction of gene expression levels, (Riddick et al., 2011) improve ability of drug response predictions. (Haider et al., 2015) show that copula based multivariate random forest framework enhances the accuracy and provides improved variable selection.

3 METHODS

We benefit from subset selection by the methods given below. Also we includes determined singletask and multitask learning methods to generate an ensemble model. Parameters of these models are obtained by using optimization algorithms. Moreover the way of combination for ensemble model is detailed and illustrated.

3.1 Feature Selection

As the number of genes is greater than the number of samples, we applied a gene selection procedure that exploits the MalaCards database (Rappaport et al., 2013). From this database, one can get the list of genes currently known to be related to the disease of interest. We generated a set of keywords that are based on the cancer types of the cell lines and downloaded the list of genes related to the cancer cell lines. This constituted a list of 1545 genes. We used the intersection of this list with the list of genes in the gene expression data of the data sets used.

3.2 Gradient Boosting Regression

For regression problems, Gradient Boosting Regression (GBR) (Friedman, 2002) is a powerful machine learning algorithm. GBR is an ensemble model composed of many weak learners largely represented by decision trees. By adding each weak learner iteratively to the existing model, shortcomings of the current strong learner is compensated. As a part of our ensemble model we use LSBoost which is found in MATLAB Statistics and Machine Learning Toolbox. We set *Learners* to Tree with default parameters. The other two important parameters for GBR are *NLearn*, number of learners in the model, and *LearnRate*, learning rate for shrinkage. We set *NLearn* and *LearnRate* to 100 and 0.1 which are the popular choices for GBR. By utilizing GBR with defined parameters we obtain good predictive model.

3.3 Trace-norm Regularized Multitask Learning

Instead of training machine learning tasks individually, Multitask Learning (MTL) considers related tasks simultaneously. Training tasks concurrently help tasks be better learned (Caruana, 1998). To benefit from MTL, tasks, such as various anti-cancer drugs, should be related to each other.

Like the other regularization functions, trace-norm regularization adjusts the learning models to prevent over fitting by penalizing the complexity. Trace-norm, also known as the nuclear-norm, is a familiar case of Schatten p-norm where $p = 1$. Based on trace-norm, Trace-Norm Regularized Multitask Learning(Ji and Ye, 2009) considers this problem:

$$\min_{W} \sum_{i=1}^{n} f(W) + \lambda \|W\|_{*} \qquad (1)$$

We used grid search to optimize regularization parameter, λ, from the list of 0.1, 1, 10, 100 for both data sets. We used the MATLAB implementation of MALSAR(Zhou et al., 2012) for TRMTL.

3.4 Kernelized Bayesian Multitask Learning

(Gonen and Margolin, 2014) propose a method which includes novelties such as using a shared subspace for all tasks to eliminate noise and overcoming problem of missing values. This method, called kernelized Bayesian multitask learning (KBMTL), is convenient for both binary classification and regression problems. We use regression with the default parameters given at the implementation of KBMTL.

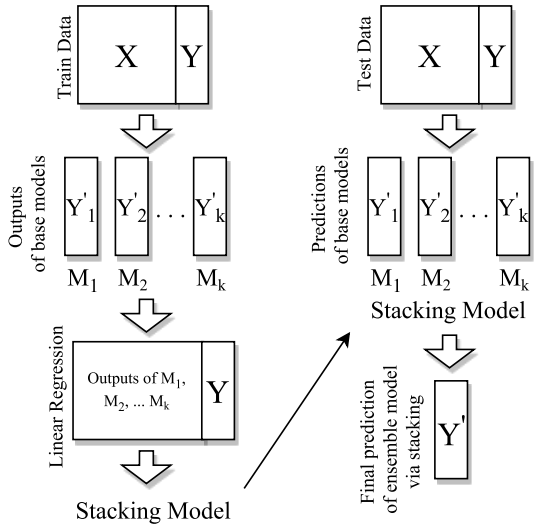


Figure 1: Stacking algorithm.

3.5 Ensemble Model

Ensemble learning is the way of combining various machine learning algorithms to acquire better predictions. There are several ensemble models such as averaging, voting,stacking etc. (Sewell, 2008). We design an ensemble model which consists of the above learning methods by stacked generalization(Wolpert, 1992). In stacking, outputs of base predictors and target values for training data are used to generate linear combinations. By using predictions of base predictors as feature vectors, stacking model with the obtained coefficients is used to combine models (Figure 1).

As the stacking model, we experimented with both linear regression and regression tree where we got better results *via* linear regression. Although model parameters are usually derived by 2-folds for stacking, we used 5-folds where we achieved better performance.

4 EXPERIMENTAL RESULTS

4.1 Data Sets

To evaluate our model we use two major data sets for cell line-drug responses and gene expression data of relevant cell lines.

Genomics of drug sensitivity in cancer (GDSC) consists of 265 drugs, 1074 cell lines and 224,510 drug response values. Natural log of half maximal inhibitory concentration ($\log(IC_{50})$) and area under the dose-response curve (AUC) values are provided by GDSC thereby we evaluate our model with both of them. Also gene expressions of cell lines are presented as RMA normalized basal expression profiles with some deficiencies. After we removed those cell lines without gene expression data, 1014 cell lines remain. Numbers of experimented cell lines for drugs range between 363 and 940 .

Cancer therapeutics response portal (CTRP) contains 481 drugs and 860 cell lines. Sensitivity scores (AUC) of drug - cell lines and average log2-transformed gene-expression values for each gene and cancer cell line are used to evaluate our model. Analogously we removed cell lines with no gene expression data and 823 cell lines remain. Furthermore, for some drugs, there are insufficient number of cell lines with response value. To avoid this inadequacy, we set a limit on the sample size of the drugs. Consequently we discard drugs with less than 250 samples and consider 439 drugs with sufficient response values. Among these 439 drugs , minimum and maximum numbers of experimented cell lines are 299 and 809 respectively.

4.2 Data Preprocessing

For TRMTL and KBMTL, data is split into train and test , than we normalize train data to have zero mean and unit standard deviation. And to normalize test data, mean of train data is subtracted from test data and divided by standard deviation of train data.

The process of dimensionality reduction lower the number of attributes and applying kernel trick linear models transform to non-linear models. For these purposes, using the (Gaussian) radial basis function kernel (RBF) is known method.

We choose parameter of σ by using internal 5-fold grid search algorithm for each data set. Parameter ranges are generated referring the mean of pairwise Euclidean distances between data points (Gonen and Margolin, 2014). As we obtain the ranges, [22, 24, 27, 31, 38, 55] and [25, 27,30,35,43,62] , 24 and 27 are selected for GDSC and CTRP data sets.

For tree-based algorithms such as GBR, normalization doesn't matter because of these methods only care about whether a value is greater or lower. Also there is no need to kernel trick for nonlinear learning models. Thereby, these processes are ignored for Gradient Boosting Regression and data is given to the model without normalization and using kernel.

In order to show that the ensemble model performs better than other methods we evaluate learning models with 10-fold cross validation and three different metrics, average of drugs' mean squared error (AMSE) (2), weighted average of drugs' mean squared error (WAMSE) (3) and the number of drugs

predicted best by each estimator (NDPB). AMSE and WAMSE are calculated as

$$\text{AMSE} = \frac{1}{T}\sum_{t=1}^{T}\frac{1}{n_t}\sum_{i=1}^{n}(\hat{Y}_{t_i} - Y_{t_i})^2 \quad (2)$$

$$\text{WAMSE} = \frac{1}{\sum_{t=1}^{T} n_t}\sum_{t=1}^{T}\sum_{i=1}^{n}(\hat{Y}_{t_i} - Y_{t_i})^2 \quad (3)$$

where T is the number of drugs and n is the number the sample size for each drug.

Table 1: Results for GDSC Data set (IC_{50}).

	GBR	TRMTL	KBMTL	Ensemble
NDPB	26	4	6	**229**
AMSE	1.65	1.87	1.83	**1.60**
WAMSE	1.63	1.87	1.81	**1.58**

Table 2: Results for GDSC Data set (AUC).

	GBR	TRMTL	KBMTL	Ensemble
NDPB	**160**	18	4	83
AMSE	1.51×10^{-2}	1.84×10^{-2}	1.72×10^{-2}	1.51×10^{-2}
WMSE	1.51×10^{-2}	1.85×10^{-2}	1.71×10^{-2}	1.5×10^{-2}

Table 3: Results for CTRP Data set (AUC).

	GBR	TRMTL	KBMTL	Ensemble
NDPB	68	63	10	**298**
AMSE	2.07	2.38	2.32	**2.03**
WMSE	2.09	2.40	2.33	**2.05**

As it can be seen in the Tables 1 and 3, ensemble model outperforms the other models for almost all the drugs especially for GDSC data set. And error rates decrease significantly for both of the data sets.

Individual MSE of anti-cancer drugs are presented in the Figures 2(a) , 2(b) and 2(c) for IC50 and AUC values on GDSC data set and AUC values on CTRP data set respectively. Ensemble model outperforms the base models for 229 out of 265 drugs on GDSC data set and 298 out of 439 drugs on CTRP data set.

4.3 New Activity Predictions

After training our model, we predict non-experimented drug-cell line pairs to define whether a drug is sensitive on a cell line or not. We present the drugs that are predicted to be most active (and corresponding cell lines) in Tables 4 and 5.

With the model we designed, it is revealed which cell line is sensitive to which drug *in slico*, (e.g. Bortezomib is sensitive on SW756). Also we can respond to the question of 'Which drug is more effective on a given cell line?' (e.g., Epothilone B is more active than Thapsigargin on IOSE-397).

Performed *in vivo* experiments confirm the predictions of our model on drug-cell line pairs indicated at Table 4. For instance, Bortezomib is efficacious on SW756 cells and among the other drugs experimented, the combination of bortezomib with eeyarestatin efficiently suppressed clonal growth of SW756 cells (Brem et al., 2013). Also (Shi et al., 2016) shows that docetaxel controls the progression of tumor and docetaxel is conjugated *via* ester linkage to improve the therapeutic efficacy in HSC-3 cells.

Similar experiments exist in the literature for the given pairs at Table 5. For example, synergy is observed by using LOR-253 with BRD-A05821830 or BRD-A28746609 in sequential and concurrent treatments on NCIH226 cells (Cukier et al., 2012).

Table 4: Predictions on GDSC Data set.

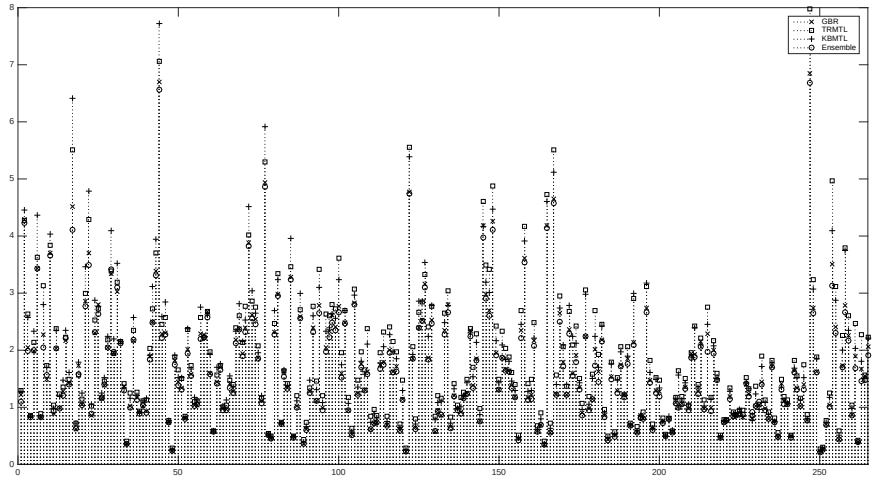
Compound	Cell Line	IC50
Bortezomib	SW756	-7.50
Docetaxel	HSC-3	-6.83
Epothilone B	IOSE-397	-6.07
GSK2126458	RCH-ACV	-5.86
AICAR	A673	-5.68
SN-38	SUP-B15	-5.59
YM155	OCI-LY7	-5.31
Vinorelbine	RCH-ACV	-4.83
Thapsigargin	IOSE-397	-4.79

Table 5: Predictions on CTRP Data set.

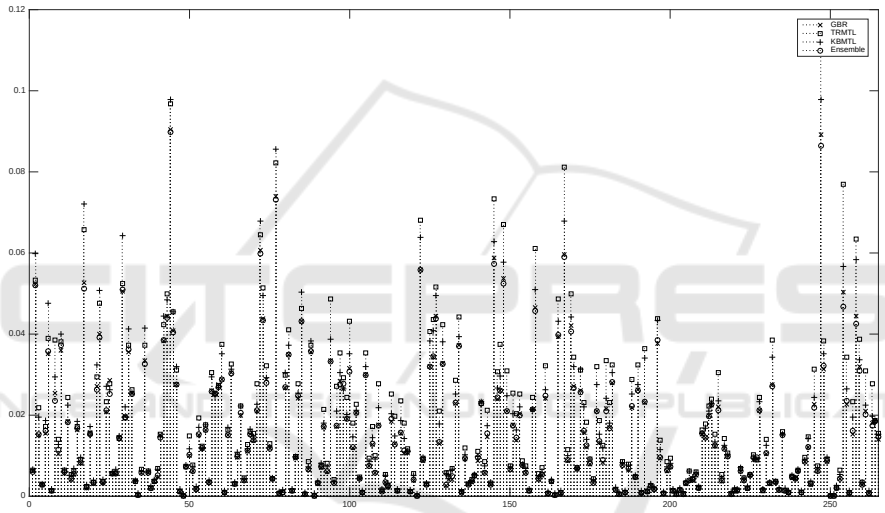
Compound	Cell Line	AUC
BRD-K13662825	D283MED	0.05
BRD-K27624156	TE14	1.69
BRD-A05821830	NCIH226	1.78
BRD-A28746609	NCIH226	2.05
BRD-K02130563	AMO1	2.11
BRD-K82109576	NCIH1793	2.50
BRD-K92428232	NCIH1793	3.00
BRD-K23547378	NCIH1793	3.08
BRD-K76674262	NCIH1793	3.16

5 CONCLUSION

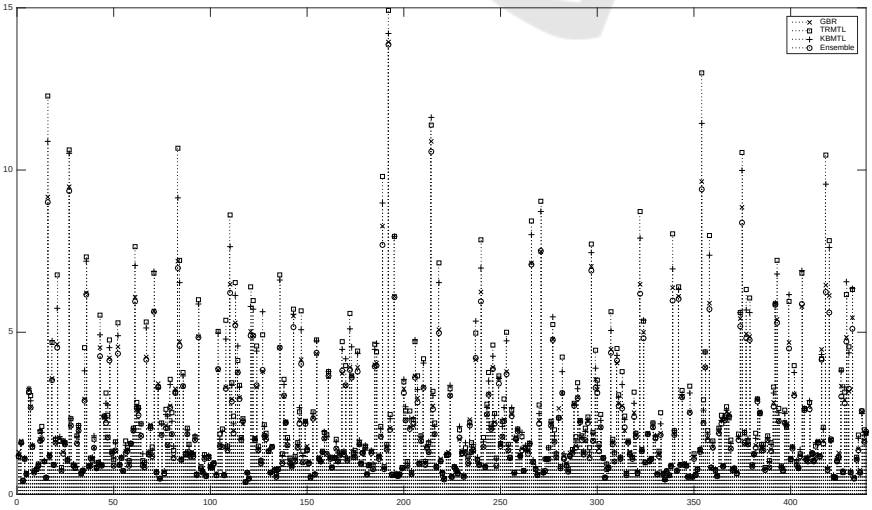
In this study, we design an ensemble model which combines three distinctive learning models, GBR, TRMTL and KBMTL To validate our model we use two largest accessible data sets for sensitivities on drug cell line pairs. Cross validation results on these data sets show that our model surpasses the others. In the light of these results, we made new predictions for pairs that are not available in the original data sets.



(a) GDSC (IC_{50}



(b) GDSC (AUC)



(c) CTRP (AUC)

Figure 2: MSE for each drug (Dataset (Metric)).

Enhancement on the predictions of our model arises from selecting proper models to combine and the way of combination. We select three distinctive models, and combine them by using stacked generalization.

There are several extensions that we plan to study. First, designed ensemble model can be extended by the other learning models or the other ways to combine models. As stated, these selections play a key role in ensemble models. Besides that, after overcoming the matching problems of drugs or cell lines arising from varied denomination, model can be trained by using more balanced data sets for each drug by unifying different data sets. Furthermore, used features are important for models. For drug response prediction, traditional way is using gene expression data but features can be extended *via* integration of drugs' chemical information and other genomic features.

ACKNOWLEDGEMENTS

This study is supported by The Scientific and Technological Research Council of Turkey, Grant no: 115E274.

REFERENCES

Bansal, M., Yang, J., et al. (2014). A community computational challenge to predict the activity of pairs of compounds. *Nature Biotechnology*, 32(2):1–3.

Brem, G. J., Mylonas, I., et al. (2013). Eeyarestatin causes cervical cancer cell sensitization to bortezomib treatment by augmenting ER stress and CHOP expression. *Gynecologic Oncology*, 128:383–390.

Caruana, R. (1998). Multitask Learning. In *Learning to Learn*, pages 95–133. Springer US, Boston, MA.

Cortés-Ciriano, I., van Westen, G. J. P., et al. (2015). Improved large-scale prediction of growth inhibition patterns using the NCI60 cancer cell line panel. *Bioinformatics*, 32(1):btv529.

Costello, J. C., Heiser, L. M., et al. (2014). A community effort to assess and improve drug sensitivity prediction algorithms. *Nature Biotechnology*, 32(12):1202.

Cukier, H., Peralta, R., et al. (2012). Preclinical dose scheduling studies of lor-253, a novel anticancer drug, in combination with chemotherapeutics in lung and colon cancers. In *AACR; Cancer Res*, volume 72.

Dong, Z., Zhang, N., et al. (2015). Anticancer drug sensitivity prediction in cell lines from baseline gene expression through recursive feature selection. *BMC cancer*, 15(1):489.

Friedman, H. (2002). Stochastic gradient boosting. *Computational Statistics and Data Analysis*, 38(4):367–378.

Gonen, M. and Margolin, A. A. (2014). Drug susceptibility prediction against a panel of drugs using kernelized Bayesian multitask learning. *Bioinformatics*, 30(17):i556–i563.

Haider, S., Rahman, R., et al. (2015). A Copula Based Approach for Design of Multivariate Random Forests for Drug Sensitivity Prediction. *PLOS ONE*, 10(12):e0144490.

Jackson, S. E. and Chester, J. D. (2015). Personalised cancer medicine. *International Journal of Cancer*, 137(2):262–266.

Ji, S. and Ye, J. (2009). An accelerated gradient method for trace norm minimization. In *Proceedings of the 26th annual ICML*, pages 457–464. ACM.

Menden, M. P., Iorio, F., et al. (2013). Machine Learning Prediction of Cancer Cell Sensitivity to Drugs Based on Genomic and Chemical Properties. *PLoS ONE*, 8(4):e61318.

Qin, Y., Chen, M., et al. (2015). A network flow-based method to predict anticancer drug sensitivity. *PLoS ONE*, 10(5):1–14.

Rappaport, N., Nativ, N., et al. (2013). MalaCards: an integrated compendium for diseases and their annotation. *Database : the journal of biological databases and curation*, 2013:bat018.

Rees, M. G., Seashore-Ludlow, B., et al. (2015). Correlating chemical sensitivity and basal gene expression reveals mechanism of action. *Nature Chemical Biology*, 12(2):109–116.

Riddick, G., Song, H., et al. (2011). Predicting in vitro drug sensitivity using Random Forests. 27(2):220–22410.

Seashore-Ludlow, B., Rees, M. G., et al. (2015). Harnessing Connectivity in a Large-Scale Small-Molecule Sensitivity Dataset. *Cancer discovery*, 5(11):1210–23.

Sewell, M. (2008). Ensemble learning. *RN*, 11(02).

Shi, L., Song, X.-B., et al. (2016). Docetaxel-conjugated monomethoxy-poly(ethylene glycol)-b-poly(lactide) (mPEG-PLA) polymeric micelles to enhance the therapeutic efficacy in oral squamous cell carcinoma. *RSC Adv.*, 6(49):42819–42826.

Wolpert, D. H. (1992). Stacked generalization. *Neural Networks*, 5(2):241–259.

Yang, W., Soares, J., et al. (2013). Genomics of Drug Sensitivity in Cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells. *Nucleic Acids Research*, 41(D1):D955–D961.

Zhang, N., Wang, H., et al. (2015). Predicting Anticancer Drug Responses Using a Dual-Layer Integrated Cell Line-Drug Network Model. *PLoS computational biology*, 11(9):e1004498.

Zhao, Z., Fu, G., et al. (2013). Drug activity prediction using multiple-instance learning via joint instance and feature selection. *BMC Bioinformatics*, 14 Suppl 1(Suppl 14):S16.

Zhou, J., Chen, J., and Ye, J. (2012). User's Manual MALSAR: Multi-tAsk Learning via StructurAl Regularization. *Arizona State University*.