A GENERATIVE RECOMMENDER SYSTEM WITH GMM PRIOR FOR CANCER DRUG GENERATION AND SENSITIVITY PREDICTION

Krzysztof Koras¹  Marcin Możejko¹  Paulina Szymczak¹  Adam Izdebski¹  Eike Staub²

Ewa Szczurek¹,*

ABSTRACT
Recent emergence of high-throughput drug screening assays sparkled an intensive development of machine learning methods, including models for prediction of sensitivity of cancer cell lines to anticancer drugs, as well as methods for generation of potential drug candidates. However, the concept of generating compounds with specific properties and simultaneous modeling of their efficacy against cancer cell lines has not been comprehensively explored. To address this need, we present VADEERS, a Variational Autoencoder-based Drug Efficacy Estimation Recommender System. The generation of compounds is performed by a novel variational autoencoder with a semi-supervised Gaussian mixture model (GMM) prior. The prior defines a clustering in the latent space, where the clusters are associated with specific drug properties. In addition, VADEERS is equipped with a cell line autoencoder and a sensitivity prediction network. The model combines SMILES string representations of anti-cancer drugs, their inhibition profiles against a panel of protein kinases, cell lines’ biological features and measurements of the sensitivity of the cell lines to the drugs. The evaluated variants of VADEERS achieve a high $r = 0.87$ Pearson correlation between true and predicted drug sensitivity estimates. We show that the learned latent representations and new generated data points accurately reflect the given clustering. In summary, VADEERS offers a comprehensive model of drugs’ and cell lines’ properties and relationships between them, as well as a guided generation of novel compounds.

1 Introduction
Kinase inhibitors are a class of anticancer drugs that target specific mutated kinases and disregulated biological processes in tumor cells [1]. As such, they constitute flagship examples of personalized cancer treatments [2, 3]. Drugs can be represented using SMILES (Simplified Molecular-Input Line-Entry System) strings, which use a chemical grammar to specify the chemical structure through text sequences [4]. In addition, the set of kinase inhibitors is deeply investigated experimentally. They are commonly characterized by their inhibition profiles, measuring their strength of inhibition of a panel of kinases [5, 6]. In contrast to information about just the putative targets of the drugs, inhibition profiles can also account for the off-target effects. In addition, the sensitivity of cancer cell lines to kinase inhibitors was measured by large-scale experiments [7, 8, 9]. The molecular features of these cancer cell lines, such as gene mutations and gene expression were also profiled [7, 8, 10]. Despite their limitations, cancer cell lines commonly act as laboratory proxies for patients’ tumors and it is known that their molecular features are key determinants of their response to anticancer drugs [8, 11]. While a number of kinase inhibitor drugs is already successfully applied in the clinic, the mechanism of resistance to treatment and a large number of cancer mutations that could be additionally targeted to circumvent this resistance creates a pressing need for novel drug discovery [12, 13, 14]. Unfortunately, the current pre-clinical attempts of proposing novel compounds proves inefficient, as the drug candidates fail further stages of clinical trials, yielding the process of novel drug discovery a daunting, time and money consuming task [15, 16, 17].

Machine learning, in particular deep generative models, transform the field of molecule discovery, providing promising drug candidates with with desired chemical properties [18, 19, 20, 21, 22, 23, 24].

¹Faculty of Mathematics, Informatics and Mechanics, University of Warsaw
²Merck KGaA, Translational Medicine, Department of Bioinformatics
*szczurek@mimuw.edu.pl
Key problems. This work addresses several important research problems.

• **Existing generative molecule models are not directly applicable to kinase inhibitors.** They require large amounts of compounds for training, while the number of known kinase inhibitors is scarce. Moreover, they do not account for the molecular features of the drugs and of the tumors that the drugs are supposed to act on. Drug sensitivity is a function of both compound’s and tumor’s features, and it is the relationship between these two feature sets that determines the treatment outcome.

• **Existing machine learning models for drug sensitivity prediction are not generative.** Combining the functionalities of prediction and generation in a single model has the potential to mutually strengthen the performance of the model in both tasks, while regularizing the model and preventing overfitting to a single task.

• **The data available for the drugs and the cell lines pose a difficult integration problem with missing data:** for some drugs, only the sensitivity of the cell lines to these drugs was measured and not their inhibition profiles, and vice versa. Finally, there exist compounds for which only the SMILES strings are known.

Proposed solutions. In this work, we propose a novel generative framework for simultaneous kinase inhibitor discovery and sensitivity prediction. The framework restricts the vast space of potential generative model hypotheses by accounting for a large variety of experimental data (Fig. 1a). Specifically, we cluster the drugs by their inhibitory profiles, and provide the clustering of the drugs together with the drugs’ SMILES representations, cell line molecular features, the inhibitory profiles and the sensitivity values as input to the model for training. Due to the fact that for some drugs the inhibition profiles are not available, the clustering provides only partial cluster labels for the drugs, posing a semi-supervised clustering problem. The generative drug module of the framework is implemented using SS GMM VAE, a new semi-supervised variational autoencoder (VAE) model with a Gaussian mixture model (GMM) prior (Fig. 1p). SS GMM VAE infers representations of the drugs’ SMILES and enables generation of specific types of kinase inhibitors, guided by the clustering of their inhibitory profiles within the GMM prior. In addition, the framework includes also a cancer cell line module for identification of representations of cancer cell lines and a sensitivity prediction module that performs the prediction of the sensitivity of the cell lines to the drugs (Fig. 1c, d).

On the most general level, the proposed framework can be thought of as an extension of a recommender system with side information [25, 26, 27, 28, 29] with a generative model. In our particular application, in the generative recommender system the objects correspond to drugs from the family of kinase inhibitors, users to cancer cell lines, while the scores correspond to the sensitivity of the cell lines to the drugs. Hence the name of the framework, i.e. Variational Autoencoder-based Drug Efficacy Estimation Recommender System (VADEERS).

Key contributions. This work offers the following key novel contributions:

• VADEERS, an integrative framework that combines i) generation of kinase inhibitor drugs with ii) finding their representations, iii) modeling of cancer cell lines and their representations, and iv) prediction of cancer cell line sensitivity to drugs (Fig. 1p).

• SS GMM VAE, which is trainable with partial cluster labels. We introduce a novel formulation of the prior, which, in contrast to previous GMM VAES, enables semi-supervised cluster inference without an additional inference model. Thanks to SS GMM VAE, VADEERS is able to generate novel drugs having specific types of inhibitory profiles and readily predict their their sensitivity profile on cancer cell lines.

2 Related work

Machine learning models for drug sensitivity prediction Multiple machine learning models were proposed for the prediction of the sensitivity of cancer cell lines to the drugs [30, 31, 32, 33, 34], including recommender system-based approaches [35, 36, 37]. All these methods lack the ability of generating novel compounds.

Deep generative models for anticancer drug discovery The majority of existing methods for compound generation focus on generating compounds with specified chemical properties, without taking into account the broader biological context, e.g. efficacy of compounds against cancer cell lines or other cancer models. Recently, Born et al. [38] proposed a model aiming at generating compounds that target specific gene expression profiles via a hybrid VAE acting as the generator of compounds. In the proposed reinforcement learning paradigm, the compound generator serves as an agent, while the output of the model predicting drug sensitivity serves as a reward function, which allows to train the agent to produce more and more effective compounds against a given gene expression profile. Joo et al. [39] proposed a conditional VAE, in which generation of new molecular fingerprints is conditioned on drug sensitivity. Related problem was also approached without resolving to probabilistic generative models by efficient Monte Carlo tree search [40]. VAEs have also appeared in the context of drug sensitivity modeling focusing more on the prediction aspect [41], or applied to cancer models, rather than compounds [32, 33].
**Recommender systems with generative components** Recommender systems were traditionally applied in the field of e-commerce, where user decisions are recorded online. Generative adversarial network-based models proved useful in dealing with the lack of explicitly negative samples in such applications \cite{44,45,46,47}. GANs were also used to imitate user behavior dynamics in reinforcement learning-based recommender systems to better approximate the reward function and simulate the environment in this setting \cite{48,49}. We are not aware of recommender systems equipped with VAE that accounts of a given clustering of the objects.

**GMM VAEs** GMM VAEs are extensions to standard VAEs. Recall that VAEs \cite{50} are latent variable, generative models, where sampling from a prior distribution \(p(z)\) in the latent space \(Z\) is followed by a sampling from \(p_{\theta}(x|z)\) in the data space \(X\). The probability distribution \(p_{\theta}(x|z)\) is modeled using a neural network called decoder. Since usually the log marginal likelihood \(p(x)\) is intractable, its following evidence lower bound (ELBO) is maximized instead:

\[
\mathcal{L}_{ELBO}(X) = \mathbb{E}_{q_{\phi}(z|x)} \left[ \ln p_{\theta}(x | z) \right] - D_{KL}(q_{\phi}(z|x) || p(z)),
\]

where \(q_{\phi}(z|x)\) is the variational approximation of a posterior distribution \(p(z|x)\), and \(D_{KL}\) stands for Kullback–Leibler divergence. \(q_{\phi}(z|x)\) is usually modeled as a Gaussian distribution \(\mathcal{N}(\mu(x), \text{diag}(\sigma(x)))\) where \(\mu(x)\) and \(\sigma(x)\) are outputs from a neural network called an encoder.

Notably, a different choice of the prior distribution \(p(z)\) may impose different trade-offs between the simplicity of model optimization and the expressive power of the modeled distribution. For example, the standard normal prior \(p(z) \sim \mathcal{N}(0, I)\) carries the simplicity of optimization of \(D_{KL}(q_{\phi}(z|x) || p(z))\), at the cost of not imposing any particular structure on the latent space, nor utilizing any prior knowledge regarding the data. Another popular choice of a prior \(p(z)\) is a GMM \cite{51,52,53,54,55,56,57,58,59,60,61,62,63,64,65}. The GMM prior naturally corresponds to clustering, where the points from the same cluster come from the same Gaussian distribution and thus group together in the latent space. In this context, the previous GMM VAE models can be divided into semi-supervised \cite{55,56,57,58,59} and unsupervised \cite{52,51,60,61,62,63,64,65} clustering methods. Importantly, the previous semi-supervised GMM VAE models required an additional classifier for training procedure.

\[
p(z | x) = \sum_{k=1}^{K} \pi_k \mathcal{N}(z | \mu_k, \Sigma_k).
\]

3 Methods

3.1 SS GMM VAE

We propose an extension to the classical GMM VAE by allowing a semi-supervised learning of the GMM prior. In a GMM, for a given point \(x\) there is a categorical hidden variable \(C \sim \text{Cat}(\pi_1, \ldots, \pi_K)\), defining the component of the mixture for that point. The conditional probability of \(z\) given the component \(C = k\), is then defined by a Gaussian distribution \(\mathcal{N}(\mu_k, \Sigma_k)\), for \(k = 1, \ldots, K\). Therefore, in the case when the \(C\) variable is not observed, the likelihood for point \(z\) in GMM is computed by marginalizing over the values of \(C\):

\[
p(z) = \sum_{k=1}^{K} \pi_k \mathcal{N}(z | \mu_k, \Sigma_k).
\]
In SS GMM VAE, we consider that the categorical variables defining the mixture components for each point in the latent space are partially observed for some of the training data. More formally, the training input data $D$ with $N$ samples can be divided into two disjoint sets $D_o$ and $D_h$, with $D=D_o\cup D_h$. The set $D_o=\{x^{(1)}, \ldots, x^{(n)}\}$, where $n\leq N$, is a set of samples $x^{(i)}$ for which the component variable $C^{(i)}$ is observed and $C^{(i)}=k^{(i)}$, where $k^{(i)}\in\{1, \ldots, G\}$, for $G\leq K$. We further refer to these observed component values as the guiding labels. The guiding labels can be defined by an independent, given clustering of the samples in some external data space. In such a case, the external data is referred to as guiding data. Note that with $G<K$ some of the assumed components will not appear as a guiding label for any training sample. Such components correspond to additional clusters of samples that exist but are never observed. By allowing additional components in the latent space, we still are able to model these clusters in the latent space. In contrast to $D_o$, the set $D_h=\{x^{(n+1)}, \ldots, x^{(N)}\}$, is a set of samples, for which the components are hidden. In such a setting, we define the latent prior $p(\bar{z})$ as a generalization of Eq. (2) in the following form

$$p(\bar{z}) = \begin{cases} N(\bar{z}|\mu_k^*, \Sigma_k^*) & \text{if } \bar{z} \text{ is a sample for input } x^{(i)} \in D_o \text{ and } C^{(i)} = k^* \\ \sum_k \pi_k N(\bar{z} | \mu_k, \Sigma_k) & \text{otherwise,} \end{cases} \tag{3}$$

where $k^*$ indicates the particular Gaussian component (cluster), $K$ is the total number of components, and $\pi_k$ is the weight of component $k$. Indeed, Eq. (3) reduces to Eq. (2) in the case when $D_o=\emptyset$. Note that contrary to other semi-supervised GMM VAE approaches, such formulation of the prior does not require an additional model for the prediction of the component variable $C$ for training. To our knowledge, this is the first application of such a simple yet efficient approach.

We further consider a reformulation of the ELBO in Eq. (1) in the following, equivalent form:

$$\mathcal{L}^{ELBO}_D = \mathbb{E}_{q_\phi(z|x)} \left[ \ln p_\theta(x|z) + \ln p(z) + \mathbb{H} [q_\phi(z|x)] \right], \tag{4}$$

where $\mathbb{H} [q_\phi(z|x)]$ denotes the entropy of the posterior.

As typically done for VAE, the expected value in Eq. (4) is approximated by sampling $L$ point(s) from $q_\phi(z|x)$. In VAEs, the goal is to maximize the ELBO, while when training neural networks in general commonly the goal is to minimize a cost function. Therefore, with $L=1$, the loss function for SS GMM VAE is defined by

$$\mathcal{L}_D(z^{(i)}) = -\ln p_\theta(x^{(i)}|z^{(i)}) - \ln p(z^{(i)}) - \mathbb{H} [q_\phi(z|x^{(i)})], \tag{5}$$

where $x^{(i)}$ indicates the $i$-th data point, $z^{(i)}$ is a sample from a $q(\bar{z}|x^{(i)})$, and $p(\bar{z})$ is given by Eq. (3).

### 3.2 The VADEERS framework overview

The proposed VADEERS framework consists of three major modules: drug module (Fig. 1b), cancer cell line module (Fig. 1a), and the sensitivity prediction module (Fig. 1d). Additionally, the framework utilizes a provided clustering of the drugs based on their inhibition profiles. The whole VADEERS architecture has two inputs, one for the drug module and another to the cancer cell-line module, and four outputs in total.

The input to the drug module is a vector representation of a drug’s chemical formula, expressed as its SMILES string. The drug module consists of an encoder, which projects the data into a lower-dimensional latent space, and two decoders: the first one outputs the input’s reconstruction, while the second predicts the drug’s inhibition profile (IP), i.e., the vector of inhibition strengths across a panel of protein kinases. The model underlying the implementation of the drug module is the SS GMM VAE, here, the input samples $x^{(i)}$ correspond to SMILES, the guiding data is defined by the inhibitory profiles of the drugs, and the guiding labels by the clusters of these inhibitory profiles. In this way, we transfer the clustering of inhibition profiles to the latent space, as the latent representation of drugs sharing the same cluster label $k^*$ are made to follow the same Gaussian distribution in $Z$. Importantly, the parameters of GMM, i.e. $(\pi_k, \mu_k, \Sigma_k)$ for $k$ in $\{1, \ldots, K\}$, can be learned via gradient descent together with the remaining parameters of VADEERS, yielding a complete model of the data, including the GMM prior. The use of GMM as a prior then allows to sample $\bar{z}$ from a particular of component of $p(\bar{z})$ e.g. corresponding to a particular guiding label.

The cancer cell line module is implemented as an autoencoder taking vector representation of a cell line’s biological features as input to the encoder, and returning its reconstruction from the decoder.

The encoders of drug and cancer cell line modules allow to find lower-dimensional, informative data representations of drugs and cell lines, respectively. These representation are then passed as an input to sensitivity prediction module, which predicts the numerical value indicating the sensitivity of that cell line to that drug. Here, this value is represented by log half maximal inhibitory concentration (IC50) [67], defined as a drug concentration needed to reduce cell viability by 50%.
3.3 VADEERS model’s cost function

Recall from section 3.2 that drug module of VADEERS has two decoders corresponding to reconstructed compounds’ input and compounds’ inhibition profiles (IP). Combining Eq. (5) with the fact that decoders’ outputs are continuous, we define the drug module’s (DM) loss function for a single compound as:

\[
    \mathcal{L}_{DM}(\tilde{x}^{(i)}_S, \tilde{x}^{(i)}_I, \tilde{x}^{(i)}_C, \tilde{z}^{(i)}) = r_S \cdot \text{MSE}(\tilde{x}^{(i)}_S, \hat{x}^{(i)}_S) + r_I \cdot \text{MSE}(\tilde{x}^{(i)}_I, \hat{x}^{(i)}_I) - r_P \cdot \ln p_{\lambda}(\tilde{z}^{(i)}) - r_E \cdot \mathbb{E}[q_\phi(\tilde{z}^{(i)} | \tilde{x}^{(i)}_S)] \tag{6}
\]

where \(\tilde{x}^{(i)}_S\) and \(\tilde{x}^{(i)}_I\) are the i-th compound’s SMILES continuous vector representation and its reconstruction, respectively, \(\tilde{x}^{(i)}_C\) and \(\tilde{x}^{(i)}_C\) are true and predicted inhibition profiles, respectively, \(\tilde{z}^{(i)}\) is a \(\tilde{z}\) sample corresponding to the i-th compound, \(r_S\) is the positive real-valued weight corresponding to the compounds’ input reconstruction error, MSE denotes mean squared error, \(r_I\) is the weight of the IP prediction error, \(r_P\) is the weight corresponding to the prior likelihood, \(r_E\) is the weight of encoder’s entropy, and the last term corresponds to the entropy of latent variables returned by the encoder.

In the case of cancer cell line module (CCLM), the loss function is given simply by the reconstruction error between the cell lines’ input and its reconstruction:

\[
    \mathcal{L}_{CCLM}(\tilde{x}^{(j)}_B, \tilde{x}^{(j)}_B) = \text{MSE}(\tilde{x}^{(j)}_B, \hat{x}^{(j)}_B), \tag{8}
\]

where \(\tilde{x}^{(i)}_B\) and \(\tilde{x}^{(j)}_B\) are cell line’s input features and their reconstruction, respectively. Finally, the loss corresponding to sensitivity prediction module (SPM) is the error between continuous true and predicted IC50 values defined for compound-cell line pair:

\[
    \mathcal{L}_{SPM}(y^{(i,j)}, \hat{y}^{(i,j)}) = \text{MSE}(y^{(i,j)}, \hat{y}^{(i,j)}), \tag{9}
\]

where \(y^{(i,j)}\) and \(\hat{y}^{(i,j)}\) is a true and predicted IC50 corresponding to i-th compound and j-th cell line, respectively. The loss for the whole model is the weighted sum of above expressions:

\[
    \mathcal{L}_{Model}() = \mathcal{L}_{DM}() + r_{CCLM} \cdot \mathcal{L}_{CCLM}() + r_{SPM} \cdot \mathcal{L}_{SPM}(), \tag{10}
\]

where \(r_{CCLM}\) and \(r_{SPM}\) are weights corresponding to cancer cell line and sensitivity prediction modules’ errors, respectively (arguments are replaced by \(\cdot\) for simplicity). The formulation with the vector \(r\) of weights allows to change model’s emphasis by controlling these hyperparameters.

3.4 Dataset

The analyzed dataset \(\mathcal{D} = \{X_S, X_I, X_B, Y_R, Y_G\}\) consists of five parts, where \(X_S \in \mathbb{R}^{304 \times 300}\) denotes drugs’ SMILES vector representations obtained with the Mol2vec model [68], \(X_I \in \mathbb{R}^{117 \times 204}\) denotes drugs’ inhibition profiles across a panel of protein kinases, \(X_B \in \mathbb{R}^{222 \times 241}\) denotes a matrix of cell lines biological features, \(Y_R \in \mathbb{R}^{922 \times 304}\) denotes a matrix with drug response indicators for a given cell line \(c\) and drug \(d\), and \(\bar{y}_G \in \mathbb{R}^{117}\) denotes a vector of guiding labels for a subset of considered drugs (see below).

Here, we utilized inhibition profiles from \(X_I\) to assign compounds to their functional categories. To this end, compounds were clustered according to their inhibition profiles using K-means, with the number of clusters set to \(G = 3\). Cluster assignments resulting from this approach were then used as the guiding labels for the 117 compounds with known inhibition profiles. See Supplementary Methods for more details on the dataset.

4 Results

We evaluated three versions of the proposed model, differing by the way the drug module was implemented: i) a classical VAE with the standard normal prior (“Vanilla VAE”), ii) the SS GMM VAE as described in Section 3.1 with GMM prior and loss function given by Eq. (6) and (10), however, only weights \(\pi_k\’s\) and components’ means \(\mu_k\’s\) were the trainable parameters of the GMM prior (Eq. (3)), while components’ covariance matrices \(\Sigma_k\’s\) were fixed as identity matrices (“SS GMM VAE constrained”), iii) the SS GMM VAE as described in Section 3.1 in its least constrained version, where all parameters of the GMM, including \(\Sigma_k\’s\), were trainable (“SS GMM VAE unconstrained”).
Table 1: IC50 and IP prediction performance for VADEERS with different versions of the drug module (top three rows), and two other models as reported in the corresponding works (bottom two rows). The models of Liu et al. and Koras et al. lack the generative ability and do not perform inference of inhibition profiles, hence the lack of corresponding metrics.

| Model                        | IC50 RMSE | IC50 Pearson | IP RMSE |
|------------------------------|-----------|--------------|---------|
| VADEERS w. Vanilla VAE       | 1.33 ± 0.022 | 0.87 ± 0.006 | 1.13 ± 0.109 |
| VADEERS w. SS GMM VAE constrained | 1.33 ± 0.023 | 0.87 ± 0.006 | 1.09 ± 0.062 |
| VADEERS w. SS GMM VAE unconstrained | 1.34 ± 0.012 | 0.87 ± 0.004 | 1.04 ± 0.030 |
| Liu et al. [69]               | —         | 0.89         | —       |
| Koras et al. [36]            | —         | 0.82         | —       |

4.1 Predictive performance

The predictive performance of the IC50 estimation was assessed by calculating the root mean squared error (RMSE) and Pearson correlation between the true and predicted IC50 values. In addition, we computed the RMSE between the true and predicted inhibition profiles, corresponding to the second decoder in drug module (Table 1). This procedure was repeated five times with different random data splits (see Supplementary Methods for details on model architecture and experimental setup).

Despite the large differences in the complexity of the prior distribution, the three model versions perform almost equally well in terms of IC50 prediction. This suggest that models achieved the limit of predictive performance for this particular dataset. Although the optimization of the IC50 prediction was not the main goal of this study, the low RMSE and high correlation indicate that VADEERS correctly captures drug and cell line features and reliably predicts the sensitivity of unseen cancer cell lines to kinase inhibitor drugs.

In general, it is hard to compare existing methods for drug sensitivity prediction due to differences in considered data (both feature type and volume), modeling framework, and evaluation and data split procedures. Nevertheless, we have included results for two other models. In terms of Pearson correlation between true and predicted IC50, VADEERS variants achieve second best performance, being slightly outperformed by DeepCDR model by Liu et al. [69], which was the best performing model compared to several others according to analysis in [69]. Still, VADEERS is the only multi-task framework in this comparison and the fact that it achieves comparable performance to models focusing on the single task of sensitivity prediction while simultaneously generating drugs and their inhibition profiles is a notable accomplishment.

In contrast to IC50, the three evaluated model versions do differ in terms of the ability to reconstruct inhibition profiles (Table 1), measured by RMSE between true and reconstructed IPs. The best result in that regard is achieved by the SS GMM VAE unconstrained model (RMSE = 1.04). Such a result is expected, as lower constraints on the latent space representations make it easier for the model to optimize this metric. However, note that in the described setup the IP RMSE metric was computed for the training data, therefore it should rather be interpreted as model’s ability to converge w.r.t. this particular metric than model’s predictive performance. Still, this result suggests that the nature of the latent space is important with regard to the decoding, in the sense that this task is not entirely dependent on the decoder alone and performance in this task is improved by imposing a latent space’s structure.

4.2 Latent space structure

Figure 2 compares the structures of the latent spaces of the three considered models. It is clear that in both SS GMM VAE models the clustering defined by the guiding labels is preserved in the latent space (Fig. 2b, c), i.e. points with the same guiding label are grouped together. By visual assessment, the clusters are the most clearly separated for the SS GMM VAE unconstrained model (Fig. 2c). This is also reflected by the corresponding Silhouette scores that are much higher for GMM models than for Vanilla VAE, with the highest one obtained by SS GMM VAE constrained (Fig. 3b). Interestingly, the latent clustering is to some extent preserved also for the Vanilla VAE model version (Fig. 2a).
suggests that the sole presence of the IP decoder encourages compounds with similar IPs to group together. However, the use of the GMM prior imposes that explicitly. Most importantly, the GMM prior defines the clusters of latent drug representations by associating them to the GMM components, with each guiding label obtaining its separate cluster. In this way, first, we are able to assign a label to a new drug by finding its latent representation and component. Second, we are able to generate new drugs with a pre-specified guiding label.

Figure 3: Numerical assessment of models’ generative performance. All presented metrics are averaged over five experimental runs, with error bars corresponding to standard deviations across experimental runs. (a) Silhouette score of latent representations, with compounds’ guiding labels as compounds’ true cluster labels. (b) Silhouette scores of generated inhibition profiles, with GMM components from which samples are drawn as true cluster labels. (c) Average RMSE (left panel) and Pearson correlation (right panel) between true and generated feature-wise, within-cluster IPs’ statistics, shown for cluster means (centroids) and STDs. Average metrics are taken by first averaging over all three clusters and next over the experimental runs.

4.3 Generative performance

In a VAE, new data points can be generated by first sampling from the latent prior and then passing each sample $\mathbf{z}$ to a decoder. The use of a GMM instead of a normal prior allows to perform this process more precisely; the sample $\mathbf{z}$ can be obtained from a given, $k$th Gaussian component, which should reflect the actual properties of the compounds in the guiding data space. This is the case in this study, where the guiding labels stem from the clustering in the space of the drugs’ IPs. In Fig. 4, we verify this hypothesis by visualizing the IPs of the generated samples.

The IPs generated by the Vanilla VAE model do not form any visually discernible clusters (Fig. 4a). In contrast, the samples generated from both SS GMM VAEs clearly confirm that the above assumption is correct; samples generated from different components are also distinguishable after decoding, i.e., the information regarding the latent component is preserved in the generated data space (Fig. 4b, d). Interestingly, not only the grouping of the data points into clusters, but even the actual mutual spatial arrangement of those clusters is preserved between the true IPs (Fig. 4a), latent space (Fig. 2b, c), and the generated IPs (Fig. 4b, c). However, note that the points are visualized after PCA. Fixing GMM components’ $\Sigma_k$ to $I$ impacts the generated IPs; SS GMM VAE constrained produces more concise and better-separated clusters than unconstrained (Fig. 4c, d), which is also reflected by corresponding Silhouette scores (Fig. 3).

The similarities between the true and generated IPs can also be shown without resolving to dimensionality reduction methods by computing per-cluster, feature-wise statistics such as mean or standard deviation (STD) (Fig. 5), where feature-wise means can be thought of as clusters’ centroids. The IPs generated by both variants of SS GMM VAE exhibit an excellent concordance with true data in terms of cluster means (Fig. 5b). This is apparent on both absolute values level and correlation across features within a given cluster. For example, for a true data, cluster 2 in general corresponds to relatively high inhibition, but for some kinases inhibition is low, and low inhibition of exact same kinases

Figure 4: True and generated inhibition profiles visualized in 2D. (a) The true IPs for the 117 available drugs. (b) 900 IPs generated from the Vanilla VAE. (c) IPs generated from the SS GMM VAE constrained model. 300 samples are drawn. (d) IPs generated from the SS GMM VAE unconstrained model. Again, 300 samples are drawn per-component. Colors correspond to guiding label or a corresponding S-SGMM component, see Fig. 2 for legend.
is observed for the generated data. While differences between SS GMM VAE constrained and unconstrained in terms of generated IP centroids are hard to assess visually, this is not the case for the within-cluster, feature-wise STDs (Fig. 5b). Again, the effect of fixing GMM components’ STD is visible; for the constrained model, within-cluster STDs are much smaller compared to the true ones. This also demonstrates that IP decoder has relatively low variance; namely, it is unable to compensate for the low variance of samples from \( p(\mathbf{z}) \) in order to bring the generated data’s STD closer to the true one. In case of the unconstrained model, the STD is higher and closer to the true one. This clearly demonstrates that in the absence of constraints, the learned components’ STDs are larger, and more closely resemble the true data. Indeed, for this particular model, the average value in the covariance matrices \( \Sigma_k \) is 9.25. These differences are also clear when assessed by computing the RMSE between true and generated IPs’ STD averaged across all three components (Fig. 5c).

In essence, numerical results support all the observations made based on visual assessment. The quality of clustering in the latent space is the highest for SS GMM VAE constrained model (mean Silhouette score across five experimental runs 0.095), followed by SS GMM VAE unconstrained and the lowest value obtained by Vanilla VAE (Fig. 3). Similarly, SS GMM VAE constrained obtains better clustering quality of generated IPs than the unconstrained version (Silhouette scores 0.223 and 0.177, respectively, Fig. 3h).

In contrast, SS GMM VAE constrained obtains slightly worse results than unconstrained in terms of within-cluster statistics similarity between true and generated IPs (Fig. 3h). Both constrained and unconstrained models are similarly close to the original data in terms of cluster centroids (average RMSE between true and generated centroids across three clusters of 5.228 and 4.627, respectively), especially in terms of correlation (average Pearson correlation 0.928 and 0.947, respectively). As in Fig. 3h), the differences are more noticeable when considering within-cluster STDs; both models achieve similar correlation (0.783 and 0.796, respectively), but SS GMM VAE constrained is worse than unconstrained w.r.t RMSE (9.602 for constrained and 6.407 for unconstrained).

![Figure 5: True and generated IPs’ feature-wise, within-cluster (a) means and (b) STDs.](image)

### 5 Conclusions and discussion

In this work, we propose VADEERS, a multi-task framework for generation of novel drugs with specific types of inhibition profiles and simultaneous drug sensitivity prediction. The framework exploits a novel SS GGM VAE model that enables semi-supervised clustering of the drugs’ representations in the latent space. We showed that the framework achieves state-of-the-art sensitivity prediction performance, and preserves a given clustering structure of the drugs both in the latent space and in the space of the predicted inhibitory profiles.

One of the limitations of the proposed model is its inability to generate data points with totally arbitrary features. Namely, the model allows to generate new data points with properties that strictly reflect the clustering observed in the training data. In principle, this could be bypassed by performing various operations on multiple generated data points, however, testing this hypothesis was not in the scope of this analysis. Another important limitation corresponds to the analyzed data; a different choice of data for drugs’ representations (e.g. representing SMILES strings as graphs) and guiding data might be more suitable for generating molecule candidates, which, at least in theory, could be synthesized. Both above aspects are directions of future work regarding this study.

This work introduces several general concepts important for drug sensitivity modeling and compound generation. The proposed SS GMM VAE model is generic and not limited only to modeling compounds. The notion of optimizing latent space with guiding labels can potentially be beneficial and improve the performance of generative models also in other applications. Moreover, the proposed model offers additional functionality not exploited in this study. For example, setting the number of Gaussian components \( K \) greater than number of unique labels \( G \) might lead to identification of novel subgroups of samples, not limited to the original choice of guiding labels. In summary, VADEERS opens new avenues in integrative modeling of cancer data and generation of anticancer compounds.

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Competing interests

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S1 Supplementary Methods

S1.1 Dataset

The primary source of drug sensitivity data for cell lines was the Genomics of Drug Sensitivity in Cancer (GDSC) database [7, 10]. The set of 304 compounds in X extracted from GDSC database was represented by their chemical structure indicated by corresponding SMILES strings. In order to convert SMILES strings into numerical vector representations, we used the pre-trained Mol2vec model [68] treating it as SMILEs featurizer which produces 300-dimensional vectors of continuous values. These representations served as an input to the drug module.

Another considered features of compounds were their inhibition profiles, i.e., their binding strengths across a panel of 294 protein kinases. Such inhibitory profiles were available and extracted for 117 compounds from the HMS LINCS KINOMEscan data resource [70]. The value for a given compound-kinase pair represents a percent of control, where a value of 100% means no inhibition of kinase binding to its ligand in the presence of the compound, and where low value means a strong inhibition [71, 72].

Data to characterize the 922 cell lines were downloaded from the GDSC. For the molecular features of the cell lines, we considered only the genes coding for kinases present in the KINOMEscan dataset, as well as subset of putative gene targets of considered compounds. This resulted in a set of 202 genes, for which mRNA expression levels (202 features) and binary mutation calls (21 features) were extracted for all cell lines. Furthermore, the dummy-encoded tissue type was added, producing additional 18 binary features, yielding the final set of 241 biological features for 922 cell lines.

For the drug response indicators in Y we used the log half maximal inhibitory concentration (IC50) [67] values from GDSC. For a given compound-cell line pair, IC50 is defined as the drug concentration needed to reduce cell viability by 50%. Note that some values in Y were missing since not every cell line is screened against every available compound.

S1.2 Experimental setup, VADEERS model architecture, training and implementation

The validation and test sets were constructed by randomly selecting two sets of 100 unique cell lines each. We then extracted the compound-cell line datapoints containing selected cell lines and used them to construct validation and test sets, while the rest of the pairs corresponding to the remaining 722 unique cell lines constituted the training set.

The hyperparameters of the model were empirically determined using the validation set. The encoders for both drug and cancer cell line modules were fully-connected forward networks with two hidden layers with 128 and 64 neurons, respectively. All of the decoders followed a similar architecture, but with 64 neurons in a first hidden layer and 128 in a second. The latent space dimensionality in both drug and cancer cell line modules was set to 10.

The sensitivity prediction module was a fully-connected network with three hidden layers with 512, 256 and 128 neurons, respectively, and an output layer outputting an IC50 prediction. Dropout with $p = 0.5$ was applied at the first and second layer. ReLu activation function was used throughout the whole model.

Model training was performed on 200 epochs using the Adam optimizer [23] with a learning rate of 0.005 and batch size of 128. The whole model was trained together for the first 150 epochs, after which, drug and cancer cell lines modules were frozen and sensitivity prediction module alone was trained for another 50 epochs with a newly set learning rate of 0.001, decreasing by a factor of 0.1 with every 10 epochs. In addition, every 1000 training steps there was a break devoted to only training the drug module part. During each break, drug module was trained for 100 epochs using only compounds with known inhibition profiles, with the batch size of 8. For the purpose of experiments, the r loss function weights were all set to 1. Both the number of unique guiding labels and components in GMM prior were set to 3, i.e, $G = K = 3$.

The neural networks related code was implemented using Python 3.8.8, PyTorch 1.10.0 and PyTorch Lightning 1.5.0. K-means clustering for the guiding data was implemented using scikit-learn 1.0.1 [74].