AI for predicting chemical-effect associations at the universe level - `deepFPlearn`

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Abstract

A plethora of chemical substances is out there in our environment. All living species, including us humans, are exposed to various mixtures. Our society is accustomed to developing, producing, using, and dispersing a diverse and vast amount of chemicals with the original intention to improve our standard of living. However, many chemicals pose risks, such as developing severe diseases, if they occur at the wrong time in the wrong place. For the majority of the chemicals, these risks are not known. Chemical risk assessment and subsequent regulation of use require efficient and systematic strategies to characterize the hazard and exposure of chemicals. Even with high throughput, experimental methods to assess the hazard of chemicals are still lab-based and, therefore, too slow to keep up with the pace of chemical innovation. Existing computational approaches, e.g., ML-based, are influential on specific chemical classes or sub-problems but not usable on a large scale. Further limitations are the lack of applicability to chemicals outside the training data and the availability of sufficient amounts of training data. We present the ready-to-use and stand-alone program `deepFPlearn` that predicts the activity between chemical structures and effects on the gene/pathway level using a combined deep learning approach. We trained a deep autoencoder for feature reduction prior to training a deep feedforward neural network to predict the chemical target association. We received good prediction qualities for endocrine disruption gene targets. Further, we showed that our feature compression preserves relevant chemical structural information. Using a vast chemical inventory as input for the feature compression did not reduce our good prediction quality but allowed us to capture a much more extensive range of chemical structures. We showed that our program could indeed predict meaningful associations of chemicals and effects beyond the training range for both classes. Further, `deepFPlearn` applies to hundreds of thousands of chemicals in seconds. We provide `deepFPlearn` as an open-source and flexible tool that can be easily retrained and customized to different application settings at `https://github.com/yigbt/deepFPlearn`.

Keywords: Deep learning, toxicology, binary fingerprint, autoencoder, molecular structures

1 Introduction

Humans and ecosystems are exposed to a vast number of chemicals that may threaten their health. While chemical products are important for maintaining our standard of living and chemicals form the building blocks of life, some chemicals are hazardous, and their safety needs to be thoroughly evaluated. The risk of a chemical depends on its inherent toxicity (hazard) and the present amount of the chemical in the environment (exposure). The list of chemicals humans and ecosystems may be exposed to is vast, and the set of chemicals of anthropogenic origin is rapidly growing: The Chemical Abstracts Registry Service grew from 20 million in 2002 to currently 169 million unique chemical substances [1]. Certainly, many chemicals listed in this registry are not relevant for exposure since they are not used in larger quantities. The estimated number of chemicals available on the global market highly varies between 30 000 to 100 000 [2, 3, 4] up to 350 000 [5]. It is hard to define the correct number due to several barriers and uncertainties that exist. However, the authors from [4] reviewed their own and the most recent estimation by [5] and showed that the results on the actual number of chemicals in commerce are not that different, ranging around 40 000 to 69 000, and both reports draw similar conclusions and recommendations. The number of substances detected in humans is of similar order of magnitude. More than 50 thousand substances have been

compiled from scientific texts that reported detection in blood and are listed in the Blood Exposome DB [6]. Contamination with anthropogenic chemicals is of analogous concern in the environment [7, 8] and more than 3000 substances are currently listed in a database of emerging pollutants across Europe [9].

Environmental exposure poses a major risk for the health of humans and ecosystems. Environmental and life-style rather than genetic factors have been defined as the major cause for many chronic diseases [10] and the observed growth in the incidence of non-communicable chronic diseases can only be explained by changing environmental determinants [11, 12]. Exposure to chemicals has been a major concern for wildlife populations [13, 14, 15]. Up to 26% of aquatic species loss may be attributed to exposure to chemical mixtures [3, p. 245], [16].

Risk assessment fails to keep up with the pace of chemical innovation. The range of chemicals humans or ecosystems may be exposed to, and the observed hazards of individual chemicals clearly call for an efficient and effective risk assessment and subsequent thorough regulation of chemical use. Also, a "toxic-free environment" has been designated a key priority for the European Union (EU) [17]. However, the European Environment Agency forecasts that exposure to mixtures of chemicals, including hazardous, will further increase [3, pp. 248–249]. Also, the throughput of regulatory processes is slow compared to the pace of chemical innovation. E.g. of the more than 21 000 chemicals registered under Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), the European legislation regulating industrial chemicals, more than 1000 have been designated low priority for further work, because of no further concern, or already implemented risk management and more than 1800 have been designated high priority, because data generation was ongoing or risk management under consideration. However, for the vast majority of more than 18 000 substances, the need for suitable regulatory actions still needs to be determined [18]. It has been estimated that evaluation of a substance of potential concern under the REACH legislation takes 7–9 years, during which exposure may continue [3, pp. 248–249]. Also, approximately 70% of the registration dossiers that were evaluated have been found to be incomplete or not compliant [19]. In summary, traditional approaches to chemical regulation perform well; however, they are too slow to master the number and growth of substances on the market. Predictive *in silico* approaches that build on the integration of different data sources may contribute to solving this challenge – not necessarily by replacing experimental approaches, but at least by prioritizing substances for further evaluation.

***In silico* approaches for toxicity prediction.** A range of different approaches for predicting toxicity *in silico* have been developed, including Structural Alerts, Read across, and Quantitative Structure Activity Relationships (Quantitative Structure Activity Relationships (QSAR)) [20]. Structural alerts and rule-based models constitute a simple but powerful approach to toxicity prediction and build on using individual chemical substructures as indicators for toxicity [21]. These methods rely on either human-expertise-based or data-derived rules and are easy to interpret. However, since there is no mechanism that enforces the completeness of rules, there is a high risk of false-negative predictions [20].

Read-across builds on predicting the unknown toxicity of a substance by extrapolation from a set of highly related substances with known toxicological properties. Read across is a commonly used alternative to animal experiments for filling data gaps in registration dossiers. However, applicability of read-across is restricted to a subset of substances for which sufficient information of related compounds is available [22].

QSARs relate molecular descriptors to toxicity or other properties of a chemical [23, 24]. Local QSARs are either built on a set of related chemicals or on expert knowledge on a shared mode of action of a group of chemicals. Models derived from a diverse set of chemicals are called global QSARs [20]. Descriptors used in QSAR include physicochemical properties and different representations of the molecular structure or properties thereof and more recently also high throughput screening-derived data on biological activity. 2D QSAR uses descriptors derived from the 2D-structure graph of a molecule that are identical for isomorphic graphs (graph invariants) [24]. A frequently used family of descriptors are molecular fingerprints that record the occurrence of local and regional substructure elements in the graph [25]. The 3D QSAR considers the non-covalent interactions between the molecule under consideration and a receptor. In the simplest case, descriptors are based on sampling the force acting on a probe atom that is placed on a grid around the molecule under consideration [24]. Additionally, also 3D-derived fingerprints have been used as descriptors [25].

QSAR approaches utilize multivariate statistical models, like regression or discriminant analysis, to relate molecular descriptors to toxicity. More recently, with the growth in available training data and methodological advancements in artificial intelligence, global QSARs built on machine learning models became available.

Machine learning in 21st century toxicology. Toxicology is currently experiencing a paradigm shift from relying primarily on apical endpoints in animal models to more integrated strategies, combing prediction and high-throughput testing for a range of different, often molecular, endpoints. This paradigm shift strongly builds on the hypothesis that knowledge on toxicity-associated changes of the regulatory molecular

processes of a cell or an organism, i.e. changes at the level of regulatory pathways will eventually allow better predictions on how substances affect humans or the environment. Screening initiatives, in particular the Tox21 program [26], test thousands of substances versus hundreds of bioassays that inform on an effect on the molecular processes known to be most relevant in toxicity. The availability of these data enabled the development of a new variant of global QSAR methods: the machine-learning based prediction of the association of substances with molecular pathway responses.

The Tox21 Challenge was announced in 2014 with the aim to reveal how well independent researchers could predict the interference between compounds and biochemical pathways given a dataset of chemical structures only. A set of 12 000 chemicals which were measured for 12 different toxic effects was provided for the challenge, and the aim was to develop computational methods that were able to successfully predict those effects. Several computational methods have been developed during this challenge that involved machine learning. The best performing method was the `DeepTox`[27] pipeline. In brief, the chemical representation of the compounds was normalized, a large number of descriptors was computed, and deep learning models were trained and evaluated based on the provided test data. Later, these models were successfully validated by the challenge initiators with additional data that had been hold back during the challenge. This pipeline reported AUC values above 85% for the prediction of the association between the provided chemicals and the 12 targets. Further, the authors showed that the concept of deep learning to learn simple objects in the lower layers and combinations of those to more complex objects in higher layers, as shown in image recognition, also holds in toxicology. Hidden neurons in their deep learning models represent known molecular substructures - toxicophores, which have been identified manually by experts for decades.

`eToxPred` [28] was developed to quickly estimate the toxicity of large collections of low molecular weight organic compounds. It employs a Restricted Boltzman Machine classifier and a generative probabilistic model to predict a Tox-score. The reported accuracy is 72%. In a different approach by [29], a support vector machine and random forest were used to build single-label models. Here, the problem of class imbalance has been resolved by methods of under-sampling the data. Four methods were explored to construct multilabel models that can predict the interaction of one chemical against multiple targets simultaneously. The reported accuracy was between 74 to 81%. `TarPred`[30] is a web application for predicting therapeutic and side effect targets of chemical compounds. However, it is not available anymore. The `DeepChem` Project [31] is a Python library that provides datasets, functions, and tutorials for several use cases, with the aim to democratize deep learning for science in general, and for chemistry in particular. It can be used to develop or, as a reference, to compare custom computational approaches in the field. None of these approaches provides a readily usable program to be employed for classification or retraining.

The main limitation of the above-mentioned (and other) machine learning (Machine Learning (ML)) approaches in toxicology is the lack of applicability to chemicals outside the training data and the availability of sufficient amounts of training data. A specific challenge is that the descriptors need to be fine-grained enough to capture the particularities of molecular initiating events and coarse-grained enough to allow for machine learning. In consequence, the (high) dimensionality of the descriptors/features stands in large contrast to the (low) amount of available labeled training data.

Here, we present `deepFPlearn` – a ready-to-use deep learning tool that combines feature reduction with a deep autoencoder and subsequent prediction with a deep feed forward neural network to predict the associations between chemical structures and gene targets that are involved in endocrine disruption (Endocrine Disruption (ED)). Substances may act as endocrine disruptors if they mimic or interfere with the body's hormones. We decreased the discrepancy between large descriptor size and limited amount of labeled training data by i) using a simple representation of chemical structure - the binary fingerprint of moderate size, and ii) by applying feature compression prior to the actual prediction of the association to an effect. Further, we overcame the domain extrapolation problem by training the autoencoder on a huge repertoire of chemical structures and showed that the prediction quality on the subset of labeled training data for ED remained high. We demonstrate the capabilities of `deepFPlearn` via application to a recently published classification of endocrine disrupting chemicals and show that selectively interacting chemicals are classified by `deepFPlearn` with significantly higher confidence than others.

2 Methods and data

Representation, similarity, and visualization of chemical structures. The molecular structure of chemical compounds was encoded in binary topological fingerprints (Fingerprint (FP)) using Python's `RDKit` [32, version 2020.03.2] with the parameters: minimum path size: 1 bond, maximum path size: 7 bonds, fingerprint size: 2048 bits, number of bits set per hash: 2, minimum fingerprint size: 64 bits, target on-bit density 0.0. These fingerprints were generated from chemical structure information provided in the form of International Chemical Identifier (InChI) or Simplified Molecular-Input Line-Entry System (SMILES) strings. All training data files containing chemical structure and target association information were serialized

using Python's pickle module. Uncompressed (original binary fingerprint) and compressed features of the molecules were visualized in 2D space using the UMAP algorithm [33] and the following metrics. Tanimoto similarity was used to evaluate molecular similarity of the fingerprint representations. Pearson correlation was used to evaluate similarity of compressed features. A k-means clustering with $k \in [2..7]$ was applied to the resulting coordinates of the *uncompressed* features. The assigned clusters were translated to color codes in the visualizations of both uncompressed and compressed features.

The deep learning tasks were implemented using the Python library of the `TensorFlow` framework [34, version 2.2.0], Python's `TensorFlow` wrapper `Keras` [35, version 2.3.1], and the `Scikit-learn` framework [36, version 0.23.1].

A deep regularized autoencoder (Autoencoder (AE)) was constructed for dimensionality reduction of the binary fingerprints. The AE had a symmetric shape with one-dimensional input and output layers of the size of the input fingerprint L_{FP}. The number of hidden layers N_H and their sizes $S_i, i \in [1..N_H]$ were defined in dependency of L_{FP} and the desired latent space size L_z:

$$N_H = \lfloor \log_2(L_{FP}/L_z) \rfloor \tag{1}$$

$$S_i = L_{FP}/2^i \quad i \in [1..N_H] \tag{2}$$

The Rectified Linear Unit (ReLU) activation function was used towards inner layers, and the Sigmoid activation function was used towards the output layer. The AE model was compiled using the Adam optimizer with a default learning rate of 0.001, a default decay of 0.01, and the binary cross-entropy as a loss function.

A deep neural network was constructed as a sequential feed-forward neural network (Feed forward Neural Network (FNN)) for the classification task. The dimensions of the stacked layers depends on the mode of action of `deepFPlearn`. If feature compression via the autoencoder was enabled, the FNN was used subsequently of the AE and the length of the one-dimensional input layer of the FNN matched the length of the latent space L_z vectors. Otherwise, the number of neurons in the input layer matched the length of the binary fingerprint L_{FP}. The hidden layers were of decreasing sizes, followed by an output layer of size 1. The number of hidden layers $\hat{N}_H$ and their sizes $\hat{S}_j, j \in \left[1..\hat{N}_H\right]$ depended again on the provided input size L_{input} (which is either L_{FP} or L_z). The last four layers with only a few neurons (e.g. less than 32 in the example case of $L_{FP} = 2048$) were not included.

$$\hat{N}_H = \lfloor \log_2(L_{input})/2 \rfloor - 4 \tag{3}$$

$$\hat{S}_j = L_{input}/2^j \quad j \in [1..\hat{N}_H] \tag{4}$$

Dense layers were used with the ReLU activation function towards hidden layers and default kernel regularization of 0.001. The Sigmoid activation function was used towards the output layer. All hidden layers were followed by a dropout layer with a dropout rate of 0.2. The FNN model was compiled using the Adam optimizer with a default learning rate of 0.001, a default decay of 0.01, and the mean squared error as a loss function.

Different datasets were collected from the literature and from public databases. A manually curated dataset S was downloaded from the supplemental material of [29]. It contained chemical-target associations for 7248 chemicals and 6 gene targets. The six considered target genes were: *androgen receptor* (Androgen Receptor (AR)), *estrogen receptor* (Estrogen Receptor (ER)), *glucochorticoid receptor* (glucochorticoid Receptor (GR)), *thyroid receptor* (Thyroid Receptor (TR)), *Peroxisome Proliferator-Activated Receptor gamma (PPARg)*, and *Aromatase*. See supplemental Figure 1 for an overview of the size and class distribution of this data. Chemicals that interact with these targets can cause endocrine disruptions (ED) in humans. Originally, this data had been retrieved from bioassay data of the Tox21 program [26], and carefully transformed to binary associations by [29]: Associations were considered as not available (Not Available (NA)) if no bioassay data was available, and as 1 or 0, if an association between chemical and gene target had been confirmed in a bioassay or not, respectively. For details on the data preparation, thresholding and preprocessing of this dataset we refer to the original publication [29]. The dataset S was extended by the artificial target *endocrine disruption* (ED) that combines all existing targets with a logical OR operation. Chemicals in the S dataset were identified by their SMILES representation, and encoded as binary topological fingerprints as described above.

Further, a dataset D was generated from the 719 996 chemicals listed in the CompTox Chemistry Dashboard [37, accessed on 2020/07/13]. Binary topological fingerprints were generated from the provided InChI identifiers as described above.

For benchmarking we downloaded the Tox21 Challenge dataset, and the Side Effect Resource (SIDER) dataset from MoleculeNet [38], a database of benchmarking datasets for classification problems in molecular machine learning.

For training the deep neural networks (AE and FNN models) we enabled early stopping and fallback mechanisms (model checkpoints). A k-fold cross-validation was applied for training the FNN model, with

a default value of $k = 5$.

A hyperparamter tuning (gridsearch) of batch sizes (64, 128 and 256), different optimizers (Stochastic Gradient Descent (SGD), Adam), and learning rates (0.01 and 0.001) was applied to each individual target model. The best performing values were selected in the final models for further prediction tasks (see above). Validation loss was monitored. The training procedure was stopped if it did not improve by a certain value min_{delta} (default: 20, can be adjusted through program settings) for a provided number of epochs (patience). The model weights were restored to the respective checkpoint model. Subsequently, a full model containing the complete training set was trained with the same settings. The weights of *all* k models, the *best*, and the *full* model were saved in `.hdf5` format. Training histories were stored in `.csv` format, and a respective visualization showing accuracy, loss, validation accuracy, and validation loss across the training epochs was provided as an `.svg` image. The whole training procedure was logged. Logged metrics were accuracy and validation accuracy per training epoch (FNNs only), loss and validation loss per training epoch, prediction results of test data, area under the curve (Area under the curve (ACC)), and matthews correlation coefficient (Matthews Correlation Coefficient (MCC)).

Implementation. `deepFPlearn` was implemented as a Python (version 3.7.6) package with three different usage-modes. The first mode is *convert* which imports the dataset (for training or prediction) and calculates chemical fingerprints for all structures from their respective SMILES or InChi representation. A combined Pandas dataframe is created that contains the SMILES/InChi representation, the calculated fingerprint, and all targets. This dataframe object is then serialized to disc as a Pickle file which has the advantage that importing data is fast for subsequent sessions. The second mode in `deepFPlearn` is *training*. The neural networks can easily be (re-)trained with any dataset that associates chemical structures with an effect. During the training all necessary information is logged to validate and evaluate the trained models. Finally, in its third mode, `deepFPlearn` can be used to *predict* the associations between a provided list of chemical compounds and effects using a selected (pre-trained) model. This model can either be one of our provided models that predicts associations to estrogen, androgen, glucocorticoid, thyroid receptors, peroxisome proliferator-activated receptor gamma, or aromatase, or an additionally trained model using `deepFPlearn` training mode and a custom dataset.

All settings regarding the neural networks can be globally adjusted, and the individual mode of action as well as respective individual settings can be provided in the form of a JavaScript Object Notation (JSON) configuration file.
Dependencies to external libraries and software are managed using `conda`[1]. The respective `YAML` configuration file for the platform-independent conda environment is part of the source code repository. A singularity container[2] was set up that encapsulates the whole project at the state of publication, including required resources, source code, compiled package, and test data. The `deepFPlearn` software package, conda environment and a singularity container are publicly available, details see section 7.

3 Results

We aimed to develop a stand-alone, ready-to-use deep learning approach to associate chemicals with targets on the gene/pathway level. Further, we aimed to evaluate the potential of feature compression to increase the applicability of this approach to substances beyond the limited amount of available training data. We implemented our ideas in the program `deepFPlearn`, and describe the results of our training procedures and subsequent validation in the following.
Our workflow combined a feature compression step using a deep autoencoder (AE) followed by a classification step using a deep feed forward neural network (FNN), see Figure 1. The research questions at hand were: i) What is the impact of the feature compression prior to the classification? ii) How much structural variety can we capture in this prepended step without a negative impact on the subsequent prediction quality? iii) How is the performance of our models compared to existing approaches? iv) Can we predict plausible results on unknown data?

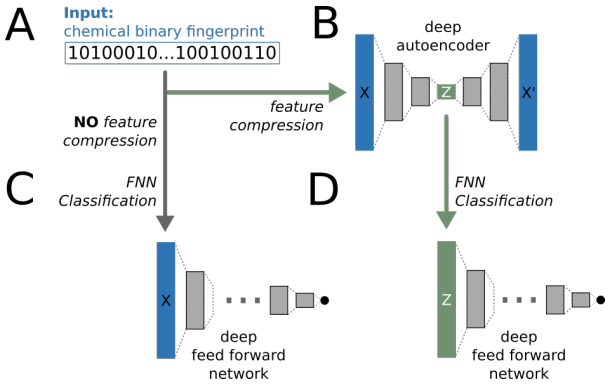

Figure 1: The `deepFPlearn` workflow. A) The binary chemical fingerprints serve as input for the neural networks. B) A deep autoencoder (AE) is used to compress the binary fingerprints. C) A deep feed forward network (FNN) is used for direct classification of the input. D) A deep feed forward network (FNN) is used for classification of the compressed input. Sizes of layers, activation and loss functions are different for each network and depend on the input size, see methods section.

We applied three different training settings based on the

[1] `https://www.anaconda.com`
[2] `https://sylabs.io/`

selected datasets S and D (details see methods 2 Different datasets), and evaluated the respective performance: First, feature compression was disabled (*no* AE, Figure 1 path from A to C) such that only the FNNs were trained for each individual target of the S dataset using the full-length molecular fingerprints. Second, a *specific* feature compression was applied to the chemical fingerprints of the S dataset followed by training the FNNs using the compressed input features (*specific* AE, Figure 1 from A over B(S) to C(S)). Third, a *generic* feature compression was applied to the chemical fingerprints of the D dataset which is based on the entire repertoire of chemicals stored in the CompTox Database. Subsequently, the FNNs were trained using the compounds together with available target association data from S (*generic* AE, Figure 1 from A over B(D) to C(S)).

The deep feed forward neural networks were trained in a 5-fold cross validation. The weights of the *best*, and the *full* models for each target are saved in `.hdf5` format. These can be restored in the prediction step, and consequently be used for final validation and further application.

Algorithm 1 shows a formal description of the full `deepFPlearn` workflow for training.

Algorithm 1: Simplified workflow of the training procedure: Training data is provided and optionally an autoencoder (AE) is trained or its weights are loaded. When an AE is used, features are compressed prior to classification with the feed-forward network (FNN).

```
Data: X feature matrix and Y target matrix
Result: Train deepFPlearn in 5-fold cross validation,
        return AE models, best and full models of FNNs
if compressFeatures then
    if trainAE then
        encoder = trainAutoencoder(X)
    end
    else
        encoder =
         loadAutoencoder(options.encoder-weights-file)
    end
    trainFeatures = compressFeatures(X, encoder)
end
else
    trainFeatures = X
end
foreach target t do
    (X_t, Y_t) = drop_na(trainFeatures, Y, t)
    scores = []
    models = []
    while (train, test) in Kfold(k = [1 : 5], X_t, Y_t) do
        // model of current fold
        models[k] = trainFNN(X_t[train], Y_t[train])
        scores[k] = model.evaluate(X_t[test], Y_t[test])
    end
    // best model
    save(models[scores.maxIdx(scores[MCC])])
    // train and save full model
    modelFull = trainFNN(X_t, Y_t)
    save(modelFull)
end
```

Prediction *without* feature compression performed worst. The training stopped early before 300 training epochs were reached, and the models were perfectly able to predict the 0's — meaning no association between chemical and effect — in the validation data, when no feature compression was applied. Training accuracy and loss values almost reached a value of 1, and 0 respectively, see Figure 3 A - top panel (uncompressed) for a selected target set and supplemental Figure 2 for all results. The good performance on the test data right after the first training epoch can be explained by the over-represented fraction of 0's in the validation and training sets. All these issues indicated that the models learned the training data by rote and that the imbalance of 0 and 1 associations had a substantial effect on the final performances of the models. To confirm that we applied a down-sampling procedure. We sampled from the 0-associated compounds such that the ratio between 1's and 0's in the training set was $0.5, 0.6, \ldots, 1.0$. We observed that we could reduce the previously observed issues by downsampling the 0's at the expense of validation accuracy and loss, see supplemental Figure 3.

Feature compression improved training performance and preserved relevant structural information. Two different deep auto encoders (AE) were trained: one using the *specific* dataset S, and the other using the entire repertoire of $\sim 770k$ chemical structures that were downloaded from the CompTox Database as a more *generic* dataset D. Topological fingerprints of size 2048bit served as input and latent space dimensions of $L_z \in [1024, 512, 256]$ were tested. Best training performances could be reached for $L_z = 256$ in both cases. The *specific* AE trained for 130 epochs, while the *generic* AE trained for 160 epochs. Both reached a validation loss of 0.215. See Figure 2 A for the training histories of the AEs. Figure 2 B shows a UMAP visualization of the high-dimensional uncompressed feature space and the low-dimensional compressed latent space of dataset S. When coloring compounds both from the uncompressed and compressed space with labels that were calculated on the uncompressed feature space, it is clearly visible that a similar cluster association appears in the Uniform Manifold Approximation and Projection (UMAP). This strongly indicates, that relevant (structural) information is preserved during feature compression.

FNN training with *specific* feature compression yielded good prediction performance. The second variant of FNN training used feature compression. In particular, features were compressed using the encoder of the *specific* autoencoder. Subsequently, the FNNS were trained individually for each target with a 5-fold cross validation. We observed that, with around 650 epochs, the FNN training with compressed feature inputs took much longer compared to our first training variant where

we did not use feature compression. Compare Figure 3 A – top and middle panel. Validation accuracy and loss values were above 0.8 and below 0.2, respectively (on average across the five folds of the cross validation, see Figure 3 A – middle panel (specific AE) and supplemental Figure 2 for the full set of models). The areas under the curve reached values above 0.82. Specificity values were above 93 % for all gene targets, and we reached up to 61 % sensitivity.

FNN training with *generic* feature compression preserved good prediction performance. In the third setting features were compressed using the encoder of the *generic* autoencoder. We observed that the number of training epochs for training the FNN models increased slightly up to 720, see Figure 3 A – bottom panel. The training and prediction quality was comparably high with a slight drop of only 1% on average in terms of ROC-AUC, compared to the feature compression using the *specific* AE, see Figure 3 B. The ratio between positive (1) and negative (0) associations between chemical and gene target differed substantially between the individual targets, see Figure 3 C. As expected models with a more balanced class distribution performed better – compare Figures 3 B and C. The ED model is an exception here. It can be considered as better balanced on the one hand, but as a more generic predictor on the other hand.

We refer to our supplemental Figures 2, 4 and 5 for all investigated performance metrics of all models.

Training and prediction using benchmark datasets confirmed our concept.

As a proof of our concept regarding the feature compression using the AE in general, and the potential to extrapolate to a larger set of compounds using the *generic* AE in particular, we tested our approach on a selection of benchmark datasets for molecular machine learning provided by MoleculeNet [38]. We selected the Tox21 Challenge dataset which also associates chemicals and gene targets, and the Side Effect Resource (SIDER) database that associates drugs with grouped adverse drug reactions. These datasets contain 7831 and 1427 compounds, and 12 and 27 targets, respectively, and comprised binarized associations between those compounds and the targets. The same issues as for our initial training dataset also hold true for these datasets, i.e. many associations were not available (NA values), and there is a high imbalance between the number of class associations, i.e. we observed an 1/0 ratio of 0.05 (Tox21) and 1.9 (SIDER) (on average across all targets), respectively. We followed the recommended [38] metric and splitting patterns to generate training data from these datasets. Our trained models performed slightly better than described in the MoleculeNet and as implemented in the `deepchem` library. In particular, we reached a maximum of ROC-AUC of 0.86 in the Tox21 case, and 0.68 in the SIDER case, see Figure 4 A and B, where MoleculeNet reported 0.83 and 0.67 for the deep learning approaches implemented in `deepchem`. Additionally, as expected we observed only a small drop of performance loss on the benchmarking datasets when we used our *generic* AE for feature compression, see Figure 4 C.

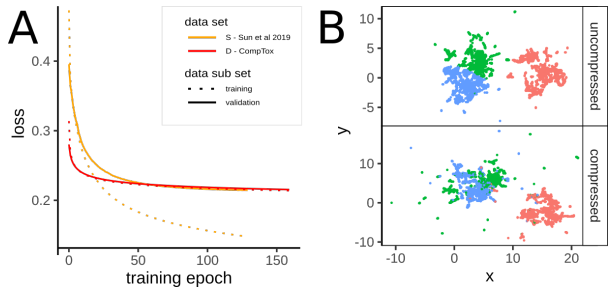

Figure 2: A) Training and validation loss during training of the *generic* (D – CompTox) and the *specific* (S – Sun et al. 2019) autoencoder. B) UMAP visualizations of uncompressed and compressed representations of all compounds from S dataset; color indicates cluster assignment of a k-means clustering with $k = 3$ on the uncompressed features.

`deepFPlearn` is ready to be applied to huge datasets.

We used `deepFPlearn` with generic feature compression and a selection of the trained models (ER, AR, and ED) to identify potential further associations among the huge amount of compounds in the CompTox dataset D. For the majority of those compounds the probability to act as endocrine disruptors at all was not known. From the investigated 719 997 compounds, 51 467 (AR), and 61 336 (ER) were returned to be associated with at least one of these two targets with a probability $P > 0.75$.

Recently, Escher et al. [39] classified the association between selected compounds in six of the high throughput Tox21 assays, including AR and ER. The aim has been to evaluate whether the observed effect was likely due to specific action via the mode of action (Mode of Action (MoA)) under consideration or rather due to unspecific consequences of cytotoxicity. We selected the 141 and 103 compounds which had been investigated and classified for androgen and estrogen receptor, and for which we have a `deepFPlearn` prediction probability in the dataset D as described above. These compounds were not part of the training set. `deepFPlearn` was able to significantly (according to a Kolmogorow-Smirnow test of the respective probability distributions) classify the selective compounds (specificity ratio in relation to experimental cytotoxicity > 10) best. For all other compounds (with specificity ratios < 10) `deepFPlearn` returned unsecure probabilities (mainly below 0.5), see Figure 4 D.

Further, we manually selected some predicted associations (ED model), that were not part of the S (train) data set, among the top 200 (most probable positive predictions) and bottom 200 (most probable negative predictions) and empirically investigated their biological feasibility. In our positive predictions we found compounds like Estriol, 17alpha-Ethinylestradiol, 17beta-Ethinylestradiol, or Mestranol, and Prednisolone, Dex-

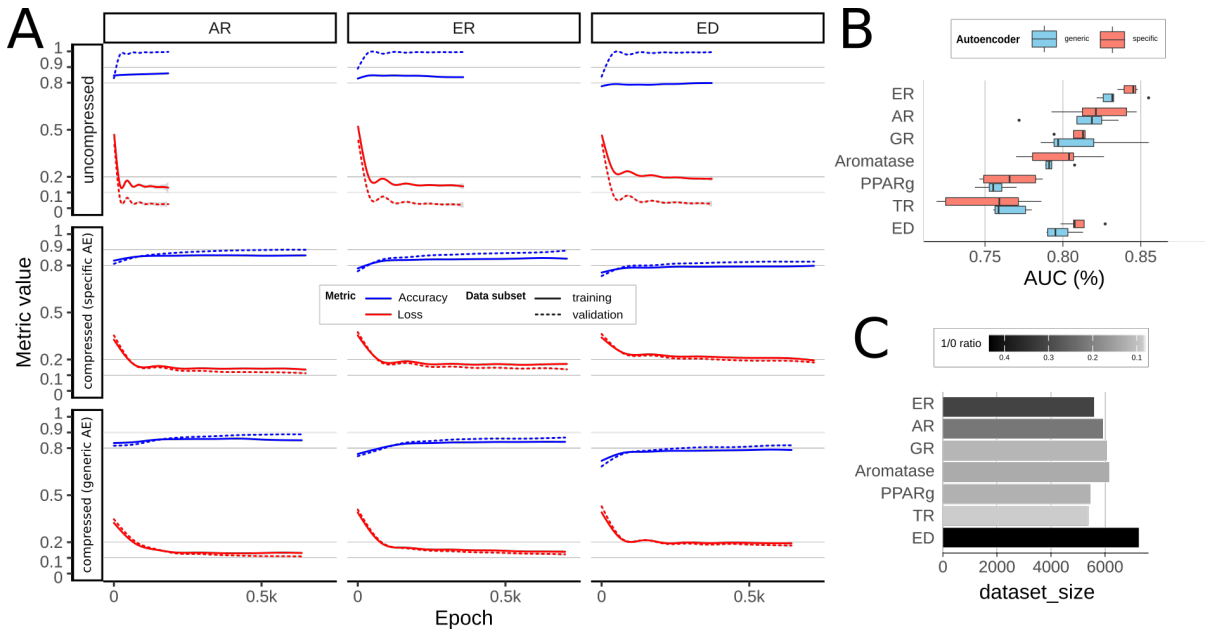

Figure 3: A) Training histories of the feed forward neural networks stratified by the selected targets/models for androgen (AR) and estrogen (ER) receptors, and endocrine disruption (ED), and the degree of feature compression (uncompressed, specific, and generic); shown metrics are accuracy (dotted, blue), validation accuracy (straight, blue), loss (dotted, red) and validation loss (solid, red) during training. The variance in metric values per epoch results from different folds of the 5-fold cross validation. B) Comparison of the AUC values of individual models using the specific and generic AE. C) Sizes of the individual data sets per target, stratified by the ratio of 1 and 0 associations. Training histories for the other targets can be found in the supplement.

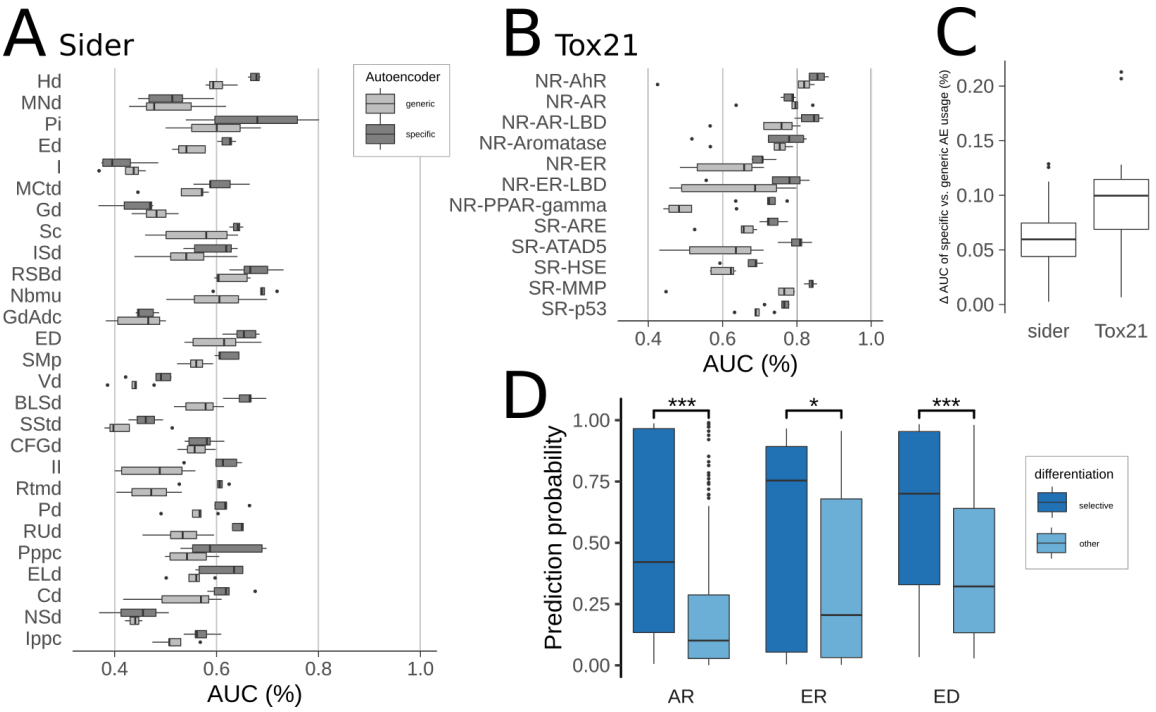

Figure 4: Comparison of the AUC values of individually trained models of the selected benchmarking data – A) Sider, and B) Tox21 – using the specific and generic AE. The abbreviations of the gene/pathway targets are extracted from the original publications. Their interpretation is not required in the scope of this study. C) Comparison of the AUC difference between specific and generic AE of the selected benchmarking data sets. D) `deepFPlearn` prediction probability using AR, ER, and ED model of compounds that have been experimentally measured for quantified target association and respectively differentiated into selective and non-specifically acting compounds. Probability distributions are compared using the Kolmogorow-Smirnow test, and significance levels for rejecting the null hypotheses that both distributions are similar were: ***, **, and * for p-values below 0.001 and 0.01, and 0.05, respectively.

amethasone, Betamehtasone and respective derivates that are well known to interact with the human estrogen

receptors and pathways, or to interact with the glucocorticoid pathway. Interestingly, some of those were also identified to selectively interact with the androgen receptor in cell assay screenings [39]. Among the candidates with the highest probabilities for the association to any of the endocrine disruption targets we found compounds like Ezlopitant dihydrate dihydrochloride, 5-Bromo-2,2-diethyl-5-nitro-1,3-dioxane, or Schinifoline, a metabolite of the Japanese Pepper plant Zanthoxylum schinifolium. To our knowledge, those substances have not been tested in bioassays so far. Among the candidates with the lowest probablities ($P < 0.01$) we identified derivates of carbamic, acetic, or amino acids, that have never been discussed in the context of steroid hormone related endocrine disruptions.

4 Discussion

There is a great need for systematic prediction of chemical-effect associations in the field of toxicology. In particular for the prioritization of chemicals for experimental screening, a smart selection of chemicals for monitoring, and for the design of novel chemicals. Although a number of approaches and implementations exist that, in part, address these challenges, there is no actual tool that can be readily applied on a large scale, and that be easily retrained with additional data sets. While MoleculeNet [38] and Deepchem [31] provide powerful frameworks for developing learning applications on chemicals, readily applicable tools, e.g. for predicting ED, are missing.

With `deepFPlearn` we present a ready-to-use application that enables to investigate any set of chemicals for their potential associations to gene targets that are involved in endocrine disruption. It is a deep learning approach, and we provide the possibility to retrain the integrated models to any kind of further associations of interest.

The small number of available labeled training data stands in large contrast to the high number of features that are necessary to describe the molecular structure of a chemical. We decided to use the topological fingerprint of size 2048bit since it had been shown that this variant of the fingerprint returns the most promising results in different machine learning approaches [29]. The natural interaction of chemicals and biomolecules is also biased towards "no interaction" (label of 0) such that the data suffers from a substantial imbalance between 1 and 0 labels.

Assessing the association of chemicals and biomolecules requires to measure a range of concentrations per substance and per assay and thus poses a substantial effort even if high-throughput technologies are used. Thus, there is – and will always be – a lack of labeled training data since the number of substances for which associations have been determined is small compared to the size of the universe of chemicals. Due to the high speed in which new chemicals are developed, this situation is very unlikely to change in the foreseeable future. To make things worse, many positive associations (label of 1) are potentially wrong due to mistakes during the interpretation of the screening results, like unclear effect tresholds, high variability in the experimental designs, and respective limitations in the statistics of modeling the observed effect.

We suspect that the imbalance of the training data is the main reason that the deep learning models overfit, and correcting this imbalance decreased overfitting at the expense of training performance. We were able to overcome the discrepancy between large descriptor size (fingerprint) and the limited amount of training data by introducing feature compression using a deep autoencoder on the simple binary fingerprint representation. Further, we improved domain extrapolation by training the autoencoder on a large repertoire of chemicals without reducing the predictive power of the subsequent classification with a deep feed forward network.

We tested different training situations, i) without using feature compression, ii) training an autoencoder with a subset of chemicals ((specific) AE), and iii) training the autoencoder on a larger set of chemicals (*generic* AE). We could prevent our subsequent classification models from overfitting by using either of the autoencoders. Further, we reached good training performances with ROC-AUC values above 80%, with satisfying sensitivity up to 63%, and specificity up to 97%. These values dropped by only 1% upon the usage of the generic AE, which allows to capture a much wider range of chemical structures without reducing the prediction quality of our classification models. So we argue that while we achieve comparable accurracy to existing approaches, our concept of feature reduction trained on a large set of chemicals makes the approach more robust regarding imbalanced data sets and of more general applicability regarding the diversity of substances.

The application to the large CompTox dataset returned a high number of chemicals classified as associated or not to selected gene targets. Most importantly, among the positive predictions we found compounds that have not been part of our training set but are well known to interact with human estrogen or the glucocorticoid receptor or related pathways. Our results also provide lists for candidates that have not yet been tested in bioassays but might be cross-checked or prioritized for testing regarding their involvement in endocrine disruption. Examples are Ezlopitant dihydrate dihydrochloride, 5-Bromo-2,2-diethyl-5-nitro-1,3-dioxane, or Schinifoline, which were the three candidates with the highest probabilities for an ED potential in our analysis. Likewise, on the bottom of the lists we identified substances with probapilities < 0.01, such as derivatives of carbamic, acetic, or amino acids, that have not yet been discussed to be connected to steroid hormone related endocrine disrup-

tions. This supports our prediction quality, and enhances the confidence in our models. The observed high values for specificity also suggest a potential application of `deepFPlearn` to exclude undesirable secondary effects during drug design. We suggest a more detailed analysis of the predicted associations and respective experimental validation in up-coming studies to confirm or decline potential secondary effects in endocrine disruption. The performance of our models is in line with the results on the compounds that were experimentally investigated by [39] where `deepFPlearn` returns low prediction probabilites for unspecific binders as well. Although, a rather broad distribution of prediction probabilities for selective binders suggests that there is still room for methodological improvement, many of the compounds predicted with a very high probability are indeed selective binders.

5 Conclusion

With `deepFPlearn` we were able to model the associations between chemical structures and effects on the gene/pathway level with a deep learning approach. In contrast to existing approaches and implementations, `deepFPlearn` is a ready-to-use tool. It comes as a stand-alone Python software package, and (additionally) wrapped in a Singularity Container to overcome the dependency on the operating system and required software. `deepFPlearn` is able to capture a much wider range of substances than those contained in the training data of the classification network, and it can be applied to classify hundreds of thousands of chemicals in seconds. With its different application modes we provide the flexibility to train custom models with any meaningful dataset that associates chemicals with an effect. We are convinced that `deepFPlearn` substantially contributes to the systematic *in silico* investigation of chemicals, e.g. for generating hypotheses on substance-effect associations that have so far not been investigated. With `deepFPlearn` we can cope with the large, constantly and rapidly growing chemical universe and support a prioritization of chemicals for experimental testing, assist in the smart selection of chemicals for monitoring, and contribute to the sustainable design of future chemicals.

6 List of abbreviations

ACC Area under the curve . . . 5

AE Autoencoder . . . 4

AR Androgen Receptor . . . 4

ED Endocrine Disruption . . . 3

ER Estrogen Receptor . . . 4

EU European Union . . . 2

FNN Feed forward Neural Network . . . 4

FP Fingerprint . . . 3

GR glucochorticoid Receptor . . . 4

InChI International Chemical Identifier . . . 3

JSON JavaScript Object Notation . . . 5

MCC Matthews Correlation Coefficient . . . 5

ML Machine Learning . . . 3

MoA Mode of Action . . . 7

NA Not Available . . . 4

PPARg Peroxisome Proliferator-Activated Receptor gamma . . . 4

QSAR Quantitative Structure Activity Relationships 2

REACH Registration, Evaluation, Authorisation and Restriction of Chemicals . . . 2

ReLU Rectified Linear Unit . . . 4

SGD Stochastic Gradient Descent . . . 5

SMILES Simplified Molecular-Input Line-Entry System . . . 3

TR Thyroid Receptor . . . 4

UMAP Uniform Manifold Approximation and Projection . . . 6

7 Declarations

Availabilty of data and materials

We provide the `deepFPlearn` Python package on GitHub `https://github.com/yigbt/deepFPlearn`. The software is distributed under the GNU General Public Licence (v3.0, 29th June 2007). We further provide a ready-to-use Singularity Container image containing all required tools and libraries as well as the `deepFPlearn` package in the first release state, which built the basis of this manuscript at `https://cloud.sylabs.io/library/mai00fti/default/dfpl.sif`. All datasets used for training, and the respectively trained models are publicly available as release-asset in the package repository on GitHub.

Competing interests

The authors declare that they have no competing interests.

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Author's contribution

JS and JH planned the study; JS and CL defined the neural network architectures; JS pre-processed all data; JS, PS and MB implemented the software package; All authors analyzed the results and wrote the manuscript. All authors read and approved the final manuscript.

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References

[1] Cas, 2020. *No Title*. `https://www.cas.org/support/documentation/chemical-substances`.

[2] Fischer S, 2017. *KEMI Market List (Version NORMAN-SLE-S17.0.1.4)*. `http://doi.org/10.5281/zenodo.3959394`.

[3] European Environment Agency, 2015. *State and Outlook 2015 the European Environment*. Tech. rep., European Environment Agency.

[4] Bond GG & Garny V, nov 2019. *Inventory and evaluation of publicly available sources of information on hazards and risks of industrial chemicals. Toxicology and Industrial Health*, 35(11-12):738–751. ISSN 0748-2337. doi:10.1177/0748233719893198.

[5] Wang Z, Walker GW, Muir DC, & Nagatani-Yoshida K, mar 2020. *Toward a Global Understanding of Chemical Pollution: A First Comprehensive Analysis of National and Regional Chemical Inventories. Environmental Science and Technology*, 54(5):2575–2584. ISSN 15205851. doi:10.1021/ACS.EST.9B06379/SUPPL_FILE/ES9B06379_SI_001.PDF.

[6] Mattingly CJ, Colby GT, Forrest JN, Boyer JL, Davis AAPA, Grondin CJ, Johnson RJ, Sciaky D, McMorran R, Wiegers J, *et al.*, oct 2016. *Generating the blood exposome database using a comprehensive text mining and database fusion approach. Environmental Health Perspectives*, 9(8):769–774. ISSN 13624962. doi:10.1371/journal.pone.0154387.

[7] Anderson MG, Mcdonnell J, Ximing C, Cline SA, Balance WW, Rockstrom J, Daily GC, Ehrlich PR, Reidy CA, Dynesius M, *et al.*, 2006. *The Challenge of Micropollutants in Aquatic Systems. Science*, 313(August):1072–1077.

[8] Busch W, Schmidt S, Kühne R, Schulze T, Krauss M, & Altenburger R, 2016. *Micropollutants in European rivers: A mode of action survey to support the development of effect-based tools for water monitoring. Environmental Toxicology and Chemistry*, 35(8):1887–1899. ISSN 15528618. doi:10.1002/etc.3460.

[9] Norman Network, 2020. *EMPODAT Database*. `https://www.norman-network.com/nds/empodat/chemicalStatistics.php`.

[10] Rappaport SM, 2016. *Genetic Factors Are Not the Major Causes of Chronic Diseases. Plos One*, 11(4):e0154387. ISSN 1932-6203. doi:10.1371/journal.pone.0154387.

[11] Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, *et al.*, 2012. *A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England)*, 380(9859):2224–2260. ISSN 1474-547X. doi:10.1016/S0140-6736(12)61766-8.

[12] Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, Baldé AB, Bertollini R, Bose-O'Reilly S, Boufford JI, *et al.*, 2018. *The Lancet Commission on pollution and health. Lancet (London, England)*, 391(10119):462–512. ISSN 1474-547X. doi:10.1016/S0140-6736(17)32345-0.

[13] Köhler HR & Triebskorn R, 2013. *Wildlife ecotoxicology of pesticides: Can we track effects to the population level and beyond? Science*, 341(6147):759–765. ISSN 10959203. doi:10.1126/science.1237591.

[14] Hallmann CA, Foppen RPB, Van Turnhout CAM, De Kroon H, & Jongejans E, 2014. *Declines in insectivorous birds are associated with high neonicotinoid concentrations. Nature*, 511(7509):341–343. ISSN 14764687. doi:10.1038/nature13531.

[15] Desforges JP, Hall A, McConnell B, Rosing-Asvid A, Barber JL, Brownlow A, De Guise S, Eulaers I, Jepson PD, Letcher RJ, Levin M, Ross PS, Samarra F, Víkingson G, Sonne C, & Dietz R, 2018. *Predicting*

global killer whale population collapse from PCB pollution. Science, 361(6409):1373–1376. ISSN 10959203. doi: 10.1126/science.aat1953.

[16] Posthuma L, van Gils J, Zijp MC, van de Meent D, & de Zwartd D, 2019. *Species sensitivity distributions for use in environmental protection, assessment, and management of aquatic ecosystems for 12 386 chemicals. Environmental Toxicology and Chemistry*, 38(4):703–711. ISSN 15528618. doi:10.1002/etc.4373.

[17] European Commission, 2019. *COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE EUROPEAN COUNCIL, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS. The European Green Deal*. Tech. Rep. COM(2019) 640 final, European Commission.

[18] European Chemials Agency, 2019. *No Title*. `https://echa.europa.eu/de/universe-of-registered-substances`.

[19] European Chemicals Agency, 2018. *Evaluation under REACH: progress report 2017 — 10 years of experience*. Tech. rep., European Chemicals Agency, Helsinki.

[20] Raies AB & Bajic VB, 2016. *In silico toxicology: computational methods for the prediction of chemical toxicity. Wiley Interdisciplinary Reviews: Computational Molecular Science*, 6(April):147–172. ISSN 17590884. doi:10.1002/wcms.1240.

[21] Lepailleur A, Poezevara G, & Bureau R, 2013. *Automated detection of structural alerts (chemical fragments) in (eco)toxicology. Computational and Structural Biotechnology Journal*, 5(6):e201302013. ISSN 20010370. doi:10.5936/csbj.201302013.

[22] Vink SR, Mikkers J, Bouwman T, Marquart H, & Kroese ED, 2010. *Use of read-across and tiered exposure assessment in risk assessment under REACH–a case study on a phase-in substance. Regulatory toxicology and pharmacology : RTP*, 58(1):64–71. ISSN 1096-0295. doi: 10.1016/j.yrtph.2010.04.004.

[23] Perkins R, Fang H, Tong W, & Welsh WJ, 2003. *Quantitative structure-activity relationship methods: Perspectives on drug discovery and toxicology. Environmental Toxicology and Chemistry*, 22(8):1666–1679. ISSN 07307268. doi:10.1897/01-171.

[24] Cherkasov A, Muratov EN, Fourches D, Varnek A, Baskin II, Cronin M, Dearden J, Gramatica P, Martin YC, Todeschini R, Consonni V, Kuz'Min VE, Cramer R, Benigni R, Yang C, Rathman J, Terfloth L, Gasteiger J, Richard A, & Tropsha A, 2014. *QSAR modeling: Where have you been? Where are you going to? Journal of Medicinal Chemistry*, 57(12):4977–5010. ISSN 15204804. doi:10.1021/jm4004285.

[25] Lo YC, Rensi SE, Torng W, & Altman RB, 2018. *Machine learning in chemoinformatics and drug discovery. Drug Discovery Today*, 23(8):1538–1546. ISSN 18785832. doi:10.1016/j.drudis.2018.05.010.

[26] Thomas R, 2018. *The US Federal Tox21 Program: A strategic and operational plan for continued leadership. ALTEX*, pp. 163–168. ISSN 1868596X. doi:10.14573/altex.1803011.

[27] Mayr A, Klambauer G, Unterthiner T, & Hochreiter S, 2015. *DeepTox: Toxicity Prediction Using Deep Learning. Frontiers in Environmental Science*, 3. doi: 10.3389/fenvs.2015.00080.

[28] Pu L, Naderi M, Liu T, Wu HC, Mukhopadhyay S, & Brylinski M, 2019. *eToxPred: a machine learning-based approach to estimate the toxicity of drug candidates. BMC Pharmacology and Toxicology*, 20(1). doi: 10.1186/s40360-018-0282-6.

[29] Sun L, Yang H, Cai Y, Li W, Liu G, & Tang Y, 2019. *In Silico Prediction of Endocrine Disrupting Chemicals Using Single-Label and Multilabel Models. Journal of Chemical Information and Modeling*, 59. doi: 10.1021/acs.jcim.8b00551.

[30] Liu X, Gao Y, Peng J, Xu Y, Wang Y, Zhou N, Xing J, Luo X, Jiang H, & Zheng M, jun 2015. *TarPred: A web application for predicting therapeutic and side effect targets of chemical compounds. Bioinformatics*, 31(12):2049–2051. ISSN 14602059. doi:10.1093/bioinformatics/btv099.

[31] Ramsundar B, Eastman P, Walters P, & Pande V, 2019. *Deep Learning for the Life Sciences*. O'Reilly Media, Inc. ISBN 9781492039839.

[32] Landrum G, 2006. *RDKit: Open-source Cheminformatics*. doi:10.2307/3592822.

[33] McInnes L, Healy J, Saul N, & Großberger L, 2018. *UMAP: Uniform Manifold Approximation and Projection. Journal of Open Source Software*, 3(29):861. ISSN 2475-9066. doi:10.21105/joss.00861.

[34] Abadi M, Barham P, Chen J, Chen Z, Davis A, Dean J, Devin M, Ghemawat S, Irving G, Isard M, *et al.*, 2016. *TensorFlow: A system for large-scale machine learning*. In *Proceedings of the 12th USENIX Symposium on Operating Systems Design and Implementation, OSDI 2016*, pp. 265–283. ISBN 9781931971331.

[35] François Chollet, Author A, Another author Y, & Authors F, 2015. *Keras*.

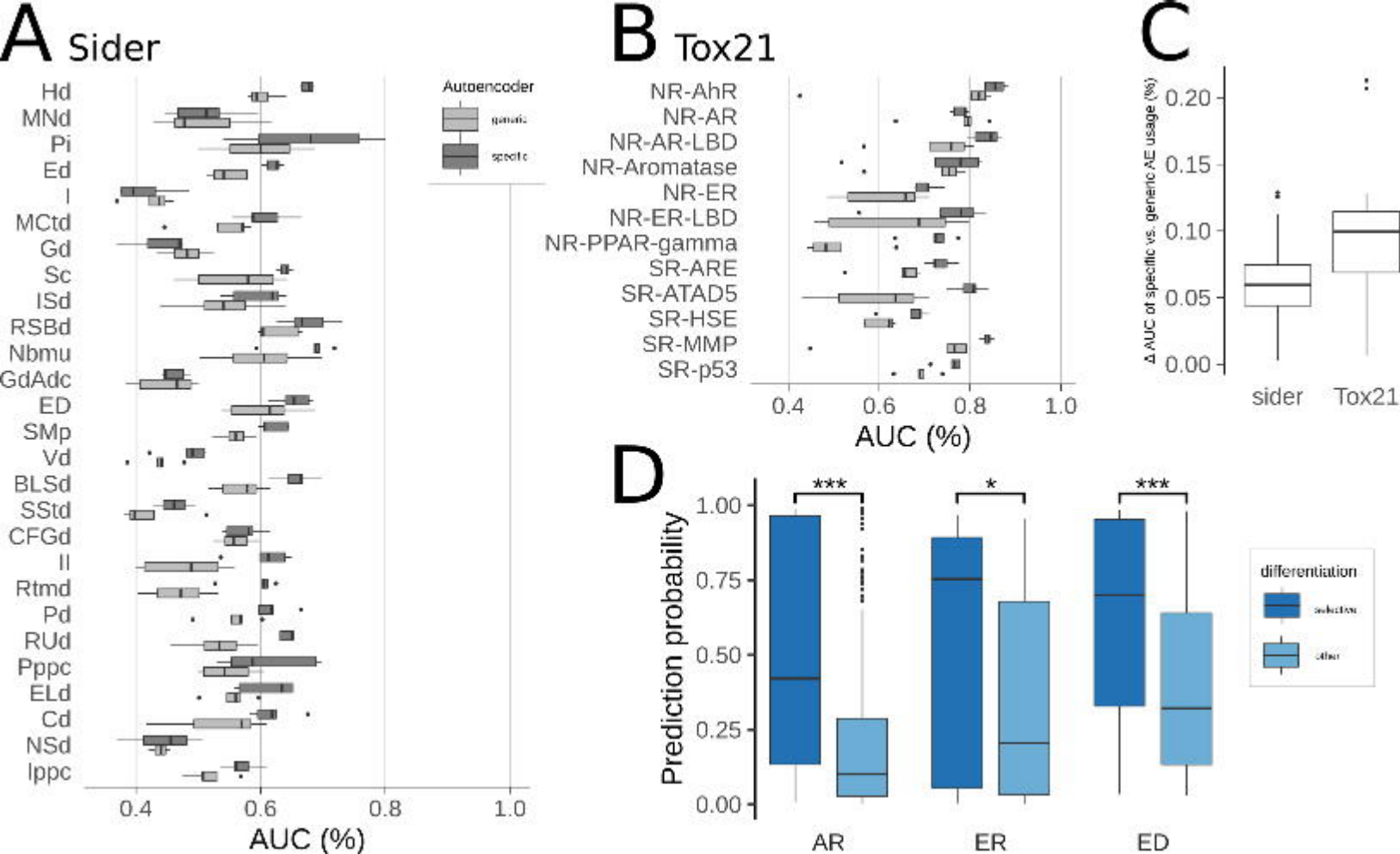
[36] Pedregosa FABIANPEDREGOSA F, Michel V, Grisel OLIVIERGRISEL O, Blondel M, Prettenhofer P, Weiss R, Vanderplas J, Cournapeau D, Pedregosa F, Varoquaux G, Gramfort A, Thirion B, Grisel O, Dubourg V, Passos A, Brucher M, Perrot andÉdouardand M, Duchesnay A, & Duchesnay EDOUARDDUCHESNAY F, 2011. *Scikit-learn: Machine Learning in Python Gaël Varoquaux Bertrand Thirion Vincent Dubourg Alexandre Passos PEDREGOSA, VAROQUAUX, GRAMFORT ET AL. Matthieu Perrot*. Tech. rep.

[37] Williams AJ, Grulke CM, Edwards J, Mceachran AD, Mansouri K, Baker NC, Patlewicz G, Shah I, Wambaugh JF, Judson RS, Richard AM, & Gov WA, 2017.

The CompTox Chemistry Dashboard: a community data resource for environmental chemistry Open Access. Journal of Cheminformatics, 9:61. doi:10.1186/s13321-017-0247-6.

[38] Wu Z, Ramsundar B, Feinberg EN, Gomes J, Geniesse C, Pappu AS, Leswing K, & Pande V, mar 2017. *MoleculeNet: A Benchmark for Molecular Machine Learning. Chemical Science*, 9(2):513–530.

[39] Escher BI, Henneberger L, König M, Schlichting R, & Fischer FC, jul 2020. *Cytotoxicity burst? Differentiating specific from nonspecific effects in tox21 in vitro reporter gene assays. Environmental Health Perspectives*, 128(7):1–10. ISSN 15529924. doi:10.1289/EHP6664.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AUC (%)
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NR-AR
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SR-ARE
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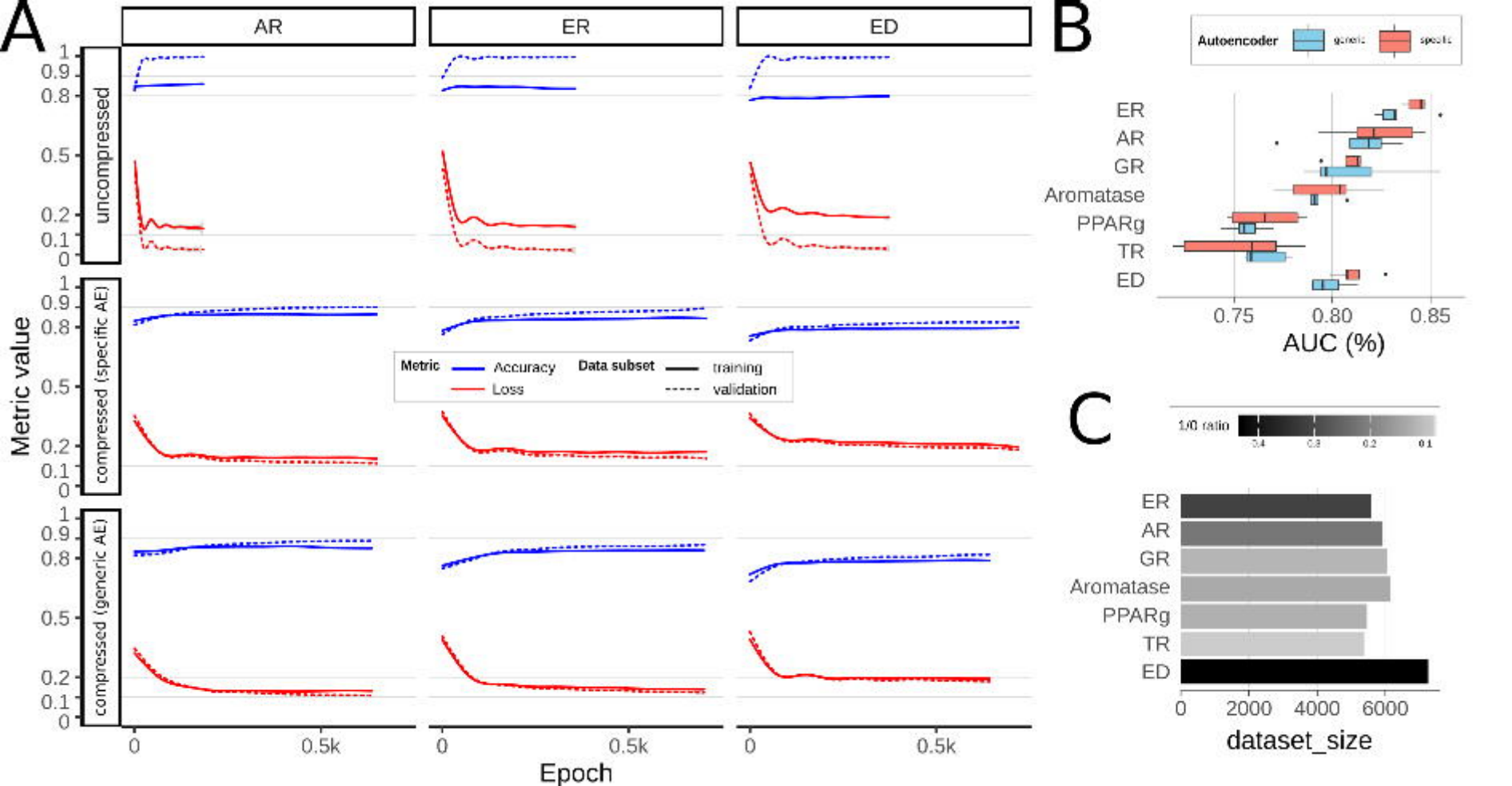
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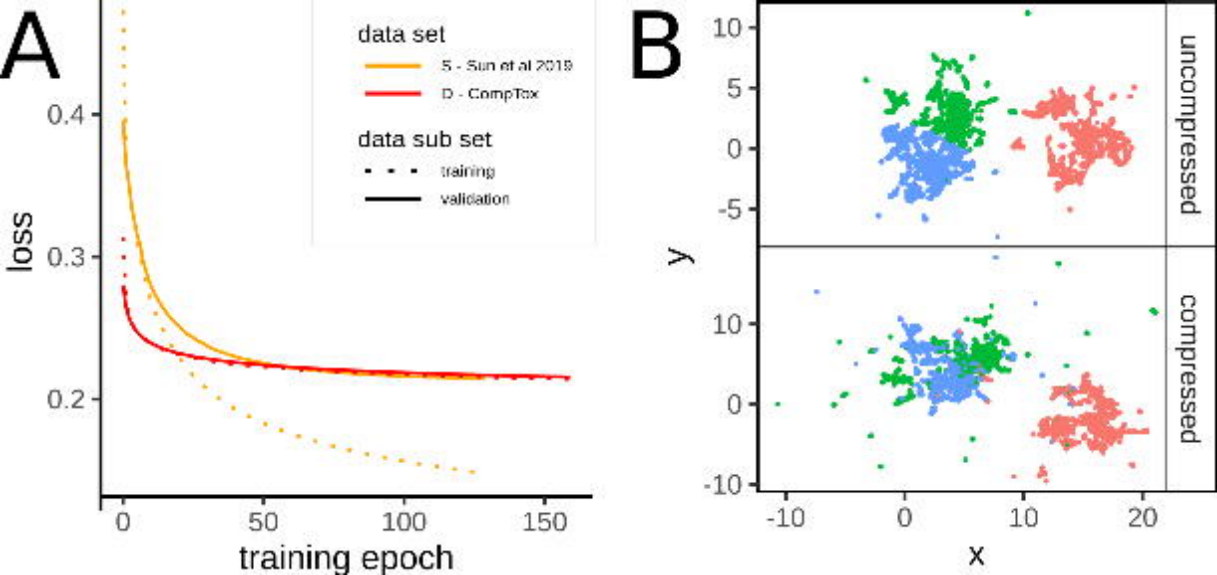
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D - CompTox
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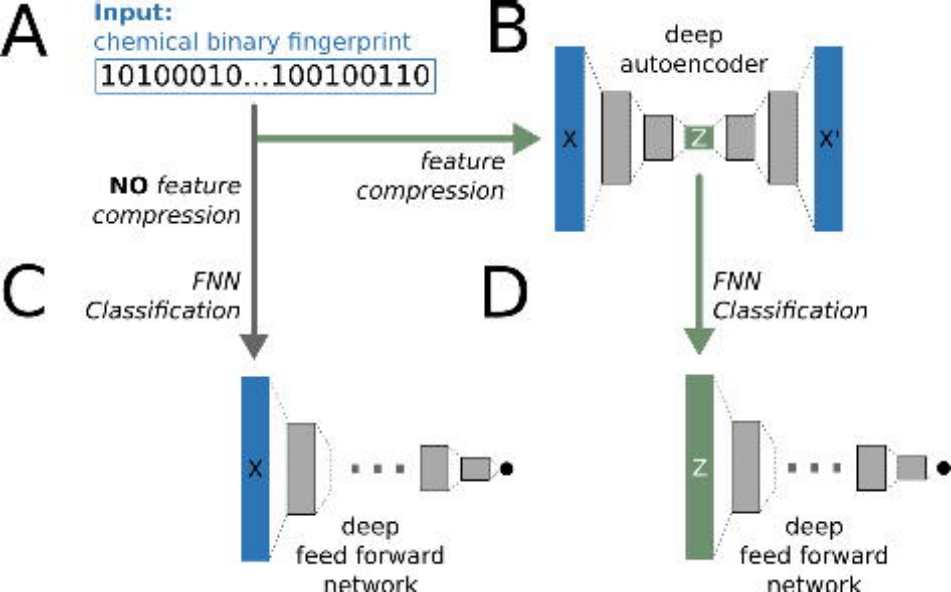
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