Low cost prediction of probability distributions of molecular properties for early virtual screening

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Abstract—While there is a general focus on predictions of values, mathematically more appropriate is prediction of probability distributions: with additional possibilities like prediction of uncertainty, higher moments and quantiles. For the purpose of the computer-aided drug design field, this article applies Hierarchical Correlation Reconstruction approach, previously applied in the analysis of demographic, financial and astronomical data. Instead of a single linear regression to predict values, it uses multiple linear regressions to independently predict multiple moments, finally combining them into predicted probability distribution, here of several ADMET properties based on substructural fingerprint developed by Klekota&Roth. Discussed application example is inexpensive selection of a percentage of molecules with properties nearly certain to be in a predicted or chosen range during virtual screening. Such an approach can facilitate the interpretation of the results as the predictions characterized by high rate of uncertainty are automatically detected. In addition, for each of the investigated predictive problems, we detected crucial structural features, which should be carefully considered when optimizing compounds towards particular property. The whole methodology developed in the study constitutes therefore a great support for medicinal chemists, as it enable fast rejection of compounds with the lowest potential of desired physicochemical/ADMET characteristic and guides the compound optimization process.

Keywords: chemoinformatics, computer-aided drug design, virtual screening, molecular fingerprints, predicting probability distributions, hierarchical correlation reconstruction

I. INTRODUCTION

Wide range of computational methods developed to support the process of search for new active compounds contribute to the significant shortening of time and lowering the expenses of the new drugs development pipelines. (1, 2) The intense progress in the computer-aided drug design field is nowadays possible thanks to the continuous gain of knowledge on the human biology, as well as the increase in the available computational power.

The widespread manipulation of chemical data by computers generates the need of the proper representation of compound structures. The most popular way of depicting chemical structure is its representation in the form of molecular descriptors or fingerprints. The former approach, calculates values of various compound parameters, such as the number of atoms of particular type, molecular weight, number of bonds of the given order, etc. On the other hand, fingerprints inform about the presence of particular chemical moieties in the molecule. There are two main fingerprint types: hashed and key-based ones. During the calculation of the hashed fingerprint, each atom constitutes a starting point of a path of a particular length. Then, for each string, a hash code is generated, which finally ends up with the string representing the whole molecule. On the other hand, in the key-based fingerprints, each position has its interpretation, as it represents the presence or absence of the given feature (being most often chemical fragments) in the molecule.

In this article we discuss the application of key-based fingerprints to predict not only the expected value, but also independently moments resembling variance, skewness, kurtosis
and higher, finally combining them into a single predicted conditional probability distribution with Hierarchical Correlation Reconstruction (HCR) approach for selected physicochemical and ADMET compound properties. The above-mentioned methodology was previously used for various applications e.g. demographic [3], financial [4], astronomical [5]. Here we often have more features than datapoints, requiring new regularization techniques proposed in this article.

Taking into account the information provided by the presented method, the potential application of the predicted probability distribution in computer-aided drug design tasks (virtual screening in particular) is discussed. Combinatorial space of chemical molecules grows exponentially with size, requiring computationally inexpensive methods to select a small percentage of promising ones during search in this space - for example of some properties to be in a desired range, allowed by proposed quantile thresholding and maximal peak analysis.

In the study, we focus on the prediction of selected physicochemical and ADMET compound features: intestinal permeability (examined via two Caco-2 permeability assays with “papp” referring to the apparent permeability), cardiotoxicity (described as the hERG channel blockage), metabolic stability (investigated as compound half-lifetime in human liver cells), plasma protein binding and solubility. The importance of their (as well as other physicochemical/ADMET properties) is undeniable. Focusing only on compound activity towards considered targets is insufficient, as even the most active compound cannot become a drug, if its physicochemical and ADMET profile is unfavorable. For example, if the metabolic stability of a compound is too low, it has not sufficient time to trigger the desired biological response. Moreover, the decomposition products formed can not only be inactive towards the target, but they can also display toxic effects. Intestinal permeability is important for orally administered drugs to effectively get to the place of action and toxicity is an obvious feature which disqualifies a compound from being a future drug.

Despite the constant increase in the amount new experimental data, which can be used to the development of new predictive models, there still a lot of difficulties, which cause that the predictions are not always sufficiently accurate.

In the study, we propose the non-standard way of dealing with such prediction uncertainty. We developed approaches, in which as an answer returned by the model is not a single value, but the whole distribution of the predicted property. It can facilitate the interpretation of the results and the predictions characterized by high rate of uncertainty are automatically detected. It constitutes great support for medicinal chemists, as it enable fast rejection of compounds with the lowest potential of desired physicochemical/ADMET characteristic.

In addition, for each of the investigated predictive problems, we detected crucial structural features, which should be carefully considered when optimizing compounds towards particular property.

II. DATASETS AND FINGERPRINTS

All compounds used in the study were fetched from the ChEMBL database (only data obtained in the human-based experiments were considered). Then, the compounds were transformed into the bit-string form, using the substructural representation developed by Klekota&Roth [6] (further referred to as KlekFP), consisting of 4860 structural keys.

III. USED HCR-BASED METHODOLOGY

This section discusses the used methodology - first normalization here of predicted property to nearly uniform distribution in [0, 1], then modeling of its (conditional) probability density as a linear combination in orthonormal basis, with independently predicted coefficients. Regularization techniques are crucial and difficult here - proposed for discussed application, optimized for log-likelihood in 10-fold cross-validation.

A. Normalization

As in copula theory [7], in the discussed methodology it is convenient to predict density for variable from nearly uniform distribution in [0, 1], hence we start with normalization.

Assuming the original variable is \( z^n \), such normalization can be done as \( y^n = CDF(z^n) \) for CDF being cumulative distribution function, e.g. using some parametric distribution with estimated parameters.

Here the distributions are often quite complex, hence we use empirical distribution instead. Specifically, all \( N \) values are first sorted, then \( n \)-th value in such order is assigned \( (n − 0.5)/N \) normalized value. If there are multiple identical values, then they are all assigned the central position: \( (n_{max} + n_{min}−1)/2N \) - allowing to also work with discrete values.

Normalization for the discussed datasets is presented in Fig. 3 allowing to translate predictions to the original variables. We can see flat ranges corresponding to discretness, which could be included in optimization of the used basis, maybe combined with Canonical Correlation Analysis as discussed in [5]. Not to complicate it is omitted in this version of article.

B. HCR probability distribution prediction

In HCR methodology we want to model densities of normalized variables as linear combinations in orthonormal basis, with
coefficients \((a_i)\) similar to moments: expected value, variance, skewness, kurtosis and higher:

\[
\hat{\rho}(Y = y|X = x) = 1 + \sum_{i=1}^{m} f_i(y) a_i(x)
\]  

(1)

where \(y\) is normalized predicted variable, \(x = (x_k)_{k=1..K}\) is feature vector - here binary fingerprints (KlekFP, \(K = 4860\)). The \((f_i)_{i=1..m}\) is orthonormal basis: \(\int_\mathbb{R} f_i(y) f_j(y) dy = \delta_{ij}\), of first \(m\) orthonormal polynomials (here \(m = 20\)), starting with \((f_1, f_2, f_3, f_4)\):

\[
\sqrt{3}(2y - 1), \sqrt{5}(6y^2 - 6y + 1), \sqrt{7}(20y^3 - 30y^2 + 12y - 1), \\
3(70y^4 - 140y^3 + 90y^2 - 20y + 1).
\]

However, \(\hat{\rho}(Y = y|X = x)\) as a linear combination can get below 0. For some applications this issue might be neglected, e.g. in discussed maximal peak analysis trying to find high probability range.

If actual probability density is required, non-negativity is ensured by further calibration: the final density is \(\rho(y) = \phi(\rho(y))/Z\) where \(Z\) is for normalization to integrate to 1, and \(\phi\) calibration function e.g. \(\phi(\rho) = \max(0, 1, \rho)\), or some more sophisticated - here there was used parameterized softplus \([8]\) function:

\[
\phi(\rho) = \ln(1 + \exp(\mu x)/\nu) / \mu
\]

(2)

with \(\mu, \nu\) parameters optimized for each dataset. Instead of integration, density was discretized to size 1000 lattice, allowing to use sums instead.

Here, as in \([3, 4, 5]\), we will directly predict these \(a_i\) coefficients with linear regression from feature vector \(x\):

\[
a_i(x) = \sum_{k=1}^{K} \beta_{ik} x_k
\]

(3)

Basic estimation of \(a_i\) from \(y\) is mean: \(1/N \sum_{n=1}^{N} f_i(y^n)\) \([9]\). Mean is value minimizing mean squared error from datapoints, hence wanting to predict \(a_i\) from variables \(x\) here, a natural approach is mean squared linear regression, in practice with required regularization to prevent overfitting - discussed further.

C. Cross-validation loglik evaluation and regularization

Discussed model as linear regression is \((\beta_{ik})_{i=1..m, k=1..K}\) coefficients, and its size can easily exceed the number of datapoints \(N\), especially if using KlekFP of \(K = 4860\) fingerprints - hence there are necessary regularization techniques.

From one side it is crucial to use cross-validation evaluation, here 10-fold cross validation: dataset is randomly split into 10 subsets, 9 of them are treated as training set, 10th as test set - it is done in all 10 ways, and finally averaged.

As evaluation there was directly used log-likelihood:

\[
1/N \sum_{n=1}^{N} \ln(\rho(y^n | x^n)).
\]

A more informative evaluation is just sorting the \((\rho(y^n | x^n))\) values - presented in Fig. 4. There could be also considered more sophisticated evaluations, e.g. directly of performance for a specific application.

One regularization technique used in tests is feature selection, here applied separately for each \((a_i)_{i=1..20}\). For this purpose, for each \(i = 1, \ldots, m\) and \(k = 1, \ldots, K\) there was calculated correlation between \((f_i(y^n))_{n=1..N}\) predicted vector and \((x_k^n)_{n=1..N}\). Such \(K \times m\) correlations are presented in Fig. 3. A natural feature selection is choosing those with absolute value of correlation above some threshold \((\approx 0.02 - 0.04)\), there is a difficulty of choosing this threshold to remove noise.

For two independent \(N\)-dimensional vectors, their correlation is approximately from Gaussian distribution centered in zero, and of standard deviation \(\sigma = 1/\sqrt{N}\). For each \(i = 1, \ldots, m\) we see \(K\) such correlations - we would like to select those of absolute value above some boundary \(\xi\). With Gaussian distribution assumption, further than this boundary there should be \(\approx p_\xi = 1 - \operatorname{erf}(\xi/\sigma/\sqrt{2})\) of cases, statistically should happen \(\chi \approx K p_\xi\) times. The idea is to fix this \(\chi\) (as expected number if uncorrelated) and select features with correlation above boundary \(\xi\):

\[
\text{select } |\text{correlation}| > \xi \quad \text{for } \xi = \sqrt{2/N} \operatorname{erf}^{-1}\left(1 - \frac{\chi}{K}\right)
\]

(4)

To systematize between datasets, there was used \(\chi = 300\) providing a good compromise. There could be also used e.g. individual optimizations - for datasets, but also for each \(a_i\).

The best performance was obtained by combining above feature selection, with further linear regression with l1 "lasso"
There is a difficulty to choose the $\lambda$ regularization parameter - here it was separately optimized for each dataset getting $\lambda \approx 3$, it could be optimized separately for each predicted $a_i$, maybe automatically e.g. depending on its number of selected features.

### D. Final approach

Here is summarized the used approach:

1) **Normalize** predicted $(z^n)_{n=1..N}$ variable to $(y^n)_{n=1..N}$ having nearly uniform distribution on $[0, 1]$.

2) For $i = 1, \ldots, m$ and $k = 1, \ldots, K$ calculate correlation between $(f_i(y^n))_{n=1..N}$ and $(x^n_k)_{n=1..N}$ vectors, select fingerprints with absolute value of correlation above threshold $\xi$.

3) Among the selected fingerprints, perform **linear regression with 11 “lasso” regularization**.

4) Having predicted all moments $(a_i)_{i=1..m}$, we calculate **predicted density** $\hat{\rho}(y) = 1 + \sum_{i=1}^m a_i f_i(y)$.

5) If we need the actual density, finally perform **calibration** ($\hat{\rho}(\hat{\rho}(y))/Z$, where $Z = \int_0^1 \hat{\rho}(\hat{\rho}(y)) dy$ can be calculated on lattice (size 1000 here), and e.g. $\hat{\rho}(\rho) = \ln(1 + \exp(y))/\mu$ with $\mu, \nu$ parameters optimized to maximize log-likelihood.

6) If needed, inverse normalization to translate the predicted density to the original variable (skipped here).

Figure 4 shows evaluations of such procedure for considered datasets: not only averaged as log-likelihood, but also sorted densities here are often narrow peaks, allowing e.g. to focus on objects with nearly certain desired parameters. Model parameters were chosen to maximize log-likelihood:

$$\lambda \sum_{n=1}^{N} \ln(\rho(y^n|x^n)),$$

However, for a specific application we could directly optimize for its performance.

While the above is appropriate for filtering objects below/above some threshold, we can also use it to restrict to inside some range: by choosing two bounds $u < v$ and restricting to objects having $\rho(v) - q(u)$ above some threshold.

### B. Maximal peak analysis

As in Fig.4 especially for high polynomial degree, predicted densities here are often narrow peaks, allowing e.g. to focus on objects (molecules) with this kind of predictions. Here for each predicted density there was found position of its maximum, from it we search left and right until density stops decreasing (or reaching 0,1) - getting left and right local minimum: in $0 \leq m_l, m_r \leq 1$. The maximal peak can be defined as $[m_l, m_r]$ range: of width $m_r - m_l$, and predicted probability $\int_{m_l}^{m_r} \rho(y) dy$.

This Figure contains points of (width, probability) of the maximal peaks, marking with color if the real value $y^n$ was indeed in $[m_l, m_r]$. We can see that restricting to objects above some thresholds for width and probability, with very high probability such predicted maximal peak indeed contains the real value - such filtering with thresholds would give a good control of the real value.

### V. Conclusions and further work

While standard approach is prediction of value, separately predicting multiple moments, here we predict the entire probability distributions - quite successfully for molecular properties from fingerprints. It allows to inexpensively extract more information, which seems valuable especially for virtual screening applications, e.g. allowing to select a percentage of them with near certainty of chosen given property being in the desired range.
This is initial article opening such look new and promising approaches, there are many directions for further development to be explored in the future, for example:

- applications in real scenarios especially virtual screening, search for new applications,
- improvements of regularization techniques, both from evaluation perspective and computational cost, considering different techniques,
- feature engineering - e.g. testing other fingerprints, combining them, calculating only the valuable ones,
- building new features, e.g. from fingerprints: $x_{ij} = [x_i = x_j]$ features (1 iff $x_i = x_j$, 0 otherwise), designing completely new ones - also of different types like molecular shape descriptors,
- optimizing for different evaluations, e.g. directly of performance for a specific application,
- optimizing the $(f_i)$ basis e.g. with Canonical Correlation Analysis, including discreteness - like in [5],
- testing more sophisticated prediction techniques for moments, like neural networks.

There could be also considered opposite application - Fig. 5 shows complex dependencies between moments and fingerprints corresponding to structural features, which might be used for their better understanding, or to directly generate molecules of desired properties.

**Figure 5.** Quantile thresholding: of $q(v) = \int_0^v \rho(y)dy$ for $v = 0.1$ (left) and $v = 0.9$ (right) for predicted density $\rho$. Top: predicted $q(v)$ (horizontal) vs real value (vertical) for halflifetime_human_liver dataset - as expected, we can see that very high values usually have very low predicted $q(0.1)$, very low values have usually very high $q(0.9)$. More practically, predicting very high $q(0.1)$ (or low $q(0.9)$), the real values are nearly always low (high). Plots below allow to evaluate it quantitatively: focusing only on predicted $q(0.1) > 0.8$ (horizontal axis), the expected value (horizontal axis) is e.g. ~ 0.1. Focusing on predicted $q(0.9) < 0.6$, the expected value is e.g. ~ 0.8. Plots on the bottom show remaining percentages of cases if performing such restriction. In practice such $v$ choice should be made based on demanded property e.g. minimal/maximal halftime in virtual screening.

**Figure 6.** Evaluation of quantile thresholding for all datasets and optimized $(v, threshold)$ parameters. Choosing $v$ and restricting to $q(v) = \int_0^v \rho(y)dy$ below (blue) or above (orange) some optimized threshold, the mean actual value was as shown in horizontal axis, at cost of restricting to a percentage of cases shown in vertical axis. For example restriction to 20% e.g. of molecules, allowed to enforce mean value in the highest or lowest 20 – 30%. Restriction to 5% enforced mean value to extremal 5-15%.

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