A Fully Computational Model for Predicting Percutaneous Drug Absorption

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The prediction of transdermal absorption for arbitrary penetrant structures has several important applications in the pharmaceutical industry. We propose a new data-driven, predictive model for skin permeability coefficients k_p based on an ensemble model using *k*-nearest-neighbor models and ridge regression. The model was trained and validated with a newly assembled data set containing experimental data and structures for 110 compounds. On the basis of three purely computational descriptors (molecular weight, calculated octanol/water partition coefficient, and solvation free energy), we have developed a model allowing for the reliable, purely computational prediction of skin permeability coefficients. The model is both accurate and robust, as we showed in an extensive validation (correlation coefficient for leave-one-out cross validation: $Q = 0.948$, mean standard error: 0.2 for log k_p).

1. INTRODUCTION

Of the various routes for xenobiotics to enter the human body, permeation through the skin has always been of particular interest for the pharmaceutical, cosmetic, and agrochemical industries. A simple computational model capable of predicting both speed and the extent of uptake into the systemic circulation after dermal application would enable pharmaceutical companies to estimate bioavailability for transdermal therapeutic systems. Such a predictive model can clearly result in reduced development costs, as it can help in eliminating possible drug candidates with insufficient transdermal bioavailability at an early stage. In the cosmetic and agrochemical industries, where the permeation of xenobiotics through the skin is usually undesirable, such a model would allow for a quick risk assessment.

Thus, in the past, several attempts have been made to predict skin permeability coefficients k_p. Since experimental data for skin permeability are still scarce, predictive models are usually based on the data set published by Flynn[1] or subsets thereof. The predictions themselves were performed either using mechanistic or empirical modeling.[2] Both approaches certainly have their merits and have reached a high level of sophistication. Mechanistic approaches may predict the time-dependent change of concentration of a diffusant in the layers of the skin, that is, the dynamics of skin penetration. They also yield information about the additional factors influencing skin permeation, for example, the contribution of the various barriers or the effect of penetration enhancers.

Empirical approaches usually predict the steady-state properties of skin permeation from molecular parameters such as molecular size and lipophilicity. These two parameters (or slight variations, e.g., molecular volume) have been used repeatedly in predictive models and seem to affect the passive diffusion of drugs through any biological barrier to a large extent. Various other descriptors (e.g., polarity, hydrogen-bond donor acidity, and hydrogen-bond acceptor basicity) have also been employed in models for predicting skin permeability.[3] However, most models require *experimental* descriptors, which make the large-scale application of these models difficult. In general, models based on computational descriptors alone were found to be less reliable and accurate than models including experimental data.

The statistical methods used in developing and validating computational models encompass various techniques such as multiple linear regression analysis,[4] principal component analysis,[5] and artifical neural networks (ANNs).[6] More recently, a number of models have been re-evaluated using fuzzy modeling.[7] While linear models (linear regression and principal component analysis) are better suited for the interpretation of the final model, there is no reason to assume that complex properties such as k_p are linear in their descriptors. Hence, nonlinear models, in particular, those based on ANNs, yield better prediction accuracy. A common drawback of these methods is their tendency to overfit, that is, to yield models able to reproduce the training data with high accuracy but exhibiting poor performance on other data sets.

Here, we present a new model for predicting skin permeability. The model itself is a so-called *ensemble model* combining *k*-nearest-neighbor models and ridge regression and—to our knowledge—has not been applied previously in this field. The model is data-driven; that is, it has to be trained

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using experimentally determined permeability coefficients. For this purpose, we have assembled one of the largest data sets of compounds with experimental data of skin permeability used so far (see the Supporting Information for relevant information). Special care was taken to generate a robust model appropriate for large-scale application to new chemical entities in drug design. Furthermore, our model was to be as general as possible in order to allow for predicting permeability coefficients for drug-like compounds. The prediction of skin permeabilities for new chemical entities is based on three readily available computational descriptors and, thus, allows for calculating percutaneous permeability coefficients completely in silico once the model has been trained appropriately.

2. MATERIALS AND METHODS

2.1. Structures and Experimental Data. For the development of the ensemble model, we compiled experimental data for 110 compounds: data for 94 compounds were from Wilschut et al.,[8] and data for the 16 additional compounds were obtained from a number of other sources.[1,6,9,10]

Titratable groups were modeled uncharged; thus, a net neutral charge resulted for each molecule. The structures were optimized with Mopac2002 (F.Q.S. Poland) using the semiempirical method PM5 followed by an ab initio optimization with GAMESS[11] employing the 3-21G basis set.[12]

The experimental values for the permeability coefficients were taken from the literature mentioned above. For a few compounds, more than one permeability coefficient was listed. In such cases, the mean of the logarithms of the permeability coefficients was used.

2.2. Calculation of Descriptors. Previously, a wide range of molecular descriptors was applied for predicting skin permeability. The octanol/water partition coefficient log $K_{\mathrm{Oct/Wat}}$ and the molecular weight MW have repeatedly been employed in linear regression analyses. The number of hydrogen bonds may be an additional parameter.[13] Fragmental[14] and solvatochromic approaches[15] were also used to predict the permeability coefficients. Pugh et al. proposed the use of the product of two descriptors, molecular weight and the sum of the modulus of the atomic charges.[5] The latter descriptor was also used in a later study.[6]

We tested a wide range of 1D, 2D, and 3D descriptors for the prediction of skin permeability. From this diverse set of descriptors, we selected a small set of relevant descriptors, yielding good prediction performance by a systematic feature selection process that is detailed below. The sum of the modulus of the atomic charge was calculated from 6-31G* charges computed using GAMESS. The cross term MW $\times$ charge was also calculated. The solvation free energy in water was computed with Mopac2002 using the COSMO continuum solvation model.[16] The calculated partition coefficient octanol/water, CLOGP [MOE property log P(o/w)], was computed employing the Molecular Operating Environment (MOE) program (MOE 2004, Chemical Computing Group). Since calculations of the acidity or basicity of a given compound are difficult to perform and the results are of high uncertainty, we did not include pK_a or pK_b or the fraction ionized at a given pH as possible descriptors.

2.3. Prediction Models. A number of different models were developed for the prediction of skin permeability. Linear models are easy to generate and allow for evaluating the importance of single descriptors with great ease. Nonlinear predictive models for skin permeability coefficients were usually created by a nonlinear regression analysis of the parameters in a given function, which had to be decided on prior to the regression analysis. Of the nonlinear models, the artificial neural networking employed by Degim et al.[6] seems superior to the traditionally derived models. Possibly, this is due to its ability to model nonlinear relationships between input and output variables.

Ensemble methods have gained increasing attention in the past decade[17,18] and are a promising approach for improving the generalization error of existing statistical learning algorithms in the regression setting. The output of an ensemble model is the average of the outputs of the individual models that belong to the ensemble. Krogh and Vedelsby[17] derive the equation $E = \bar{E} - \bar{A}$, which relates the ensemble generalization error E with the average generalization error $\bar{E}$ of the individual models and the variance $\bar{A}$ of the model outputs with respect to the average output. When keeping the average generalization error $\bar{E}$ of the individual models constant, the ensemble generalization error E decreases with increasing diversity of the models $\bar{A}$. Hence, we try to increase $\bar{A}$ by using two strategies:

1. Resampling. We train each model on a randomly drawn subset of 80% of all training samples. The number of models trained for one ensemble is chosen such that usually all samples of the training set are contained in at least one of the different subsets.

2. Variation of model type. We employ two different model types, which are linear models trained by ridge regression and k-nearest-neighbor (kNN) models with an adaptive metric.

Now, we will describe the two model types used in our approach in greater detail.

Ridge Regression. Ridge regression[19] constructs a linear model $\hat{y} = \mathbf{X}\beta + \beta_\mathbf{0}$, but instead of minimizing the sum of squared residuals $(y - \mathbf{X}\beta - \beta_\mathbf{0})^\mathbf{T}(\mathbf{y} - \mathbf{X}\beta - \beta_\mathbf{0})$, it minimizes the regularized loss function (Tikhonov regularization):

$$\mathrm{RSS}_{\mathrm{pen.}} = (y - \mathbf{X}\beta - \beta_\mathbf{0})^\mathbf{T}(\mathbf{y} - \mathbf{X}\beta - \beta_\mathbf{0}) + \lambda\beta^\mathbf{T}\beta \quad (1)$$

As the penalty parameter λ grows, the additional penalty $\lambda\beta^\mathbf{T}\beta$ shrinks the regression coefficients $\hat{\beta}$ toward zero, thereby moderately increasing the bias while considerably decreasing the variance of the constructed models. The penalty parameter $\lambda \geq 0$ controls the amount of shrinkage and can be used to fine-tune the bias−variance tradeoff. For this study, the optimal ridge penalty λ is determined automatically by leave-one-out cross validation (LOO−CV[19]) on each training fold individually. Prior to model construction, input variables are normalized by subtracting the mean and dividing by the standard deviation for each variable separately.

k-Nearest Neighbor. A k-nearest-neighbor model[19] takes a kernel-weighted average over the observations y_i in the training set closest to the query point $x \in \mathbf{R}^D$ to produce the outcome

$$\hat{y}(x) = \frac{1}{\sum w_i} \sum_{x_i \in N_k(x)} w_\mathrm{i} y_\mathrm{i} \quad (2)$$

where $N_k(x)$ denotes the k-element neighborhood of x, given a proper metric. Common choices for the metric are L_1, L_2, and L_∞ norm. Self-matches of data set points, that is, each point being considered its own nearest neighbor, are prohibited by default since this strongly biases the error on the training set.

The smoothing kernel weights w_i are distance-dependent

$$w_i = \left[1 - \left(\frac{d_i}{d_{k+1}}\right)^p\right]^p$$

where d_i denotes the distance from the query point x to the ith nearest neighbor. The parameter p of this smoothing kernel is chosen out of the set {0.0, 0.5, 1.0, 2.0, 3.0}. The number of nearest neighbors k is chosen such as to minimize the LOO−CV error on the training set. For our investigation, we employed the ATRIA implementation of a fast nearest neighbor algorithm[20] that allows the efficient computation of the LOO−CV error.

To compensate for irrelevant input dimensions, distances are computed using a weighted metric:

$$d(x, z) = \{\sum_{j=1}^{D}[m_j(x_j - z_j)]^L\}^{1/L} \qquad 0 \le m_i \qquad (3)$$

The vector m of metric coefficients is determined by computing the mutual information I between each input variable x_j and the desired output y. Since the mutual information is positive and measures the nonlinear correlation between two random variables, it can serve directly as weighting factors for the metric coefficients:

$$m_j = I(x_j, y) = H(x_j) + H(y) - H(x_j, y) \qquad (4)$$

The entropy H was calculated according to

$$H = -\sum_i (p_i \log p_i) \qquad (5)$$

For computing the relative frequencies p_i, we use a simple histogram-based scheme. The method is simple and robust. We do not perform additional feature selection. We could experimentally observe that ensembles consisting of either only linear models or only kNN models perform worse than a mixed ensemble containing models of both types.

2.4. Model Design. In the development of our nearest-neighbor model, we started with a total of 190 descriptors. First, we limited the number of descriptors in the model to a maximum of six descriptors. The quality of the models was assessed by their relative mean-square error. Each descriptor remaining in the best model was tested for its significance. Descriptors which did not increase the quality of the model were omitted. To possibly replace computationally expensive or noninterpretable descriptors, the remaining descriptors were tested for possible pairwise correlation with each other as well as for correlations with all other descriptors. The models were to possess a small relative mean standard error and as few descriptors as possible.

The resulting models were tested for their robustness by randomized 3-fold cross validation. Then, the predictive power of the most robust model was compared to the performance of the original Potts−Guy model,[4] the revised Potts−Guy[8] model, and the model by Pugh et al.[5] All models were trained using the Degim training set, and prediction was performed for the external validation data set by Degim et al.[6]

3. RESULTS

3.1. Descriptor Correlations. While developing our model, a high correlation between the descriptor MW × charge and the sum of the MOE descriptors CASA+/CASA− was observed. These latter descriptors are a measure for the positive and negative charge-weighted surface area, respectively. They are much faster to compute than the atomic charges; thus, the computationally expensive descriptor favored by Pugh et al.[5] and Degim et al.[6] could possibly be replaced by the sum of these quickly computed descriptors. However, none of these descriptors was chosen for our final model.

Although our absolute values for MW × charge differed from the values published by Pugh et al.[5] and Degim et al.[6] as a result of slight variations in the computational setup and implementations used, we observed a high correlation between our values and those published previously (R^2 = 0.956).

We observed a poor correlation between the original experimental values for the octanol/water partition coefficients and our CLOGP values (R^2 = 0.479). Closer inspection revealed that this poor correlation was not due to the computational method employed. Similar correlations were obtained for KowWin 1.66[21] and Daylight CLOGP.[22] The reason for the poor correlation is more likely to be caused by the poor quality of the experimental data listed by Wilschut, which differ considerably from more recently published values.

3.2. Final Model. While most authors of empirical models use data sets of 50 and fewer compounds,[3] we employed one of the largest data sets (110 compounds) and started with 190 descriptors in deriving our model. The descriptors for each molecule were calculated for a single minimum-energy conformation obtained from quantum-mechanics calculations. It has been shown that, in the case of small molecules, descriptors derived from single conformations correlate very well with descriptors derived from multiple conformations.[23] Our final model consisted of the descriptors SOLV, CLOGP, and MW. None of these descriptors could be successfully replaced by any other descriptor while maintaining the high correlation between experimental and predicted permeability coefficients. The descriptor SOLV is one of the computationally more expensive descriptors in our final model. Using a data set of 55 compounds, it had been pointed out for a similar descriptor of the solvation free energy that this descriptor is linearly correlated (R^2 = 0.925) to the descriptor for the polar surface area.[24] However, employing our larger data set, the descriptor SOLV was clearly superior to the descriptor for the polar surface area.

3.3. Robustness of the Model. To avoid overfitting to noise and to assess the predictivity of empirical models, these models have to be thoroughly tested for their robustness. kNN models, even when they are carefully constructed, show by design a very low training error since it is a data-driven method. Thus, a comparison of the correlation coefficients

for the training set and leave-one-out cross validation is unsuited for this type of model. Instead, we decided to perform both a leave-one-out and a randomized 3-fold cross validation of our model using the pooled data from the training and validation sets to calculate cross-validated correlation coefficients Q^2. The rationale here is that a statistical learning technique is called "robust" if it is able to achieve low test errors even when the training data sets contain a certain fraction of outliers or samples with high measurement uncertainty. For the leave-one-out cross validation, Q^2 and the relative mean-square error were determined to be 0.730 and 0.294, respectively. For the 3-fold cross validation, the data set was divided randomly into three portions. The models were trained on two portions, while the permeability coefficients for the third portion of the data set were to be predicted. The correlation coefficient between the predicted and experimental permeability coefficients Q^2 was employed to assess the robustness of the models. The cross-validated correlation coefficient Q^2 and relative mean-square error were 0.708 and 0.304, respectively. The correlation coefficients for both the LOO and the 3-fold cross validation are very similar, underlining the robustness of our model. Although the correlation coefficient may appear small, it must be noted that there exists an upper limit for the correlation coefficient for the data set employed since permeability coefficients from different laboratories for the same compound differ considerably.[25] From the data available, an average relative standard deviation for the log k_p values of $\sigma_{rel} = 0.12$ ($n = 17$) may be calculated. Employing this value, it may be estimated that a model trained on our data set without cross validation with a correlation coefficient of $R^2 = 0.77$ would completely describe the data. Other models seem to yield better correlation coefficients than our model; however, this is due to several reasons. First, correlation coefficients of cross-validated models are usually smaller than those of models derived without validation. Second, the training data sets employed are usually smaller; thus, they cover a smaller range of chemical space; that is, many models are limited to molecules with molecular weights less than 350 Da. Models derived from such pruned data sets presumably lack robustness and predictive power. Finally, linear models may use large numbers of descriptors in comparison to the number of data points, and thus, such models are prone to overfitting. In addition to employing many descriptors, ANN models may also use a large number of weights, thus being easily overtrained.

3.4. Comparison with Other Models. Having confirmed the robustness of our selected model, we compared the predictive power of our model to three other established models. For this purpose, implementations of these models were trained using a set of 40 data points; that is, the coefficients of the different models were obtained by fitting to the training set. Employing these coefficients, a prediction of permeability was performed for each model using an external data set consisting of 11 different compounds. All descriptors and experimental data were taken from ref 6. The correlation coefficients Q^2 of all models for both the training and the validation set may appear rather high when compared to earlier publications in this field. Here, it should be kept in mind that data employed in earlier publications may differ from those employed here; that is, the errors of the experimental values for the permeability and partition coefficients may be smaller. Second, the data set is smaller than that employed for deriving, for example, our model. A comparison of the correlation coefficients and the relative mean-square errors shows that our model outperforms each of the other models, although it is based on purely computational descriptors (Table 1). Interestingly, the revised Potts−Guy model does not perform better than the original Potts−Guy model. The model established by Pugh et al. shows a remarkably high cross-validated correlation coefficient. However, the relative mean square of that model is also the largest.

Table 1. Comparison of Different Prediction Models for the Degim Training and Validation Data Sets[a]

		training set		validation set	
method	np	R^2	LOO−R^2	Q^2	rel. mse
*k*NN model (herein)	3	0.945	0.788	0.898	0.200
Potts−Guy model[4]	2	0.696	0.620	0.719	0.291
revised Potts−Guy model[8]	2	0.668	0.610	0.652	0.369
Pugh et al.[14]	2	0.737	0.642	0.848	0.419

[a] All models employed values taken from ref 6. np: number of parameters. R^2: correlation coefficient for training set. LOO−R^2: leave-one-out cross-validated correlation coefficient for training set. Q^2: correlation coefficient for external test set. rel. mse: relative mean-square error.

3.5. Dependence of Permeability on the Descriptors. The influence of each descriptor used in our final model on the calculated permeability coefficient was investigated and checked for its plausibility. In the case of single descriptors, two descriptors were set to their median values while the third descriptor was varied, and the resulting permeability coefficient was calculated using the trained model (Figure 1a). Similarly, the influence of varying two descriptors simultaneously was investigated (Figure 1b). Using this approach, we made the following observations: in our final model, the permeability coefficient decreases with a higher molecular weight of the diffusant, which is well in agreement with theoretical considerations; for the diffusion in the lipid layers of the *stratum corneum*, an exponential decrease of the diffusion coefficient with increasing molecular weight is assumed.[26] However, the permeability seems to increase for molecules heavier than 500 Da. This may be due to the fact that, in our training set, there are only four molecules heavier than 500 Da. Concerning the solvation free energy, we observed that the permeability increases with the descriptor SOLV. Thus, it seems that the less energy required for removing the molecule's hydrate shell, the easier it permeates the skin. It is not clear whether there is a linear or sigmoidal relationship between permeability and this descriptor. Finally, the logarithm of the octanol/water partition coefficient is an important descriptor for predicting the permeability coefficient. A nearly linear correlation was observed, which is in good agreement with the theory: for a simple membrane, the steady-state flux is linearly dependent on the concentration gradient across the membrane. A plateau is suggested for compounds with a calculated logarithm of partition coefficient larger than 3. This is strikingly similar to the findings for the gastrointesinal absorption of drugs, where the logarithm of the partition coefficient should ideally be in the range between 1 and 3.

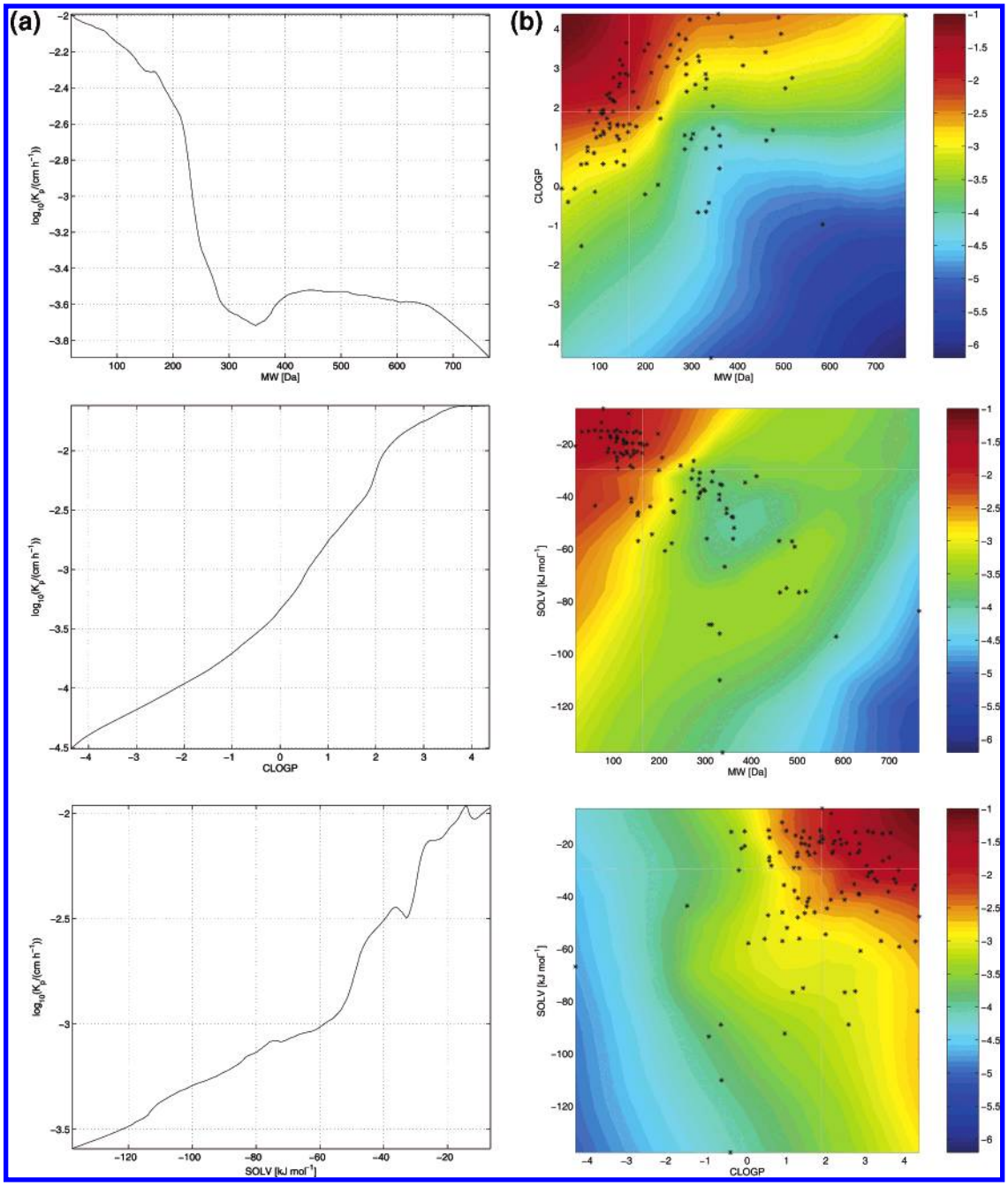

Figure 1. Dependency of permeability log k_p on the input variables for the final model. The variables not shown in the plots were set to their median values. (a) Dependency on single descriptors. The other two descriptors were set to their median values. (b) Dependency on two descriptors. The third descriptor is set to its median value. Asterisks represent data points; lines mark the median values of the descriptors shown in the plot.

4. CONCLUSION

The aim of our study was to develop a new, purely computational model to enable scientists to quickly and reliably predict skin permeability coefficients. The model was to be based on the most comprehensive set of experimental data possible. Moreover, we wanted to use a nonlinear model for predicting the skin permeability coefficients since we felt that such a model would be superior to simple linear models.

Our final model uses a novel method, namely, an ensemble approach combining *k*NN and linear models. The model is data-driven in that it is trained on a given set of experimental data. Prediction of permeability coefficients is based on only three descriptors. These descriptors are the octanol/water partitioning coefficient, the solvation free energy, and the molecular weight of a given molecule. The model presented here features a high robustness, which is a prerequisite for predicting permeability coefficients for compounds not included in the original training set reliably. Moreover, we could show that our new model features a higher prediction quality than previously reported linear models and a smaller relative mean-square error.

Since our model does not require any experimental parameter after the training of the model has been completed, that is, there is no necessity for determining the experimental octanol/water partition coefficient, it may be used as a simple, quick, and precise means for predicting skin permeability coefficients. Thus, it could considerably reduce the need for

the experimental determination of permeation coefficients for new chemical entities.

However, our model does not fully alleviate the need for determining permeability coefficients experimentally. For one thing, the model will profit from an increased amount of avalaible data, since enlarging the data set for training would increase the accuracy of predictions. Second, while predictions for compounds with calculated properties within the range of the training data set are of high quality, predictions for compounds with calculated properties outside this range are not possible. Thus, for such compounds, the permeability coefficient has to determined experimentally.

Like most empirical models, our model does not take into account a number of additional factors which influence the skin permeation like, for example, self-enhancement by fluidization of the hydrocarbon chains in the lipid barrier. Furthermore, we did not include the pK_a or pK_b values of the compounds, although the fraction of the compound ionized may be of importance for predicting the permeation of acids and bases—especially for in vivo experiments where the pH varies within the skin. Future models should aim to remedy these shortcomings of current models.

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Supporting Information Available: For each compound, the supporting material lists its CAS number, the experimental partition and permeability coefficients, and the reference from which this information was obtained. In addition, the table contains the calculated data employed for developing our model. This material is available free of charge via the Internet at http://pubs.acs.org.

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