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The Application of Gaussian Processes in the Prediction of Percutaneous Absorption for Mammalian and synthetic Membranes

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Abstract. Improving prediction of the skin permeability coefficient is a difficult problem, and an important issue with the increasing use of skin patches as a means of drug delivery. In this work, we apply Gaussian Processes (GPs) with five different covariance functions to predict the permeability coefficients of human, pig, rodent and silastic membranes. We obtain a considerable improvement over quantitative structure-activity relationship (QSARs) predictors. The GPs with *Matérn* and *neural network* covariance functions give the best performance in this work. We find that five compound features applied to human, pig and rodent membranes cannot represent the main characteristics of the silastic dataset.

1 INTRODUCTION

The problem of predicting the rate at which various chemical compounds penetrate human skin is an important issue with the increasing use of skin patches as a means of drug delivery. One key feature of this problem domain is that the target, the skin permeability coefficient (K_p), may have a strongly non-linear relationship with the compound descriptors (features). This has been demonstrated in [6] and [9] on a human skin dataset.

In [6] and [9], it is also shown that advanced machine learning techniques, especially, *Gaussian Processes* (GP), outperform quantitative structure-activity relationships (QSARs), which are widely used in the pharmacy community for human skin (but not animal skin). In this paper, we further evaluate GP on four different membrane datasets: *human*, *pig*, *rodent*, and *silastic*. We apply a simple naïve model to compare with the GPs on these datasets. The aims of the current study are to validate the Gaussian Process regression model to various animal tissues and silastic® in predicting percutaneous absorption. Furthermore, we investigate the performance of different covariance functions applied to GP in this application.

2 PROBLEM DOMAIN

Predicting percutaneous absorption accurately has proven to be a major challenge and one which has substantial implications for pharmaceutical and cos-

metic industries, as well as toxicological issues in fields such as pesticide usage and chemical manufacture. Predictive modeling is but one of many methods employed in order to increase the throughput of percutaneous absorption experiments. The use of animal models for percutaneous penetration is often considered essential, given the possible toxicity, cost and inconvenience of employing human skin during in vivo and in vitro experiments. human skin differs from that of many animals in the thickness of the stratum corneum, number of appendages per unit area and amount of skin lipids present. The widespread use of animal skin in experiments since 1992, which is often validated by comparison with human skin data, only provides partial validation as it does not specifically examine the mechanistic nature of the absorption process, as quantitative models can do. This work, therefore, documents the first development of quantitative models for percutaneous absorption across animal skin, and will allow a more accurate mechanistic comparison to be made between permeation across human and various animal skins.

In using a model system, the researcher must take into account the inherent differences of the various species employed and the parameters affecting percutaneous penetration in each species. The model selected must therefore resemble human skin as closely as possible. Various models have been proposed by researchers. [1] and [10] investigated several potential models, including rabbits, miniature swine and rats, and concluded that rabbit skin, and then rat skin, were the most permeable membranes, and that flux through pig skin most resembled permeation across human skin. Further, synthetic membranes are often chosen for in vitro studies. Their use allows greater control and manipulation of experimental conditions. Poly(dimethylsiloxane) (silastic®, Silescol®) is a widely employed model membrane, which has demonstrated good agreement with Fick's first law of diffusion ([4] and [11]).

Several approaches have been used to try to quantify and predict skin absorption. One such method involves the use of quantitative structure activity (or permeability) relationships (QSARs, or QSPRs), and another is the use of mathematical modeling. These approaches have been extensively reviewed (i.e [5]).

Usually, *lipophilicity* (P) and *molecular weight* (MW) appear to be the only significant features in QSAR forms, although subset analysis has shown the significance of other parameters [5]. P is the ratio of the solubility of a molecule between two phases; octanol, to represent the lipid phase, and water (or a buffered aqueous solution) to represent the aqueous phase. This gives quite a range as some molecules will prefer one phase to another, often across as wide a range as 10^{-7} to 10^{7}. Hence, a log scale, $\log P$, is used to simplify the notation in common use. For the same reason $\log K_p$ is used for skin percutaneous absorption rather than K_p. It is important to note that $\log K_p$ is a completely different term to $\log P$. K_p is a corrected version of concentration (in suitable units) against time, that allows comparison of permeation for different molecules. Each molecule may have different properties, particularly different solubility and $\log P$.

Recently, more new approaches, for example, artificial neural network and

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fuzzy modelling, have been applied to this problem domain. [6] has employed Gaussian Processes to analyse a human skin dataset. It has showed the underlying non-linear nature of the dataset, and provided a substantial statistical improvement over existing models. In the current study, we apply Gaussian processes (GPs) with five different covariance functions to predict the permeability coefficients of human, pig, rodent and silastic membranes.

3 Description of Datasets Employed

The four datasets, namely *human*, *pig*, *rodent*, and *silastic*, employed in this study have been collated with reference to a range of literature sources. There are 146 permeability coefficients for corresponding compounds in vitro through human skin, 15 through pig skin, 103 through rodent skin and 19 through synthetic material. These data cover a wide range of physicochemical parameters and are representative of a wide and clinically realistic range of molecules. In [9], it is shown that using five features, which are molecular weight (MW), solubility parameter (SP), lipophilicit ($\log P$), counts of the number of hydrogen bonding acceptor (HA) and donor groups (HD), results in better predictions being obtained than using only lipophilicity and molecular weight. Therefore, in this work we follow [9] to use the five compound features.

4 METHODS

Two QSPR methods were applied to the human skin data in order to provide a comparison between Gaussian Processes and previous approaches to this task. The first one was proposed by [7] and derived from the Flynn dataset [3]. It is given by $\log K_p = 0.71 \log P - 0.061MW - 6.3$. The second model is represented by $\log K_p(cm/s) = 0.74 \log P - 0.0091MW - 2.39$, which derived from a slightly larger and more robust dataset [5].

Since there are no QSAR models used to animal skins, we apply a simple *naïve model* for comparison. In the naïve model, for any input the prediction is always the same value, namely the mean of $\log K_p$ in the training set.

4.1 THE GAUSSIAN PROCESSES REGRESSION

A *Gaussian process* (GP) is defined simply as a collection of random variables which have a joint Gaussian distribution. It is completely characterised by its mean and covariance function. One usually considers the mean function to be zero everywhere. The covariance function defines nearness or similarity between the values of targets (predictions) at two input points. More details can be found in [8].

Selecting a covariance function is important in Gaussian Processes, since the covariance function encodes a priori knowledge which may be learned during the training procedure. In this work, we apply five different covariance functions [8], which are the squared exponential covariance function (SE), the neural network covariance function ($NNone$), the rational quadratic covariance function,(QR)

and two simple cases of the Matérn Class of Covariance Function, where the polynomial of order is set to 1 (*Matérn1*) and 2 (*Matérn2*) separately. Note that we apply independent identically distributed Gaussian noise with variance on the noisy observations in all five covariance functions.

4.2 PERFORMANCE MEASURE

We use *mean squared error* (MSE), *negative log estimated predictive density* (NLL), and *correlation coefficients* (CORR) to evaluate the performance of each computational model. More details can be found in [6]. For comparison, a model should have low values of both MSE and NLL, as well as a high value of the correlation coefficient (CORR) on a given test dataset.

5 EXPERIMENTS

For each dataset, we apply the *leave-one-out* technique, that is, one compound was used for testing, and all others were employed for training. This was repeated for each compound in turn. We applied a GP toolbox [8] to do GP modelling. Finally, we computed performance metrics in terms of all predictions.

Results are shown in Tables 1-4. It can be seen that GP with different covariance functions outperforms QSARs/naïve models on human, pig and rodent datasets. Furthermore, one can see that the naïve model works better than QSARs on the human skin dataset. For the synthetic skin dataset, GP with covariance *NNone* has better performance, while others give similar results to the naïve model with *RQ* even worse than the naïve predictors.

One important finding from this study is that GP modelling has completely different performance on the pig and silastic datasets, though both of them have a similar data distribution. When looking into the GP predictions for each dastset, we find that GP predictions on some chemical compounds for the silastic dataset are not good. It may suggest that five physicochemical features used in this work are key features for the pig dataset - as they are for the human data set [6] but they cannot represent the main characteristics of the silastic dataset. This is not surprising in some ways. While silastic is seen as a replacement for human or pig skin for in vitro studies, and has been shown to be useful in a number of studies (i.e. [11]), it has been shown to be limited in some respects due to its simplicity of structure and homogeneity, which cannot fully replicate human or pig skin. This was shown by Cronin et al.[2], who developed a QSPR for permeation across a silastic membrane, and found that it was dependant on molecular bulk and hydrogen bonding only. Therefore, only limited comparisons may be drawn from silastic data sets, whereas the greater similarity between human skin and those mammalian species used in this study demonstrates greater compatibility.

6 CONCLUSIONS

The results presented herein suggest Gaussian Processes regression modelling can be successfully applied to human and animal skin datasets with five specific

Table 1: Leave-one-out results on the human skin dataset

Model		**MSE**	**CORR**	**NLL**
Naïve		2.12	-1.00	-
Moss		5.93	0.07	-
Potts		15.93	0.04	-
GP	*NNone*	1.22	0.65	1.55
	SE	1.22	0.65	1.51
	RQ	1.25	0.64	1.55
	Matérn1	1.20	0.66	1.51
	Matérn2	1.21	0.65	1.51

Table 2: Leave-one-out results on the pig skin dataset

Model		**MSE**	**CORR**	**NLL**
Naïve		3.31	-1.00	-
GP	*NNone*	0.80	0.85	1.52
	SE	0.93	0.83	15.72
	RQ	0.93	0.83	15.44
	Matérn1	0.93	0.83	1.18
	Matérn2	0.99	0.82	1.63

Table 3: Leave-one-out results on the rodent skin dataset

Model		**MSE**	**CORR**	**NLL**
Naïve		1.30	-1.00	-
GP	*NNone*	0.88	0.56	1.41
	SE	0.86	0.58	1.40
	RQ	0.86	0.58	1.41
	Matérn1	0.83	0.60	1.38
	Matérn2	0.84	0.59	1.39

compound features. In this application, all five covariance functions employed work equally well on the human, and rodent skin datasets, while the neural network covariance function is better than the others on the pig, and especially synthetic membranes. We find that when selecting a suitable covariance function, the one whose principal eigenvectors can account for as much as possible of the total variance should be chosen. Finally, we find that five compound features applied to human, pig and rodent membranes cannot represent the main characteristics of the silastic dataset.

Table 4: Leave-one-out results on the synthetic skin dataset

Model		**MSE**	**CORR**	**NLL**
Naïve		5.79	-1.00	-
GP	*NNone*	3.57	0.60	2.03
	SE	5.45	0.23	2.52
	RQ	6.33	-0.70	2.96
	Matérn1	5.55	0.08	2.72
	Matérn2	5.19	0.22	2.65

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