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Research paper

Development and comparison of machine learning models for in-vitro drug permeation prediction from microneedle patch

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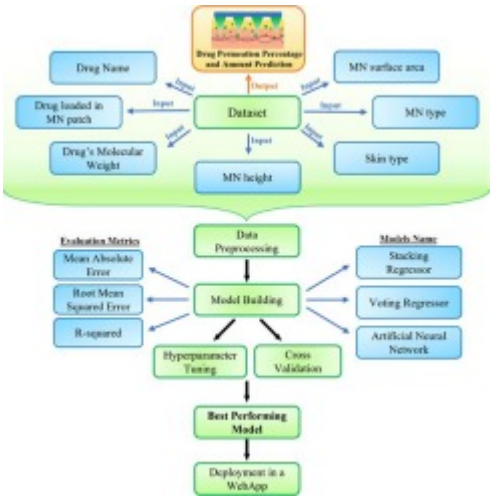
Abstract

The field of machine learning (ML) is advancing to a larger extent and finding its applications across numerous fields. ML has the potential to optimize the development process of microneedle patch by predicting the drug release pattern prior to its fabrication and production. The early predictions could not only assist the in-vitro and in-vivo experimentation of drug release but also conserve materials,

reduce cost, and save time. In this work, we have used a dataset gleaned from the literature to train and evaluate different ML models, such as stacking regressor, artificial neural network (ANN) model, and voting regressor model. In this study, models were developed to improve prediction accuracy of the in-vitro drug release amount from the hydrogel-type microneedle patch and the in-vitro drug permeation amount through the micropores created by solid microneedles on the skin. We compared the performance of these models using various metrics, including R-squared score (R^2 score), root mean squared error (RMSE), and mean absolute error (MAE). Voting regressor model performed better with drug permeation percentage as an outcome feature having RMSE value of 3.24. In comparison, stacking regressor have a RMSE value of 16.54, and ANN model has shown a RMSE value of 14. The value of permeation amount calculated from the predicted percentage is found to be more accurate with RMSE of 654.94 than direct amount prediction, having a RMSE of 669.69. All our models have performed far better than the previously developed model before this research, which had a RMSE of 4447.23. We then optimized voting regressor model's hyperparameter and cross validated its performance. Furthermore, it was deployed in a webapp using Flask framework, showing a way to develop an application to allow other users to easily predict drug permeation amount from the microneedle patch at a particular time period. This project demonstrates the potential of ML to facilitate the development of microneedle patch and other drug delivery systems.

Graphical abstract



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Introduction

Microneedles (MNs) are gaining unprecedented recognition in the field of drug delivery and diagnostics as they provide a painless and efficient means to deliver drugs and can be easily transformed into a wearable diagnostic device. Microneedle-based delivery systems can possibly transform the future by replacing the conventional transdermal and injectable delivery routes [1], [2]. Over the years, numerous research groups have designed and developed different types of MNs by employing diverse fabrication methods [1], [2], [3].

The quality of the produced MNs is assessed by a few analytical methods which test the mechanical strength, efficiency of skin penetration, drug release and permeability, non-immunogenicity, etc. A variety of instrumental methods are employed to assess the above-mentioned aspects of MNs. The effectiveness of a MNs patch is dependent on how efficiently it delivers the drug through the skin after its administration (drug release and permeation studies). For this purpose, various in-vitro and ex-vivo testing methods have been developed, for example, franz diffusion apparatus and microscopy method. For instance, the amount of drug permeation from the donor to the receptor compartment over time in a Franz diffusion cell can be measured to obtain an idea on the drug permeation profile from MNs. There have been few studies which have used either parafilm or porcine skin for establishing the drug release profiles from MNs patches [4], [5]. A few researchers have also employed fluorescence microscopy-based and in-vivo imaging systems to assess the fluorescent labelled drug release patterns from MNs in live animals [6].

However, there are some limitations of using the conventional in-vitro method, which include the high experimentation cost and the requirement of more time. Moreover, these studies indicate the quality of the produced MNs after its production. Thus, on the production floor, the method cannot be of much help in assessing the quality of the produced product. This necessitates the development of an alternative analytical tool which could be used to assess product quality before/during its production. Artificial intelligence (AI) is gaining widespread importance due to its accurate prediction capabilities in manufacturing industries. AI tools, including machine learning (ML), could provide us with valuable insights of the drug release and permeation profile even before the production of MNs. The predictions would be based on the quality attributes of the materials used (polymer/drug) and the microneedle parameters. The drug release and drug permeation meant different in the case of solid MNs. In contrast, they have the same meaning in the case of other types of MNs. In solid MNs, skin is poked first, followed by the application of the drug through various formulations such as transdermal patch, cream, etc. During the

application of the drug on poked skin, the drug may get released from the formulation but not necessarily penetrate because of the epidermis layer present between the micropores (poked part), causing low permeability [7]. In the case of other types of MNs, the drugs are delivered by bypassing the epidermis layer; hence, drug release and permeation would be the same.

In recent years, various machine learning, deep learning (DL), and computer techniques have been developed for in-vitro prediction [8], [9] and in-vitro-in-vivo correlation (IVIVC) prediction of pharmaceutical formulations [10]. ML could overcome the limitations of in-vitro testing methods and can be used to instantly assess the quality of pharmaceutical products in the manufacturing unit. However, these methods heavily rely on the availability of previous data for its training purposes. The prediction accuracy depends on the reliability of the data used during model training. Usage of insufficient training data can inversely influence the prediction accuracy of ML model. Current work shows the importance of model training in improving the prediction accuracy of ML models.

Yuan et al. created a dataset by conducting multiple in-vitro drug release and permeation experiments and developed a ML model to accurately predict the drug release amount from the hydrogel-type MNs and the permeation amount into the skin pre-treated with solid MNs. The model's prediction is based on certain parameters, including drug loading amount, drug molecular weight, skin types, microneedle type, permeation time, MNs length, and MNs surface area. They have analyzed RMSE value to evaluate model performance. RMSE value usually stays in the scale of the output feature. The RMSE value beyond that scale indicates poor performance of the model. While zero RMSE value signifies perfect fitting of the model. Therefore, lower RMSE value implies good performance of the model. The output feature, i.e., drug permeation amount and percentage, scales between 1 to 29,010 and 0 to 108, respectively. Based on their study results, the extreme gradient boosting (XGBoost) model had shown the best performance with root mean square error (RMSE) of 4447.23 and 28.24 for drug permeation amount prediction and drug permeation percentage prediction, respectively. While their Random Forest model has shown RMSE of 7043.97 for drug permeation amount prediction and 34.33 for drug permeation percentage prediction. Yuan et al. observed that the multilinear regression model had shown the poorest performance with RMSE of 23398.91 for drug permeation amount prediction and 120.33 for drug permeation percentage prediction [8]. The percentage cannot be greater than 100 but the dataset's drug permeation percentage feature scales upto 108, indicating Yuan et al. have not analysed and handled outliers. Additionally, the RMSE values they obtained for their ML models are for only one combination of training and test dataset. Furthermore, cross-validation

was not performed, and hence, the prediction results are not completely substantiated. Also, the model deployment was not done.

The present work aims to build a better-performing ML model by minimizing error (RMSE), thus making it more accurate and deploying the optimal model into a webapp. We are more focused on evaluating models using RMSE then Akaike information criteria (AIC) or Bayesian information criteria (BIC). AIC/BIC aims to select best model by comparing candidate models. Candidate models are the models trained on various combinations of independent features. AIC/BIC works by penalizing the model complexity, which can also oversimplify the problem. RMSE interpretability is better than of AIC/BIC as its values lie in the same scale of the data [11]. Here, we are intended to build more accurate model by comparing predicted values with actual one. Hence, we have used RMSE. The same dataset used by Yuan et al., has been used to construct a more precise ML model for predicting drug permeation amount. The model is optimized by selecting relevant features and analyzing their correlation using a correlation heatmap, chi-square, and analysis of variance (ANOVA) test, and removing outliers. The ML regression algorithms, such as stacked regressor and voting regressor, were evaluated and cross-validated. For evaluation, various metrics like RMSE and R-squared score were also analyzed. The best-performing model was then deployed using the Flask framework. Altogether, the research process involved four stages: i) Data preprocessing (data cleaning and visualization, feature selection, and feature engineering), ii) Model building, iii) Performance evaluation through cross-validation and RMSE and R-squared score analysis, and iv) Model deployment.

Section snippets

Data set description

The dataset used in this research was retrieved from the research paper of Yuan et al. [8]. The dataset consists of 191 combinations of parameters and 11 attributes with two targeted attributes (drug permeation amount and percentage). The details of the attributes are mentioned below in Table 1.

Yuan et al. have collected the data from six different research works of Dr. Lifeng Kang [12], [13], [14], [15], [16], [17]. The dataset has considered two types of microneedles: hydrogel-type MNs and

Results and discussions

For drug permeation prediction, stacking and voting regressor model algorithms were taken from the SciKit learn (Sklearn) library available in Python programming language. The ANN model was built using TensorFlow and Keras library. We used an Intel Core i5-powered computer with 16GB RAM to run the ML algorithm in Python programming language. The algorithms were developed and processed in a Jupyter Notebook, an open-source web application that allows users to run and execute programming

Conclusion

Voting regressor ML model is devised that exhibits superior performance in predicting percentage of drug release/permeated at a specific time period. This research work presented a detailed analysis of the data for identification of the major factors affecting the percentage of drug release/permeated followed by comparative study of various ML models, which are evaluated using several regression metrics, optimized using hyperparameter tuning, cross validated, and deployed using Flask framework.

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CRediT authorship contribution statement

Anuj A. Biswas: Writing – original draft, Investigation, Data curation, Conceptualization. **Madhukiran R. Dhondale:** Writing – review & editing, Visualization, Supervision. **Maan Singh:** Writing – original draft. **Ashish K. Agrawal:** Writing – review & editing, Supervision. **Prakash Muthudoss:** Visualization, Validation, Conceptualization. **Brahmeshwar Mishra:** Writing – review & editing, Supervision. **Dinesh Kumar:** Writing – review & editing, Validation, Supervision, Project administration,

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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