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Machine Learning predicts the effect of food on orally administered medicines

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Abstract: Food-mediated changes to drug absorption, termed the food effect, are hard to predict and can have significant implications for the safety and efficacy of oral drug products in patients. Mimicking the prandial states of the human gastrointestinal tract in preclinical studies is challenging, poorly predictive and can produce difficult to interpret datasets. Machine learning (ML) has emerged from the computer science field and shows promise in interpreting complex datasets present in the pharmaceutical field. A ML-based approach aimed to predict the food effect based on an extensive dataset of over 311 drugs with more than 20 drug physicochemical properties, referred to as features. Machine learning techniques were tested; including logistic regression, support vector machine, k-Nearest neighbours and random forest. First a standard ML pipeline using a 80:20 split for training and testing was tried to predict no food effect (F0), negative food effect (F-) and positive food effect (F+), however this lead to specificities of less than 40%. To overcome this, a strategic ML pipeline was devised and three tasks were developed. Random forest achieved the strongest performance overall. High accuracies and sensitivities of 70%, 80% and 70% and specificities of 71%, 76% and 71% were achieved for classifying; (i) no food effect vs food effect, (ii) negative food vs positive food effect and (iii) no food effect vs negative food effect vs positive food effect, respectively. Feature importance using random forest ranked the features by importance for building the predictive tasks. The calculated dose number was the most important feature. Here, ML has provided an effective screening tool for predicting the food effect, with the potential to select lead compounds with no food effect, reduce the number of animal studies, and accelerate oral drug development studies.

Keywords: drug products, computational pharmaceutics, machine learning, personalisation, digital pharmaceutics; biopharmaceutics; computational screening and prediction; permeability; pharmacokinetics

1. Introduction

Oral drug delivery is the preferred method of drug administration due to patient preference and pharmaceutical manufacturing experience capabilities. Oral drug delivery systems are an economically viable way to treat the rising number of chronic conditions ranging from heart diseases to type II diabetes. However, drug absorption from the

gastrointestinal (GI) tract is complex and variable (von Erlach et al., 2020); and can be influenced by internal patient-specific factors such as age, sex, disease state and importantly, external factors such as diet and food intake (Madla et al., 2021; Sharma and Prasad, 2021; Stillhart et al., 2020). The intake of food with orally administered drugs can alter the rate and/or extent of oral bioavailability, relative to the fasted state, referred to as the food effect (Koziolek et al., 2019; O'Shea et al., 2019; Varum et al., 2013). Certain medicines include food restrictions which the patient must adhere to for effective treatment. For example, recently, an oral preparation of the biologic semaglutide, co-formulated with a permeation enhancer was approved for type II diabetes, as an alternative to the injectable preparation. Importantly, the drug product should be taken once daily on an empty stomach, with 120 mL of water and patients must wait 30 minutes before eating. While oral administration reduces needle-related complications and costs, the strict food restrictions in relation may reduce compliance and efficacy (Bækdal et al., 2021).

The effect of food on drug bioavailability has been known for decades, but more and more presents as a challenge to the clinic. Approximately 40% of newly licensed medicines between 2010 and 2017, both immediate and controlled release drug products, approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA), reported a significant food effect or included labelling with specific restrictions in relation to food intake (O'Shea et al., 2019). A variety of reformulation strategies may be considered to eliminate the food effect, such as lipid based drug delivery systems, although that can be costly in time and resources to the manufacturer (O'Shea et al., 2019). The overarching aim for pharmaceutical scientists is to design and manufacture robust drug delivery systems to target pathologies and treat disease, which are safe and efficacious. These drug delivery systems should show low inter- and intra- individual variability and be effective in patients regardless of age, sex, disease state and food intake. Steps should be taken to de-risk the drug development by improving and automating early drug development testing and modelling and simulation provide key tools.

Pharmaceutical drug development costs and timelines continue to rise and change is needed to re-imagine the making of our medicines. As no optimal model exists, there is heterogeneity in the approaches to predicting the food effect across the pharmaceutical field. A number of *in vitro* models use dissolution testing with fasted (FaSSIF) or fed-state (FeSSIF) biorelevant media to mimic the GI environment (Klein, 2010; Mathias et al., 2015; Riethorst et al., 2016). Although, such models do not consider the drug's permeability properties and can therefore be poorly predictive. Preclinical *in vivo* animal species, in particular the canine and porcine models, can provide useful insights into the impact of food on drug absorption (Henze et al., 2019; Lentz et al., 2007). Although, significant physiological differences exist and therefore can over- or under-predict the food effect (Sjögren et al., 2014). In addition, *in silico* methods such as physiologically based pharmacokinetic (PBPK) mathematical models are used to mechanistically simulate a drug's pharmacokinetic profile under fasted or fed conditions (Riedmaier et al., 2018). PBPK models need extensive physicochemical and physiological data, which may not be available at early stage drug development. Furthermore, modelers can spend a significant period of time optimizing the models and PBPK models are limited in their ability to predict negative food effects (Cheng and Wong, 2020).

An integrated approach of combining data with advanced analytics could drive transformation, improve decision making, reduce development costs and allow drug products to reach patients faster. Traditional approaches rely on iterative, trial-and-error experiments requiring a large number of resource-intensive and time-consuming *in vitro* and *in vivo* experiments. Here, the food effect in drug delivery systems are tested on a case-by-case basis. The early drug development tests are often poorly predictive and clinical trials in humans can uncover unexpected results. While research and development (R&D) methodologies and technologies are inherently data-driven, the challenge is to unleash the value and capture the opportunities of the specialist datasets in a fast, cost-effective and sustainable way to benefit the R&D pipeline. ML, an approach to artificial intelligence (AI), has the ability to revolutionise the pharmaceutical sector by moving towards advanced modelling techniques able to achieve complex data insights within minutes (Elbadawi et al., 2021a; Elbadawi et al., 2021b). ML allows for pattern recognition from complex datasets and the ML models – which are typically learnt using data-driven algorithms – can be used to predict a given outcome (model output) from a number of features (model inputs).

The capabilities of AI and ML have been successfully leveraged in the drug discovery field (Elbadawi et al., 2020a; Schuhmacher et al., 2020b), capturing headlines in the identification new drug targets. Furthermore, a number of alliances have been built between traditional biopharma and new start-up artificial intelligence companies (Schuhmacher et al., 2020a). In the drug development process, the use of ML is still in its infancy (Schuhmacher et al., 2020a). Therefore, there is an unmet need to support the data-driven drug discovery process. A number of studies have emerged for the prediction of formulation optimisation (Elbadawi et al., 2020b; Muñiz Castro et al., 2021), side effects (Dey et al., 2018; Zhou et al., 2020), drug-microbial interactions (McCoubrey et al., 2021a; McCoubrey et al., 2021b; McCoubrey et al., 2021c), oral bioavailability (Cabrera-Pérez and Pham-The, 2018; Schneckener et al., 2019) and pharmacokinetic properties (Kosugi and Hosea, 2021), which could expedite the lengthy drug pipeline and improve the attrition rate. However, the use of ML techniques to predict the food effect is still underdeveloped.

Our study aimed to use ML technologies to predict the food effect from an extensive database of over 300 drugs with a diverse set of chemical features and over 20 drug properties or features. Previous studies have investigated ML in the prediction of the food effect on smaller datasets with different methodologies (Bennett-Lenane et al., 2021; Gatarić and Parojčić, 2019; Gu et al., 2007). As opposed to a 'plug-and-play' standard ML approach, a strategic approach was implemented. A pilot study was first trained and tested, followed by three tasks using a toolkit of linear and non-linear ML algorithms (random forest, logistic regression, support vector machine and k-Nearest neighbour) to predict how the intake of food will affect drug absorption for optimal task performance. The prediction of the food effect at the preclinical stages may help to prevent costly re-formulation strategies or restrictive patient administration instructions if a food effect is identified at the phase I clinical trial stage.

2. Materials and Methods

2.1 Materials

2.1.1 Compilation of Features/Physicochemical Properties

Drug physicochemical properties were compiled from the literature publication 'BDDCS Applied to Over 900 Drugs' (Benet et al., 2011) chosen as it was a comprehensive set of drug physiochemical properties. Drug physicochemical descriptors will be referred to here as features. Features not listed in Benet et al. were obtained from PubChem, Lombardo et al (Lombardo et al., 2018) or calculated by RDKit (version 2021.03.1). RDKit is an open-source chemoinformatics software that can derive drug molecular information (Landrum, 2010). RDKit processed the simplified molecular input line entry system (SMILES) of each of the drugs, (Landrum, 2010)(Landrum, 2010)(Landrum, 2010)(Landrum, 2010), a line notation for describing chemical structures. The final set of features is listed below (Table 1) and histograms of the features are listed in the Supplementary materials (Figure S1-23). Correlations between the features was assessed using the Pearson method of correlation (Supplementary Materials Figure S24). It should be noted that our approach is based on molecular rather than biopharmaceutical properties which are available at the early stages of drug development. However, dose number and the BDDCS class are often not available until later stages of drug development.

Table 1 Features used in the study

Features	Abbreviation	Definition
Biopharmaceutics Drug Disposition Classification System	BDDCS Class	A biopharmaceutics classification system which divides compounds into four classes based on their permeability and solubility.
Maximum strength dose value	MSD	Highest unit dose of the drug (mg)
% Excreted Unchanged in Urine	% U	The proportion of drug unchanged in the body and excreted in the urine
Molecular Weight	MW Drug	Molecular Mass of the drug
pDose (mol/L)	pDose	$-\log_{10}$(Maximum Dose Strength) (molar)
ALOGPS 2.1 solubility	ALOGPS2.1 Sol	Solubility of each drug in its neutral form using Tetko's solubility in water calculated using ALOGPS 2.1
cDose Number (ALOGPS based)	cDose (ALOGPS)	cDose Number calculated using ALOGPS (Maximum Strength Dose (mg) / 250) / (10^ALOGPS2.1) * MWSol
minVSLgS 3-7.5	minVSLgS 3-7.5	Log of the lowest water solubility calculated over the pH range 3–7.5 calculated using VolSurf+

cDose Number (minVSLgS based)	cDose (minVSLgS)	cDose Number calculated by VolSurf+ (Maximum Strength Dose (mg) / 250) / ((10^minVSLgS3-7.5) * MWSol)
Calculated Log Permeability	CLogP	Logarithm of a molecules partition coefficient between *n*-octanol and using the method of Leo
Hydrogen Bond Acceptors	HBA	Electronegative ion or molecule that must possess a lone electron pair in order to form a hydrogen bond
Hydrogen Bond Donors	HBD	Heteroatom with at least one bonded hydrogen
Polar surface area ($Å^2$)	PSA	The sum of the fractional contributions to the surface area of all nitrogen and oxygen atoms calculated using the method of Clark
Rule of Five Violations	Ro5	Number of Lipinski's Rule-of-Five violations which predicts poor absorption or permeation
Polar Surface Drug Area	PSDA	Molecular weight (MW Drug) divided by polar surface area (PSA)
Single bond	Single Bond	Number of single bonds calculated by RDKit
Double Bond	Double Bond	Number of double bonds calculated by RDKit
Aromatic Bond	Aromatic Bond	Number of aromatic bonds calculated by RDKit
Number of atom	No. of atoms	Number of atoms calculated by RDKit
Total atom	Total atom	Total atomic number calculated by RDKit
Average atom	Average atom	Average number of protons = total atom/number of atom calculated by RDKit
Molecularly calculated Log Permeability	MoKa.LogP	MoKa.LogP calculated by Molecular Discovery
Molecularly calculated Log Distribution at pH 7.4	MoKa.LogD7.4	MoKa.LogD7.4 calculated by Molecular Discovery

2.1.2 Food effect classification

A dataset was collated from literature sources (Benet et al., 2011; Lombardo et al., 2018). The food effect was classified (no food effect, positive food effect or negative food effect) in humans (shown in Supplementary material, Table S1). The inclusion criteria were orally administered drugs. Suspensions, solutions, active metabolites and drugs with no food effect information were excluded.

Food effect studies for all orally administered products are required in drug development in the form of a human phase I pilot trial and a pivotal food effect study, using fasted and fed state groups (FDA, 2019). Positive food effect describes an increase in the overall extent (area under the curve [AUC]) of oral drug bioavailability as a result of the intake of the high-fat FDA meal. Conversely, negative food effect describes a decrease in the oral drug bioavailability. AUC was chosen instead of C_{max} as C_{max} was not always found in the data sources. A positive or negative food effect was classified if the 90% confidence intervals for the ratio of population geometric means, did not fall within the ratio of AUC_{fed}/AUC_{fasted} in reference to the bioequivalence limits of 80-125%, according to the FDA guidance on food-effect bioavailability and fed equivalence (FDA, 2002).

2.2 Design of the Machine Learning Tasks

The pilot task firsts randomly split into 80:20 with stratification for training and testing using the ML toolkit. The pilot tasks over-predicted the number of drugs with no food effect and a poor performance was found in the specificity. Therefore, three prediction tasks were considered; i) task one: binary classification of drugs without food effect (F0) vs with food effect (F- & F+), ii) task two: binary classification of drugs with negative food effects (F-) vs positive food effects (F+), and iii) task three: three-class classification of drugs with no food effects (F0) vs negative food effect (F-) vs positive food effect (F+). The classification of the drugs was imbalanced (F0: 235, F-: 44 and F+: 32) and therefore the accuracy of the model may be affected (Zhang et al., 2010).

In task one, the dataset was split into two groups; without food effect (F0) vs with food effect (F- & F+), **Figure 1**. The same random states were used throughout for consistency. The dataset was then randomly split into 80:20 with stratification for training and testing using the ML toolkit. The majority class (F0) was randomly split into three sub-datasets using sampling without replacement, and individual sub-tasks (sub-task 1, 2 and 3) were trained with 1/3 of the majority class data (F0) and the whole set of the minority class data (F- & F+). The task then predicted the test results according to the majority vote from every individual task. This was performed as the no food effect group (F0) was approximately three-times the size of the combination of food effect (F- & F+).
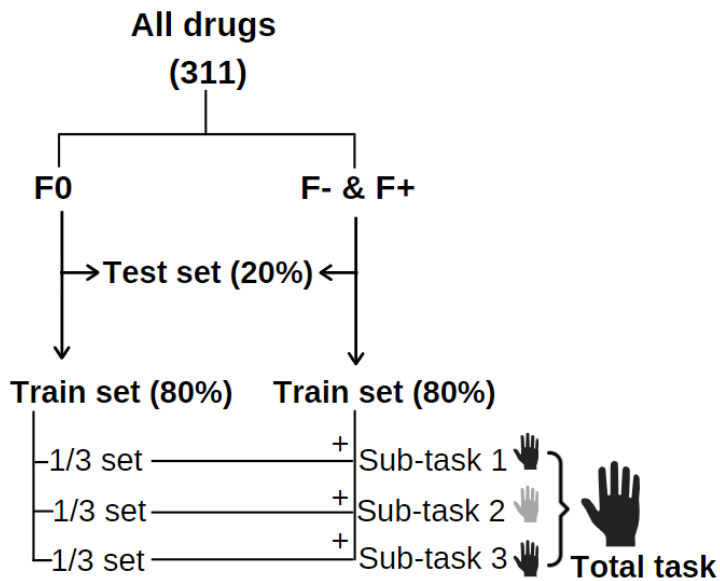
Figure 1 Task one; no food effect (F0) & food effect (F+ & F-)

Task two first removed the drugs with no food effect (F0). The resulting dataset 2 contained drugs with a food effect; classified into negative (F-) vs positive (F+) food effect (**Figure 2**). The dataset was then randomly split into 80:20 with stratification for training and testing and then the ML algorithms were used.
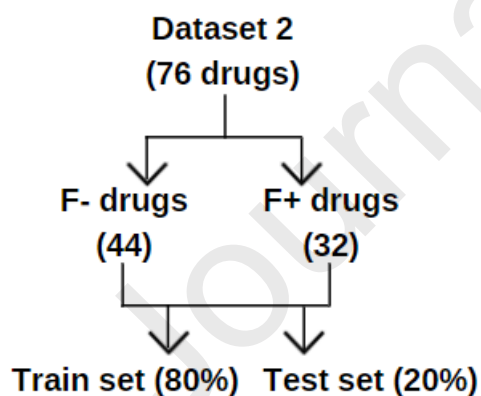

Figure 2 Task two showing (A) classification of negative food effect (F-) and positive food effect (F+)

Task three was then built, which is a combination of task one and task two. The process is shown in **Figure 3**. First, a task was tested to distinguish the food effect (F- & F+) vs without food effect (F0), using the majority vote predictions from task one. Then, for the drugs predicted to have a food effect, another task was tested to distinguish between positive food vs negative food effect, using the trained and predictive model, task two.
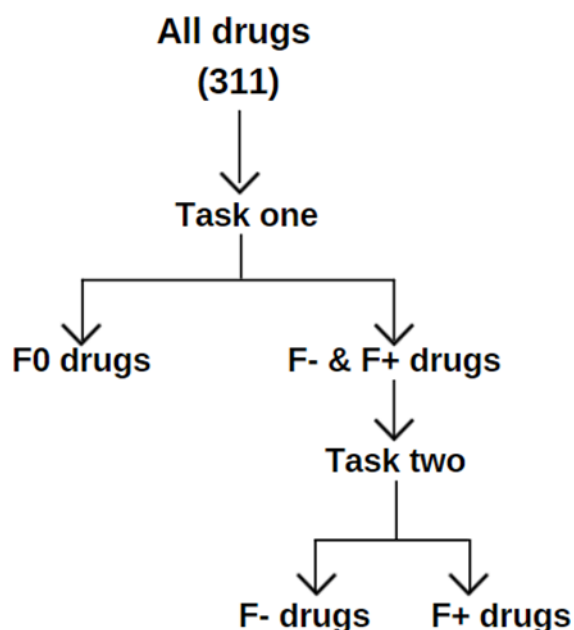
Figure 3 Task 3; combination of task one and task two – classifying food effect (F0) negative food effect (F-) and positive food effect (F+)

2.4 Task implementation

Random forest, logistic regression, support vector machine and k-Nearest neighbours algorithms were tested. Other ML algorithms, such as neural networks, were not chosen as they often perform poorly on datasets with small number of examples per group (Núñez et al., 2017; Wang et al., 2016). Tasks were performed and developed using python 3.7 (Python Software Foundation). All of the tasks were performed using the ML library for the Python programming language (scikit-learn package, v0.23.2). The tasks were built using classification algorithms with consistent random states throughout. The RF task used 30 trees for each task, with the Gini impurity for the quality of split measurement. Variance for task one and task two were calculated using forestci (version 0.5.1) (Figure S31 Supplementary materials). No hyperparameters were specified for LR. SVM used a fixed kernel called the radial basis function (RBF). For kNN, k was defined as 3 (n_neighbors=3).

2.5 Tasks evaluation metrics

All plots were constructed in Python using the Matplotlib, tSNE and Seaborn packages (Hunter, 2007; Waskom et al., 2017). For the evaluation of the tasks, the study used a number of metrics which included; (i) accuracy, (ii) sensitivity and (iii) specificity.

The confusion matrices captures various performance measurements. The rows represent the real values of the dataset, whereas the columns represent the predicted values by the classifier. False positive (FP) represent the actual negative

values that were incorrectly predicted to be positive values. True positive (TP) represent the actual positive values that were correctly predicted to be positive values. True negatives (TN) represent the actual negative values that were correctly predicted to be negative values. False negative (FN) represent the actual positive values that were incorrectly predicted to be negative values. The confusion matrix for binary classification is shown in **Figure S25 (Supplementary Materials)**. The confusion matrix for three-class classification is shown in **Figure S26 (Supplementary Materials)**.

The accuracy refers to the proportion of the number of drug samples, which were correctly predicted, true positives plus true negatives divided by total values, **equation 1**. The overall accuracy shows the ability of the ML technique to correctly predict the outputs.

$$Accuracy = \frac{TP + TN}{TP + FP + FN + TN} = \frac{Correctly\ predicted}{Total\ predicted} \tag{1}$$

Sensitivity and specificity were calculated using the weighted average. The 'weighted average' accounts for the class imbalance by computing the average of binary in which each class's score is weighted by its presence in the true data sample (Pedregosa et al., 2011). The main aim of the study was to predict the probability of the three classifications; no food effect, a positive food effect or a negative food effect and the dataset was imbalanced where the majority class was no food effect. Therefore, weighted average was used as the imbalanced class could affect the calculation of the measurement.

Sensitivity, also known as recall, is a measure of the proportion of positive values that were predicted as true positive (TP), **equation 2**. There can be a number of positive cases, which will be predicted incorrectly as false negative (FN). A higher value of sensitivity reports a higher value of true positive and a lower value of false negatives, whereas a lower value of sensitivity reports the opposite. Here, the weighted average sensitivity was shown, where the weighted contribution of sensitivity for each label was averaged by the number of samples, **equation S1 (supplementary materials)**.

$$Sensitivity = \frac{TP}{TP + FN} \tag{2}$$

Specificity is the proportion of negative values, which were predicted as true negatives (TN), **equation 3**. There will be a number of negative cases, which were incorrectly predicted as false positives. Specificity could be termed a false positive (FP) rate. A higher value of specificity shows a higher value of true negative and lower false positive rate, in contrast a

lower value shows the opposite. Here, the weighted average specificity was used, where the weighted contribution of specificity for each label was averaged by the number of samples (**equation S2, supplementary materials**).

$$Specificity = \frac{TN}{TN + FP} \qquad (3)$$

2.6 Feature importance

Feature importance assigns a score to input the features based on how useful they are at predicting a target variable. Feature importance was also assessed using RF. RF provided a rank of the importance of various features to perform the classification tasks, with a computationally light algorithm compared to other methods (Belgiu and Drăguţ, 2016). The feature importance was performed for task one and task two.

3. Results

3.1. Exploratory Data Analysis

An exploratory data analysis was performed prior the ML tasks to explore the distribution of the features and the food effect classifications. An imbalanced dataset was shown where drugs classified with no food effect made up 75.6% of the dataset, whereas 24.4% of the drugs showed a food effect (**Figure 4**). In addition, for the drugs with a food effect, a further imbalanced dataset was found, with 57.9% showing a negative food effect and 42.1% showing a positive food effect. Drugs used in this study cover a diverse chemical space showing a broad range of physicochemical properties shown by histograms of the inputs, in the **Supplementary Materials**; maximum strength dose value 0-1200 mg, MW Drug 100- 850 and cLogP -7 to 9. Figure 5 shows a representation of the dataset in the chemical space of the over 600 orally approved drugs from Benet et al. The represented drugs are shown in shades of blue, whereas the not classified drugs are shown in grey, reflecting that the drugs in the dataset are from a broad chemical space.
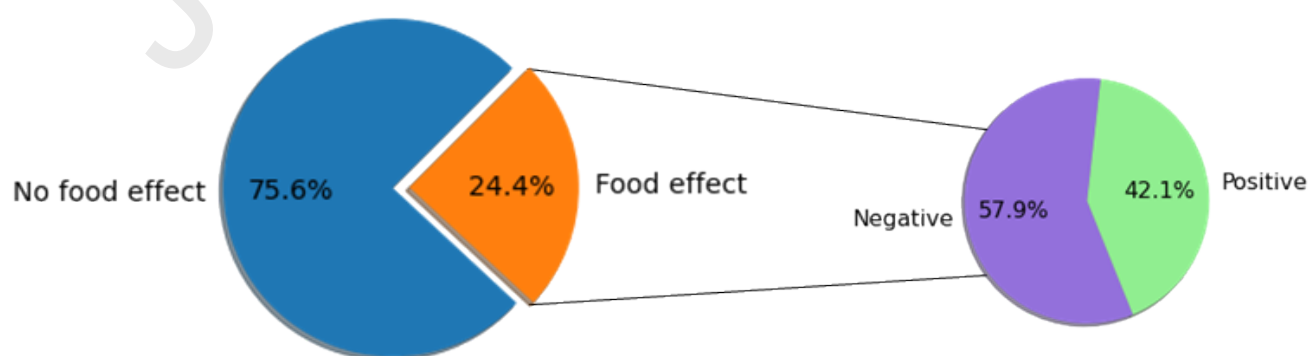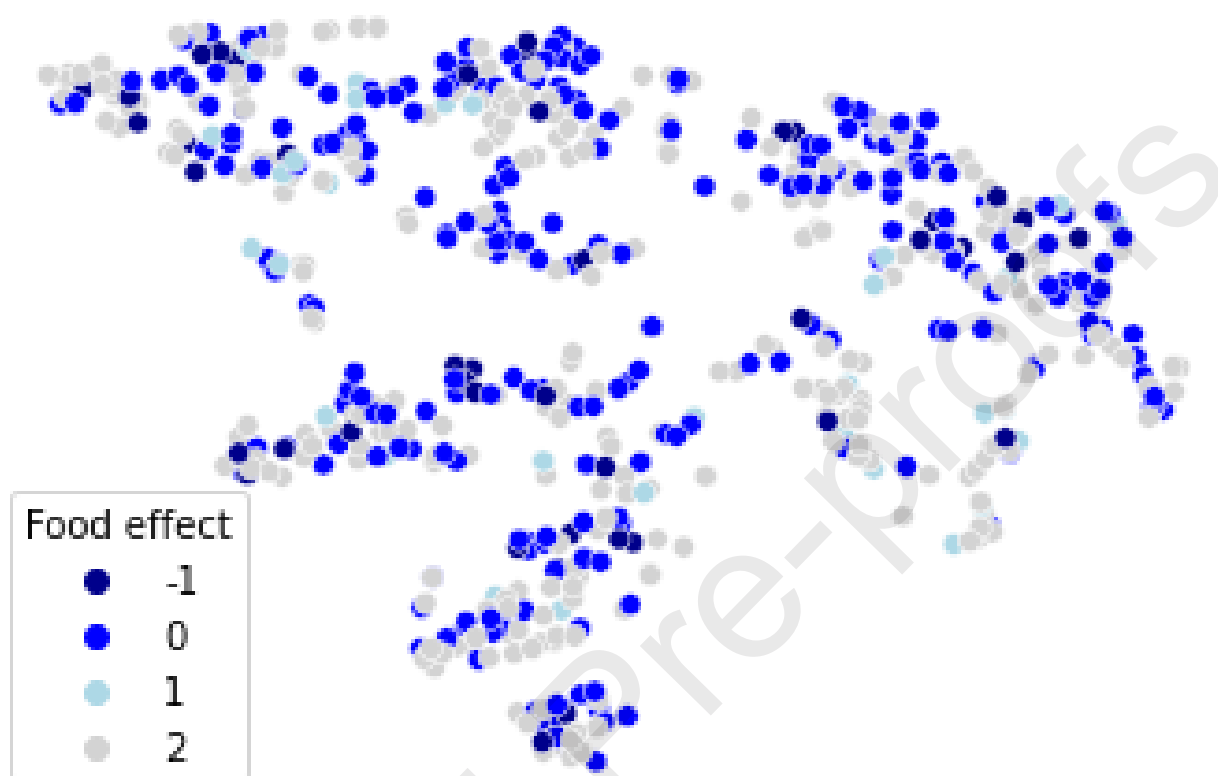
Figure 4 Food effect classification

Figure 5 A t-distributed stochastic neighbor embedding (tSNE) scatterplot of drugs classified by food effect classification; negative food effects (-1), no food effect (0), positive food effect (1) and not classified (2)

Biopharmaceutical Classification System (BCS) is based on the pioneering work of Amidon et al., which classifies drugs according to their permeability and solubility to predict the in vivo performance of drug products (Amidon et al., 1995). The Biopharmaceutical Drug Disposition Classification System (BDDCS) was proposed in 2005 based on the observation that for drugs with high intestinal permeability rates, the major route of elimination in humans was by metabolism, whereas drugs with poor intestinal permeability rates were primarily eliminated unchanged in the urine and bile (Wu and Benet, 2005). Whilst there are distinct differences between the classification systems, they are often mentioned together in the prediction of food effects. Class 1 are drugs with high solubility and high permeability/metabolism. Class 2 are drugs with low solubility and high permeability/metabolism, Class 3 are drugs with high solubility and low permeability/metabolism and Class 4 are drugs with poor solubility and poor permeability/metabolism (Wu and Benet, 2005). **Figure 6** shows that there is no food effect for the majority of drugs in all BDDCS classes and reflects **Figure 4** showing that the majority of the drugs showed no food effect.
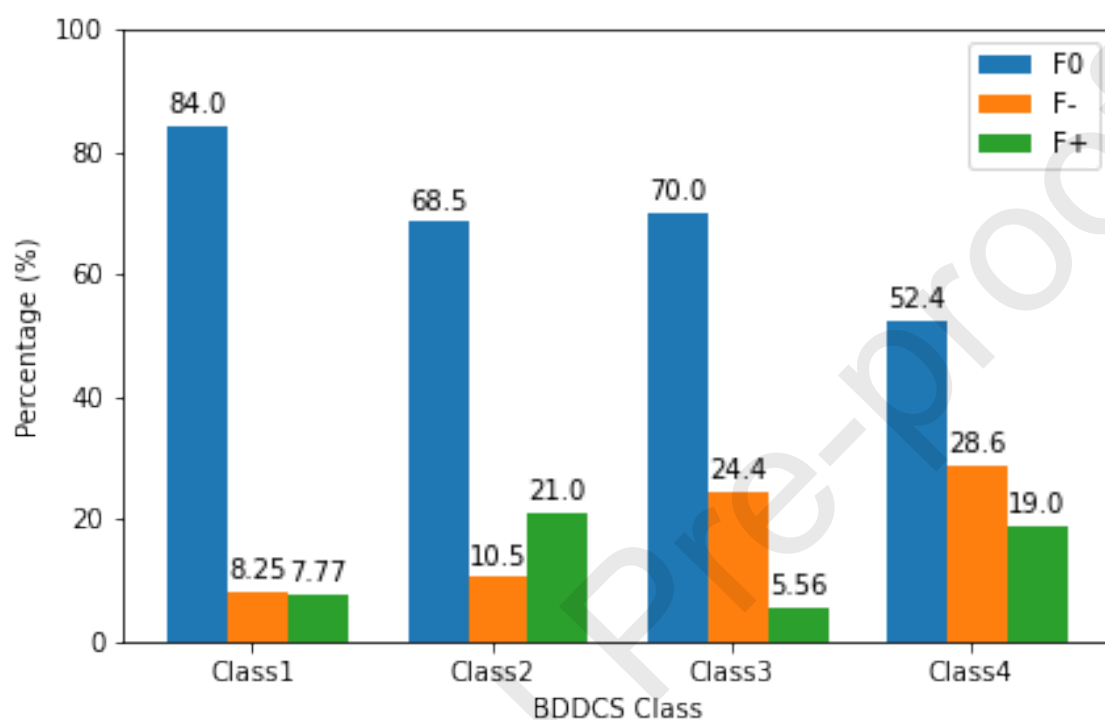
Figure 6 Distribution of drugs in the feature sets by BDDCS Class and food effect classification

3.2. Pilot study

Our approach to building a predictive model, first utilised a toolkit of ML algorithms with a standard machine learning pipeline. Here, the data was randomly split 80:20 into training and testing sets, respectively, with stratification where the testing set used blind data to test the robustness of the trained model from the dataset. Using this approach resulted in the task over predicting drugs with no food effect, shown in **Figure 7 and Figure S27 (Supplementary Materials)**. The confusion matrices showed that the majority of drugs were predicted as no food effect. While high accuracies and sensitivities were reported, the specificities were low (below 45%).
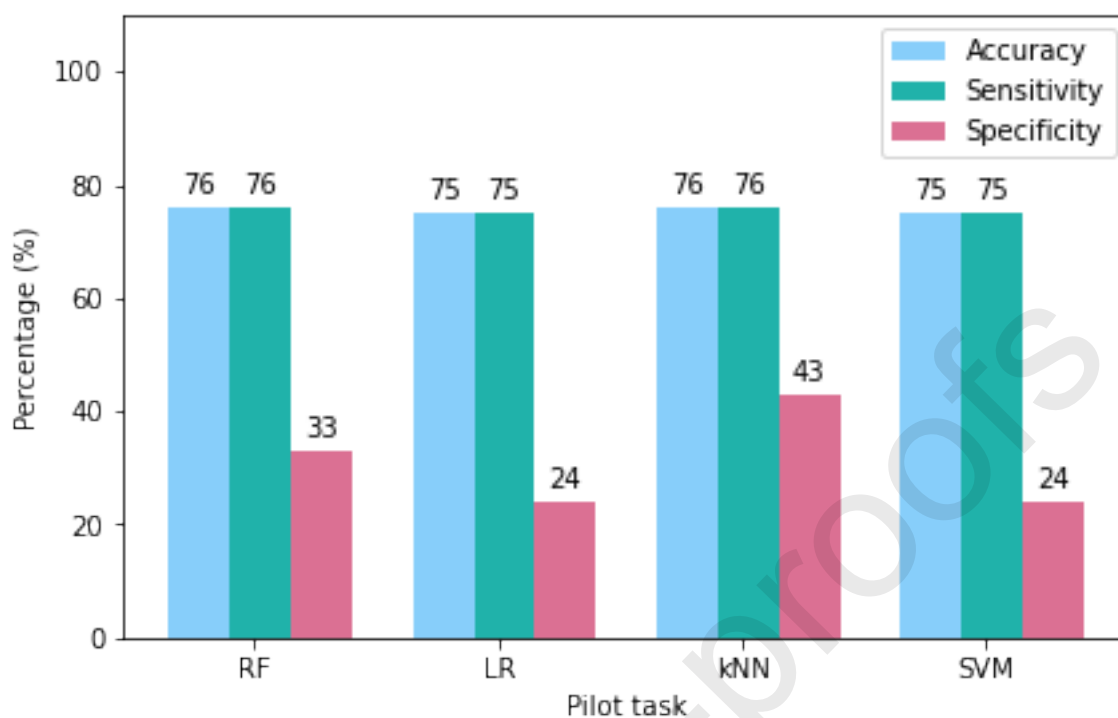
Figure 7 Predictive performance of the pilot task (F0 vs F- vs F+]) in bar plot of random forest (RF), logistic regression (LR), k-nearest neighbor (kNN) and support vector machinery (SVM)

3.3. Task Analysis

Bespoke tasks were developed with the aim to surpass the predictions obtained from the pilot task and to leverage the characteristics of the dataset. The first task, referred to as task one, sought to determine how well a model can distinguish between no food effect (F0) vs food effect (F+/-) and hence a binary classification task was modelled. In addition, given that the dataset consisted of three times as many F0 drugs than F+/- drugs, three small sub-tasks were modelled containing a third of the F+/- samples. Consequently, three different models were developed on each sub-task training dataset before being applied to the test dataset, which was consistent for each sub-task. A majority vote was taken from the three smaller sub-tasks. Figure 8 and Figure S28 (Supplementary Materials) presents the findings of task one, binary classification of F0 vs (F- & F+), where the results focus on the total task. The training accuracy was 100%. SVM showed anaccuracy and sensitivity of 75%, although the specificity was low at 23%, therefore it was not useful for this predictive task. The SVM confusion matrix reported that the drugs were over-predicted as no food effect. Overall RF performed the best with an accuracy and sensitivity of 70% and a specificity of 71%.
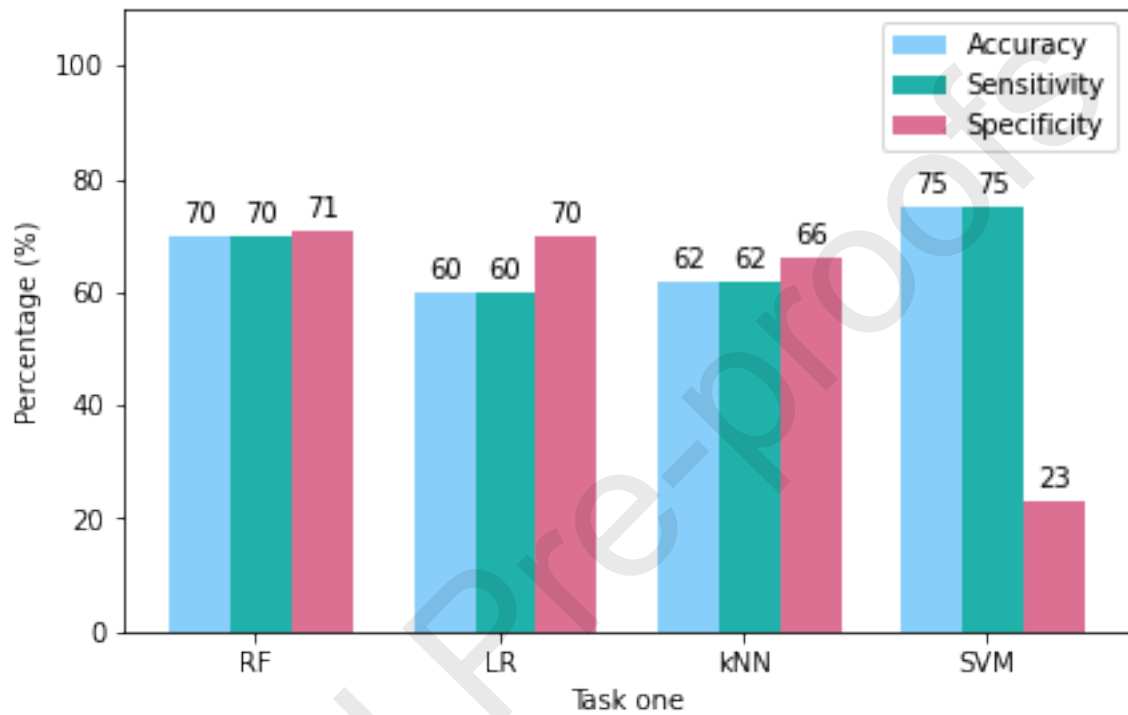
Figure 8 Predictive performance of Task one (F0 vs [F-/+]) in bar plot of random forest (RF), logistic regression (LR), k-nearest neighbor (kNN) and support vector machinery (SVM)

The second task investigated how well the model was able to distinguish between F+ vs F-, also a binary classification task. Figure **9 and Figure S29 (Supplementary Materials)** shows the evaluation results of task two (F- vs F+). The training accuracy was 100%. The accuracies, sensitivities and specificities of the binary classification reached 80%, whereas the specificity was lower at 76% for RF, LR and kNN. SVM on the other hand, showed a lower performance and achieved 60% for the accuracy and sensitivity and 40% for the specificity.
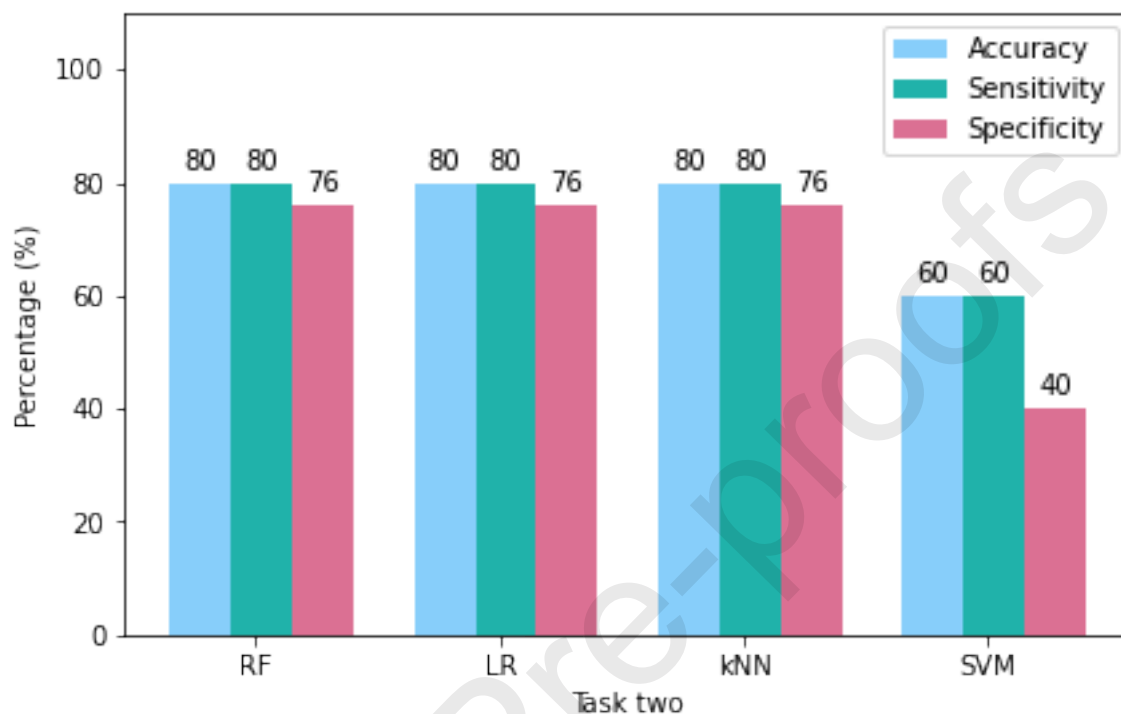
Figure 9 Predictive performance of Task two (F0 vs [F-/+]) in a bar plot of random forest (RF), logistic regression (LR), k-nearest neighbor (kNN) and support vector machinery (SVM)

The third task was a sequential task, an amalgamation of task ones and two, chosen as both tasks yielded high accuracies in comparison to the baseline task. First, the task distinguishes between F0 vs F+/-. Next, based on the drugs predicted have an effect, the task then predicted whether the drugs will have a positive or negative effect. The final accuracy will be compared to the original ground truth. Figure 10 and Figure S30 (Supplementary Materials) showed the results of task three, F0 vs F- vs F+, which is a multiple classification task. For RF, the task reported a 70% accuracy and sensitivity and a slightly higher specificity at 71%. This sequential methodology yielded a higher specificity than the pilot task (Figure 7). LR and kNN showed poorer performance. SVM, on the other hand, showed good accuracy and sensitivity of 75%, but however the specificity was low at 23% and showed the same performance as the pilot task (Figure 7 and Figure 27 Supplementary Materials).
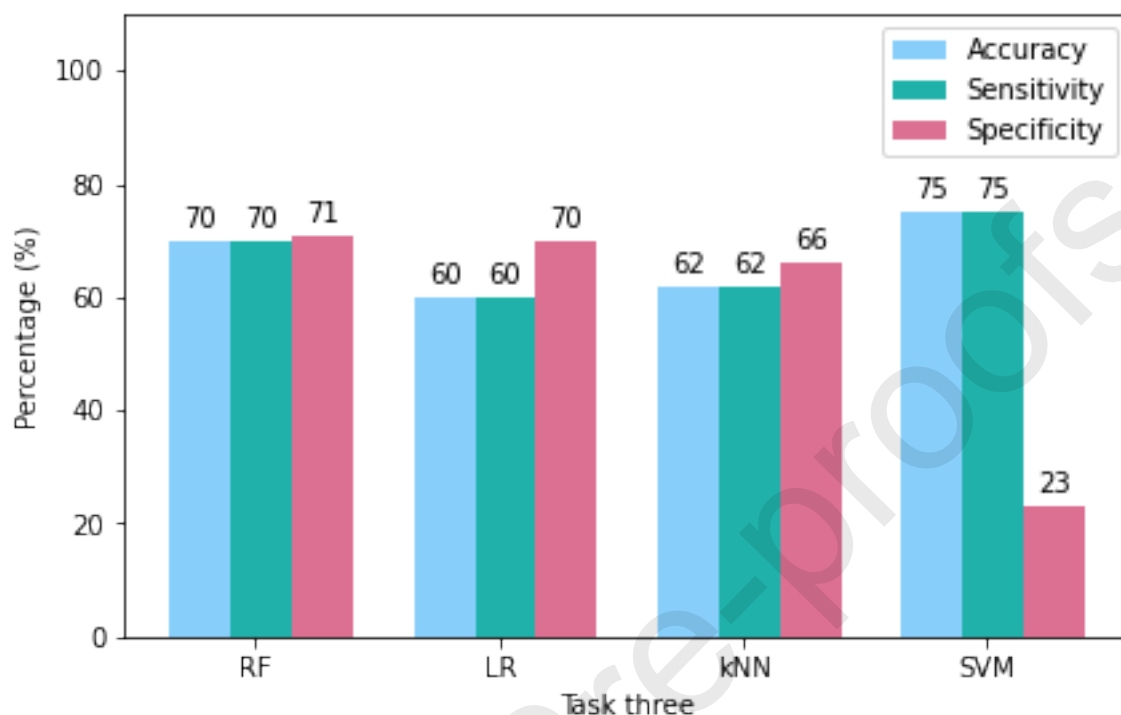
Figure 10 Predictive power of Task three (F0 vs F- vs F+) in bar plot of random forest (RF), logistic regression (LR), k-nearest neighbor (kNN) and support vector machinery (SVM)

3.4 Feature importance

Feature importance analyses were performed to identify key features in task one and task two. As shown in Figure 11 and 12, certain features were calculated by RF to be more important than others in the building of the prediction tasks one and two. Interestingly, the most important features were different for task one and task two. For task one, shown in Figure 11, cDose were the most important features (minVSLgS based then ALOGPS based). In task two, the most important feature was cDose (ALOGPS based) then PSDA, as shown in Figure 12.

These are all features calculated by *in silico* software (full definition for the features are provided in **section 2.1.1**). This could be useful in deciding which features should be determined in early stage drug development. The least important feature in both tasks were Ro5, determined by the Lipinski's rule of five, and the BDDCS class feature.
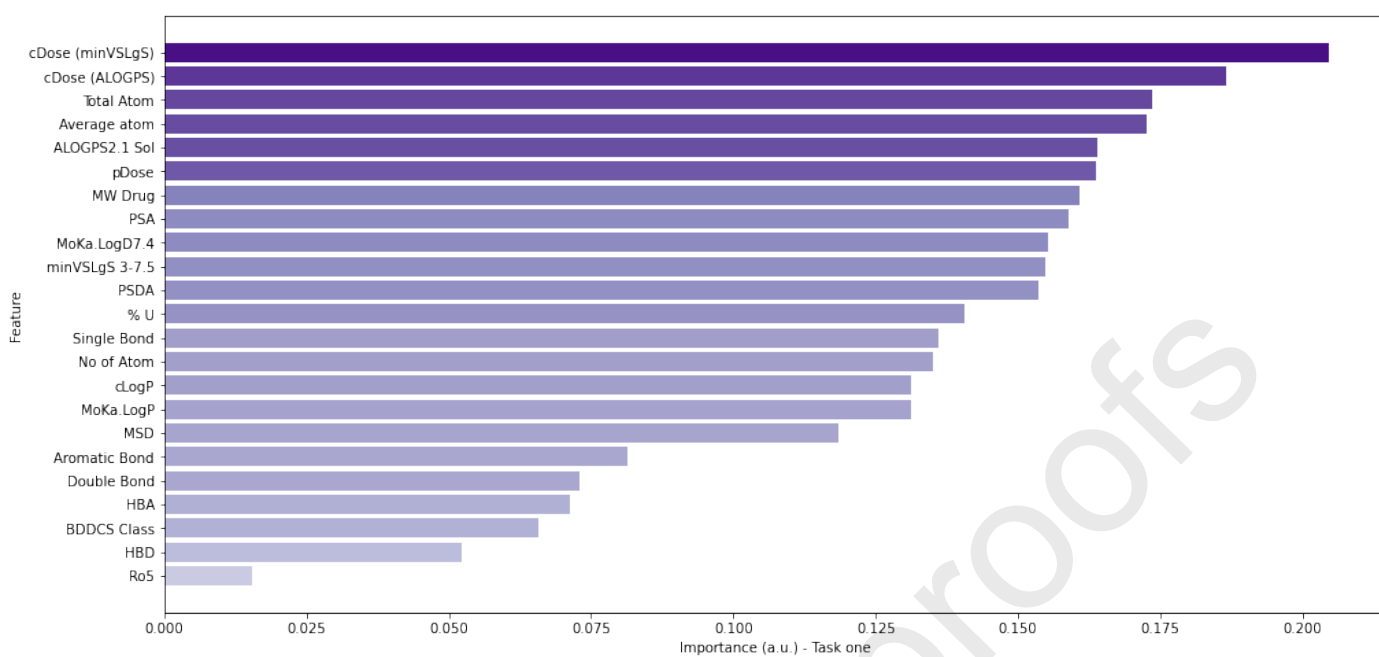
Figure 11 Feature importance analysis for 23 features calculated from the feature set used in task one. The ranking function reflects the importance of each feature in the predictive model.
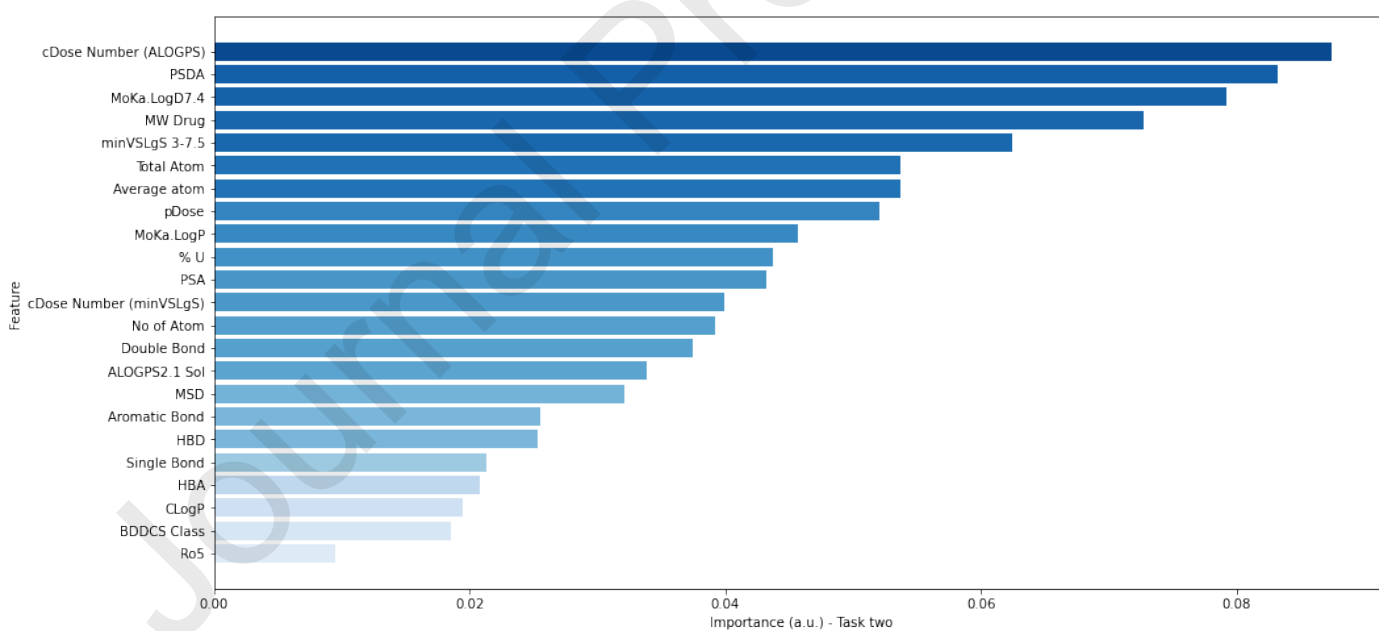

Figure 12 Feature importance analysis for 23 features calculated from the feature set used in task two. The ranking function reflects the importance of each feature in the predictive model.

4. Discussion

Prediction of the food effect is one of the key requirements for estimating the suitability of potential drug candidates. Presence of a food effect complicates the drug development process and the safety and efficacy profile of the drug. ML has become more powerful in its ability to recognise patterns with enhanced automation, and may provide insights at the early drug development stage (Paul et al., 2021). Given the highly complex nature of the GI tract, ML can potentially offer tools for the prediction of dynamic biopharmaceutics processes. Here, the dataset included *in silico* structural and activity data. The RF tasks performed the best overall compared to LR, kNN and SVM, suggesting that an ensemble-based method was needed for strong predictive performance. Importantly, the training accuracies were 100% for task one and task two. While the SVM tasks reported high accuracies and sensitivities, the specificities were consistently low as the algorithm under-predicted the food effect. Therefore, the predictive capacity of SVM for the prediction of the food effect is limited.

The RF task two achieved the highest accuracy and sensitivity of 80%, followed by task one with 71%, then task three with 70%. For binary classification, task two showed an improved performance compared with task one. The specificity of task two was high at 76%, whereas in task one the specificity was 68%**.** It must be highlighted that the accuracy of task three is lower than that of task one and two. This is due to the coding method of task three, where first task one was used, followed by task two. If these tasks incorrectly classifies the drugs or samples, it will therefore affect performance of task three. There could be propagation of error. Several reasons may contribute to the high accuracies seen here with RF. First, the dataset was large with 311 drugs and 23 features. Second, the RF algorithm has the ability to integrate a number of decision trees to train the models and solve classification issues without too much hyper-parameter tuning (Han et al., 2019).

An important approach used in this study was the feature importance analyses, part of a set of techniques called explainable ML (Bannigan et al., 2021), where scientific insights can be found from multi-dimensional datasets. The prediction accuracy of the tasks are limited by the features used in models and may not represent all of the factors contributing to the effect of food on oral drug absorption. Importantly, the model did not include the type of formulation, which can influence food-mediated changes in drug absorption. In drug development, formulation approaches can be developed to overcome the food effect (O'Shea et al., 2019; Varum et al., 2013). Another limitation of the dataset is that the pKa of the drug was not included as an input. The pH of the intestines is significantly affected by food intake (Koziolek et al., 2015a; Koziolek et al., 2015b) and therefore, pKa of the drug is a key property in predicting food effects. For example, Marasanapallea et al found that furosemide, an acidic drug with low permeability and a pKa of 3 exhibits pH-dependent dissolution rates and showed negative food effects (Marasanapalle et al., 2009). The minimum number of features that is necessary for an accurate prediction model development will be a subject of future work. Our model used *in silico* calculated features that may be the only data available at early stage drug development. Furthermore, in drug development, early datasets tend to be small with an imbalanced features space due to limited experimental data. Importantly, ML tools can be combined with other tools such as PBPK (Chen et al., 2021; Gao et al., 2021).

The feature analyses revealed that different features were important in the prediction of the binary classification of task one; no food effect (F0) vs a food effect (F-&F+), and task two; a negative food effect (F-) vs a positive food effect (F+). Drug

solubility is a key property to aid the understanding of drug absorption through the gastrointestinal tract. Drugs with lower intestinal solubility's can show an increased absorption in the presence of food, due to the increased secretion of bile. For example, oral oncology drugs frequently show positive food effect due to their poor aqueous solubility (Willemsen et al., 2016). Regional differences exist in the luminal fluid properties along the gastrointestinal tract (Vertzoni et al., 2019), therefore determining the solubility across a range of pH values, as calculated by minVSLgS 3-7.5 may be useful to determine the food effect, the fifth most important feature in task two. The feature MoKa.LogD7.4 represents the lipophilicity of the drug, the third most important feature in task two. Positive food effects are associated with drug lipophilicity by lipid emulsification and an increase in luminal solubilisation (Baxevanis et al., 2020; Porter et al., 2008). Abiraterone, for example, shows a dramatic positive food effect depending on the lipidic content of the meal (Schultz et al., 2020). Its positive food effect is attributed to its high lipophilicity, where it is highly solubilized in the lipophilic, micelle-abundant fed state gastrointestinal fluid containing bile salts and exogenous solubilizing species (Varum et al., 2013).

The two most important features in task one were cDose number (minVSLgS 3-7.5 and ALOGPS based). These features were calculated by software from the drug structure which are available in early drug development. Although, it must be acknowledged that the experimentally derived dose number is not usually available in early drug development. Dose number is an indicator of solubility-dose relationship. When the dose number is low, the drug is considered to have high solubility; when the dose number is high, the drug is considered to have low solubility. For drugs that cannot be absorbed from the GI tract because of poor solubility or slow dissolution rate, food can enhance their oral absorption by solubilisation (Gu et al., 2007). In the high fat meal used in the food effect study, the products of digestion introduce a higher concentration of bile salts than in the fasted state which leads to higher solubility and dissolution rate of lipophilic compounds. Although, food components can inhibit both influx and efflux transporters (Dou et al., 2020; Dou et al., 2018; Wu and Benet, 2005).

Whilst RF can select the most important features that can be useful for determining which features should be experimentally validated, the relationship between the features is hidden inside the many decision trees. Importantly, the model interpretation should be intuitive to a pharmaceutical scientist, as well as a machine learning scientist and the authors believe that the rank of importance highlights the most important biopharmaceutical features in an easy-to-interpret manner. The BCS/BDCCS Class has been used as an indicator for food effect prediction (Wu and Benet, 2005), although it is not always available in early drug development. Therefore it might not necessarily be available to input into a computational prediction model The BDCS can be used to predict the food effect and it was estimated to be accurate in 70% of cases (Wu and Benet, 2005). In addition, it suggests that food effect can be predicted from *in vitro* drug physicochemical properties. In our study, however, the majority of the drugs did not display a food effect. Therefore, the tool was not appropriate for this dataset. This was reflected in the feature importance where the BDDCS was one of the lowest ranked features in task one and task two.

Few studies have used mathematical modelling to predict and understand the food effect (Singh, 2005). One study built a dataset of 92 drugs and achieved an accuracy of 80% for food effect prediction (Gu et al., 2007). However, only LR was used,

a basic statistical technique, which can only handle linear relationships between input and output data, whereas the modern ML approaches used here can handle more complex relationships between inputs and outputs. A further study used a RF for food effect prediction and reported with a moderate Kappa (a metric comparing the observed accuracy with the expected accuracy) from the modelling of a dataset of 53 drugs and 11 drug properties (Gatarić and Parojčić, 2019). The most recent study used artificial neural networks (ANNs) and SVM to predict the food effect using a dataset of 141 drug compounds brought to market in the last 5 years. These models demonstrated higher food effect prediction accuracy (72% with ANN and 69% with SVM)than the BCS prediction which showed an accuracy of 46% (Bennett-Lenane et al., 2021). In addition, for the positive food effect and no food effect groups the specificities of the testing sets were 80% and 78% (SVM) and 80% and 90% (ANN), and the sensitivities were 62% and 71% (SVM) and 73% and 71% (ANN). The specificity and sensitivity of the test set for negative food effect group was not reported. Comparisons to these studies is not possible as different drugs and features were used to build these predictive models. However, our strategic ML pipeline approach based on three tasks showed that RF could predict the food effect with accuracies, sensitivities and specificities of over 70% for 300 drugs from a diverse chemical space.

Food consumption can affect the drug absorption through many different mechanisms, such as changes in the GI physiology, bile-mediated enhanced solubilisation of lipophilic drugs, inhibition of drug metabolising enzymes and transporters (Deferme and Augustijns, 2003) and by direct food-drug mechanisms. However, the key mechanisms that causes the food effect for a particular drug are often unknown (Vinarov et al., 2021). While these ML approaches cannot identify the mechanism of the food effect, if a food effect is predicted for a new drug candidate using these tasks, follow-up *in vitro*, PBPK and preclinical studies could then be designed to provide further insights into the potential mechanism of the food effect.

5. Conclusions

Our study assessed the application of ML-powered tasks for the prediction of the food effect. The RF algorithm was able to predict the food effect with accuracies, sensitivities and specificities of over 70% in three prediction tasks: food effect vs no food effect, negative food effect vs positive food effect, and no food effect vs negative food effect vs positive food effect, respectively. Feature importance revealed that calculated dose number was the most important feature underlying the development of the ML tasks. The proposed approach could enable a potential reduction in the number of animals of and humans required in food effect studies. Furthermore, it offers a useful insight at the early drug discovery and development stage and could prevent costly reformulation strategies or the failure of lead compounds at later stages if food-drug interactions are found.

Supplementary Materials: PDF file

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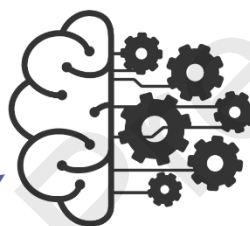
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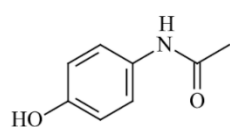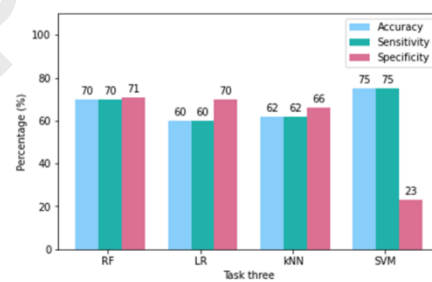
Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: