DILI_C: An AI based classifier to search for Drug-Induced Liver Injury literature

Sanjay Rathee^{1,†,*}, Meabh MacMahon^{1,2,†}, Anika Liu^{1,3}, Nicholas Katritsis¹, Gehad Youssef¹, Woonchang Hwang¹, Lilly Wollman¹, Namshik Han^{1,4,*}

¹ Milner Therapeutics Institute, University of Cambridge, Cambridge, UK

² LifeArc, Stevenage, UK

³ Centre for Molecular Informatics, Department of Chemistry, University of Cambridge, UK

⁴ Cambridge Centre for AI in Medicine, University of Cambridge, Cambridge, UK

† These authors contributed equally

Correspondence*:

Corresponding Author

nh417@cam.ac.uk, sr952@cam.ac.uk

2 ABSTRACT

Drug-Induced Liver Injury (DILI) is a class of Adverse Drug Reactions (ADR) which causes problems in both clinical and research settings. It is the most frequent cause of acute liver failure in the majority of western countries and is a major cause of attrition of novel drug candidates. Manual trawling of literature for is the main route of deriving information on DILI from research studies. This makes it an inefficient process prone to human error. Therefore, an automatized AI model capable of retrieving DILI-related papers from the huge ocean of literature could be invaluable for the drug discovery community. In this project, we built an artificial intelligence (AI) model combining the power of Natural Language Processing (NLP) and Machine Learning (ML) to address this problem. This model uses NLP to filter out meaningless text (e.g. stopwords) and uses customized functions to extract relevant keywords as singleton, pair, triplet and so on. These keywords are processed by apriori pattern mining algorithm to extract relevant patterns which are used to estimate initial weightings for a ML classifier. Along with pattern importance and frequency, an FDA-approved drug list mentioning DILI adds extra confidence in classification. The combined power of these methods build a DILI classifier (DILI_C) with 94.91% cross-validation and 94.14% external validation accuracy. To make DILI_C as accessible as possible, including to researchers without coding experience, an R Shiny App capable of classifying single or multiple entries for DILI is developed to enhance ease of user experience and made available at <https://researchmind.co.uk/diliclassifier/>.

Keywords: DILI, Drug Induced Liver Injury, NLP, Natural language processing, ML, Machine learning, AI, Artificial Intelligence

1 INTRODUCTION

Drug-Induced Liver Injury (DILI) is a class of adverse drug reactions (ADR) which is an issue in both clinical and research settings. Although DILI can be mild, resolving once administration of the problem drug is discontinued, it lies on a spectrum and can also be severe. DILI is the most frequent cause of acute liver failure in the majority of western countries Hoofnagle and Björnsson (2019) and is a major cause of

Figure 1. The steps of DILI_C from dataset of DILI positive and DILI negative papers to validations showing intergration of FDA and SIDER datasets.

26 attrition of novel drug candidates Church and Watkins (2018) and accounts for almost one quarter of clinical
 27 drug failures Watkins (2011). As new findings on DILI are often published in scientific literature, collating
 28 this data from literature is useful for risk-assessment during drug development and in the clinic. However,
 29 currently manual trawling of text from literature is the main route of obtaining relevant information about
 30 DILI from research studies. This is an inefficient process prone to human error and modern computational
 31 techniques for mining textual data can improve it, a model capable of retrieving DILI-related papers from
 32 the huge ocean of literature could be invaluable for the drug discovery community.

33 Natural language processing (NLP) involves using computational techniques to extract information and
 34 insights from text data. Previous studies have applied NLP techniques to identify relevant literature for
 35 challenges in drug discovery, including with the goal of drug repurposing Zhu et al. (2020) and collating
 36 information on COVID-19 for researchers Wang and Lo (2021). Additionally previous attempts have been
 37 made to classify adverse drug events using NLP on available data Harpaz et al. (2014). Databases of drug
 38 side effects also contain DILI-related information FDA (2021); Kuhn et al. (2016). In this study NLP is
 39 used to extract relevant patterns from literature and this knowledge is combined with information related to
 40 DILI from publicly available databases. This combined information is used to train a classifier to classify
 41 literature as DILI-related or not. Figure 1 highlights the flow of text processing for our model.

2 MATERIALS AND METHODS

42 We built an artificial intelligence (AI) model combining the power of Natural Language Processing (NLP)
 43 and Machine Learning (ML) to extract relevant literature for DILI from ocean of published papers. This
 44 model combines the information available in the title and abstracts of scientific papers with information
 45 from external databases to improve the efficacy and accuracy. A detailed procedure is available in Algorithm
 46 1 which contains all the steps to build this model.

Algorithm 1 Classify Literature as DILI Positive or DILI Negative

Input: Discovery dataframe having title, abstract and expert label for every article(D_{DF}), Validation dataframe having title, abstract only for every article(V_{DF})

Output: Validation dataframe having title, abstract and predicted label for every article(V_{DF})

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1: procedure PREDICT-DILI-LABEL
2:    $P_{tokens} = \text{CharacterArray}()$   $\triangleright$  Store tokens for DILI positive articles
3:    $N_{tokens} = \text{CharacterArray}()$   $\triangleright$  Store tokens for DILI negative articles
4:    $ML_{matrix} = \text{Matrix}()$   $\triangleright$  Matrix for ML Model data
5:    $D_{DF}\$P_{tokens} = \text{CharacterArray}()$   $\triangleright$  Discovery cohort new column for positive token
6:    $D_{DF}\$N_{tokens} = \text{CharacterArray}()$   $\triangleright$  Discovery cohort new column for negative token
7:   for each article  $A \in D_{DF}$  do  $\triangleright$  Loop to get token with NLP
8:      $\text{rowname}(ML_{matrix}) = A_{ID}$ 
9:     if  $A_{abstract} == \text{NA}$  then  $\triangleright$  Use title as abstract if abstract missing
10:       $A_{abstract} = A_{title}$ 
11:     if  $A_{label} == \text{Positive}$  then  $\triangleright$  For DILI positive abstract
12:       $A_{Pos\_tokens} = \text{Customized\_NLP\_Model}(A_{abstract})$ 
13:       $P_{tokens} = c(P_{tokens}, A_{Pos\_tokens})$ 
14:       $D_{DF}\$P_{tokens}[A] = A_{Pos\_tokens}$ 
15:     if  $A_{label} == \text{Negative}$  then  $\triangleright$  For DILI negative abstract
16:       $A_{Neg\_tokens} = \text{Customized\_NLP\_Model}(A_{abstract})$ 
17:       $N_{tokens} = c(N_{tokens}, A_{Neg\_tokens})$ 
18:       $D_{DF}\$N_{tokens}[A] = A_{Neg\_tokens}$ 
19:    $\text{columns}(ML_{matrix}) = \text{unique}(P_{tokens}, N_{tokens})$   $\triangleright$  Add unique tokens as features in ML matrix
20:   for each token column  $T \in ML_{matrix}$  do  $\triangleright$  Loop to calculate weight for each token  $W_T$ 
21:      $\alpha = \text{PosFreq}[T] / (\text{PosFreq}[T] + \text{PosFreq}[T])$   $\triangleright$  Frequency weight for each token
22:      $\beta = \text{Apriori\_Score}[T]$   $\triangleright$  Presence/Absence as frequent singleton, pair, triplet and so on.
23:      $\gamma = \text{FDA\_Score}[T]$   $\triangleright$  Presence/Absence in FDA drug list with DILI Adverse Event
24:      $\lambda = \text{SIDER\_Score}[T]$   $\triangleright$  Presence/Absence in SIDER drug list with DILI Adverse Event
25:      $W_T = \alpha + \beta + \gamma + \lambda$ 
26:   Train\_ML\_Model $[ML_{matrix}]$ 

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2.1 Data Preparation

A well curated dataset of ~28,000 DILI annotated papers was obtained from the CAMDA team (2021). This dataset was generated after filtering out the most obvious DILI literature which makes the task of classification challenging, but more representative of the challenge of sorting through real word literature beyond the obviously DILI related or entirely unrelated papers. All the papers in this dataset are labeled as DILI related (DILI positives) or not related to DILI (DILI negatives) by an experienced panel of experts. We used approximately half of this data with a balanced split of DILI positive and negative to extract insights and train a model (discovery set). The remaining half was kept as validation set.

We divided the discovery set of 14,203 papers into training (80%) and testing (20%) sets consistent with their labels. Overall, we used 5,741 DILI positive & 5,620 DILI negative as a training set and 1,436 DILI positive & 1,406 DILI negative as test set.

2.2 Natural Language Processing Model

A NLP model with some customization was used to extract the relevant information from the available training cohort (Algorithm 2). It starts with the most basic NLP step sentence tokenization on titles and abstracts, followed by word tokenization. A customized word tokenization method was developed to generate keyword sets of singleton, pairs, triplets and so on. This step generates combinations containing

only nouns and adjectives and filters out irrelevant text like stop words using R UDpipe package. These keyword sets were processed for text lemmatization and stemming to generalise the list. The output of this NLP model was a vector containing all keyword sets as features and for each of these their frequency and length (singleton, pair) was stored as weights for pattern mining. This NLP model was applied on both title and abstracts.

Algorithm 2 Customized NLP Model to extract Tokens from Abstract

Input: Abstract for an Article ($A_{abstract}$)

Output: Tokens of length 1,2,3,and so on.

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1: procedure CUSTOMIZED_NLP_MODEL
2:   for each article  $A \in D_{DF}$  do                                     ▷ Loop to get token with NLP
3:      $df = \text{Sentence\_Segmentation}[A_{abstract}]$  ▷ UDpipe split paragraph with end pattern(i.e. colon)
4:      $df = \text{Word\_Tokenization}[df]$  ▷ UDpipe split sentence with pattern like space,tab
5:      $df = \text{Word\_Lemmatization}[df]$  ▷ UDpipe change words with lemma term
6:      $df = \text{Word\_Filter}[df]$  ▷ UDpipe keep only noun, adjective, verb
7:      $df = \text{Customized\_Token\_Generator}[df]$  ▷ Yield continuous tokens as pair, triplet and so on
8:      $\text{Yield}(df\$tokens)$ 
9:    $\text{Collect}(tokens)$ 

```

2.3 Pattern Mining

Along with the total frequency of a keyword set, the frequency of the keyword and its subsets in terms of the number of papers (DILI positive or DILI negative) in which it appears was calculated. The pattern mining ML algorithm Apriori was used for this. In this way, we included the frequency of a keyword set and its subset as a factor for weighting that keyword set. A distributed processing-based implementation of Apriori was used to minimize the overall processing time.

2.4 External Cohort Integration

Since external datasets contain information which could be advantageous in classifying DILI literature, two were integrated into the model. These two publically available datasets were the FDA approved drugs list FDA (2021) and SIDER adverse events dataset Kuhn et al. (2016). From these two datasets (Algorithm 3), a list of drugs with DILI as adverse events or warning were extracted, and these drugs were given a higher weight than others without such warnings. The side effects field of SIDER database for drugs was helpful to add extra information into this highly weighted list.

2.5 Classifier

The final vector of keywords along with their updated weights was given as an input to various well-known ML & AI models (Logistic Regression, Elastic Net, Random Forest, Neural Net, Support Vector Machine, Gradient Boosting Machine, Convolution Neural Networks and LSTM) to train a classifier. The weight of a keyword was calculated by its total frequency, length, FDA and SIDER list presence or absence.

$$W_T = \sum_{i=1}^j W_{fi} * Key_i + \sum_{i=1}^j W_{li} * Key_i + \sum_{i=1}^j W_{f dai} * Key_i + \sum_{i=1}^j W_{sider i} * Key_i \quad (1)$$

In equation (1), W_T represents the total weight for a paper, key represents the weight for presence(1) or absence(0) of a keyword set, (W_f) represents the weight for frequency of a keyword set, W_l represents

Algorithm 3 Add score for presence/absence in external cohort FDA and SIDER

Input: Array of Tokens (T), FDA drug list (FDA), SIDER drug list ($SIDER$)

Output: FDA and SIDER score for each Token T_i

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1: procedure FDA_SCORE
2:    $FDA\_DILI\_Drug\_List = \text{CharArray}()$ 
3:   for each drug  $D \in FDA$  do                                ▷ Loop to get token score in FDA cohort
4:     if  $DILI \in D_{AdverseEvent}$  then                        ▷ Check Drug Adverse Event contain DILI
5:        $FDA\_DILI\_Drug\_List = D_{name}$ 
6:   for each Token  $t \in T$  do                                ▷ Loop to get token score in FDA cohort
7:     if  $t \in FDA\_DILI\_Drug\_List$  then                      ▷ Check token present in FDA DILI drug list
8:        $t_{FDA\_score} = s$                                     ▷ Allocate constant score s to token
9:     else
10:       $t_{FDA\_score} = 0$                                        ▷ Allocate zero score to token
11:    $\text{Collect}(T)$ 
12: procedure SIDER_SCORE
13:    $SIDER\_DILI\_Drug\_List = \text{CharArray}()$ 
14:   for each drug  $D \in SIDER$  do                            ▷ Loop to get token score in SIDER cohort
15:     if  $DILI \in D_{AdverseEvent}$  then                      ▷ Check Drug Adverse Event contain DILI
16:        $SIDER\_DILI\_Drug\_List = D_{name}$ 
17:   for each Token  $t \in T$  do                                ▷ Loop to get token score in SIDER cohort
18:     if  $t \in SIDER\_DILI\_Drug\_List$  then                  ▷ Check token present in SIDER DILI drug list
19:        $t_{SIDER\_score} = s$                                     ▷ Allocate constant score s to token
20:     else
21:       $t_{SIDER\_score} = 0$                                        ▷ Allocate zero score to token
22:    $\text{Collect}(T)$ 

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88 the weight for length of a keyword set (for instance singleton 1, pair 2, triplet 3), W_{fda} represents the
 89 weight for presence and absence in FDA list with DILI adverse event and W_{sider} represents the weight for
 presence and absence in SIDER list with DILI adverse event. The classifier with the highest cross-validation

Figure 2. Prediction Probabilities Plot.

90 accuracy (Gradient Boosting Machines) was tested on a put-aside test set. The results on the test set were
 91 quite promising with an accuracy of 94.89%. The model was iterated 10 times with different test set to get
 92

the average accuracy of 94.9%. Figure 2 shows the probability of every sample being positive. Any sample with a probability higher than 50% is labelled as DILI positive. The cutoff of 50% can be adjusted to closer reflect a real-world dataset which will have far more negative literature. Table 1 shows the confusion matrix for the stand-out (20%) testing set.

		True class	
		Positive	Negative
Predicted class	Positive	1335	44
	Negative	101	1362

Table 1. Confusion matrix of GBM classifier applied to stand out abstract cohort

3 RESULTS

The most effective model was Gradient Boosting Machines (Figure 3) with 94.76% accuracy when applied to the internal hold out test set of 2,842 papers, half of which were DILI positive and half DILI negative. The inclusion of FDA and SIDER datasets improved the accuracy of the GBM model in the validation set and on an additional external set (Table 2). The final model is used to predict the labels for the external validation cohort shared by CAMDA. We got encouraging results with an accuracy of 94.14% and F1-Score 94.08%. The highlight of the model was its recall value of 96.02%. Dili_C was then applied to an unseen

Figure 3. Internal accuracies for all ML classifiers (EN: Elastic Net, LR: Logistic Regression, SVM: Support Vector Machines, CN: Convolution Network, RF: Random Forest, GBM: Gradient Boosting Machines, FSB: Feature Selection Based Model) showing that GBM has the highest accuracy.

additional external set which was unbalanced DILI cohort, making it more reflective of real world data. On the additional external set accuracy was 90.25% and an F1-score of 90.94%. The recall value was improved with this set, with a value of 97.9%

4 DISCUSSION

DILI_C is a model with high accuracy which is useful to the community to classify literature as related to or unrelated to DILI, which can help do DILI risk-assessment for drugs during development, repurposing or in the clinic. Although it was developed to classify DILI literature, it has been designed to handle any adverse event classification problem so it's has applications for drug risk-assessment beyond just liver injury to toxicities in other tissues. We note that complex machine learning AI models are known to have the power to magnify weak signals . In order to minimise the pressure on ML models and reduce the risk of such

	Validation Set (14211)				Additional external set (2000)			
	Accuracy	F1 score	Recall	Precision	Accuracy	F1 score	Recall	Precision
GBM (abstract only)	0.9386	0.9376	0.9631	0.9133	0.8845	0.8936	0.9700	0.8284
GBM(+FDA)	0.9406	0.9396	0.9659	0.9147	0.8915	0.8992	0.9680	0.8395
GBM (+SIDER)	0.9414	0.9408	0.9602	0.9221	0.9025	0.9094	0.9790	0.8491

Table 2. Results for the GBM model applied to the validation set and additional external set of DILI and non-DILI literature. The inclusion of FDA and SIDER datasets improved the GBM model

erroneous magnification, during the development of DILI_C a strong focus was put on the data cleaning processing steps of the model. Another potential issue is the chance that the inclusion of SIDER dataset could introduce bias against publications relating to drugs which aren't yet included therein. Reassuringly, even without the inclusion of this database, DILI_C performs well, with an accuracy of 94.06% on the Validation set and of 89.15% on the additional external set. There is still potential to improve DILI_C in the future. Later steps like customized word segmentation, pattern mining, and external relevant cohorts add power to DILI_C and there is still plenty of scope to adjust the weights for these steps. In addition, as other databases related to drug toxicity and side effects are developed, these could be integrated to improve the model. To make DILI_C as accessible as possible, including to researchers without coding experience, an R Shiny App capable of classifying single or multiple abstracts for DILI is developed to enhance ease of user experience and made available at <https://researchmind.co.uk/diliclassifier/>).

5 CONCLUSIONS

DILI_C is a novel tool to classify literature as related to DILI or not. This is significant as it has the potential to aid researchers in drug-development and research settings during risk-assessment.

DILI_C is implemented in such a way that it can be modified to classify any other drug adverse reaction like DILI. Therefore, DILI_C code available at GitHub could be useful for researchers working in the same domain. A shiny app for DILI_C makes it user-friendly.

CONFLICT OF INTEREST STATEMENT

SR is funded by JW Pharmaceutical. MM is an employee of LifeArc. NH and WH are funded by LifeArc. AL is funded by GlaxoSmithKline. NH is a cofounder of KURE.ai and CardiaTec Biosciences and an advisor at Biorelate, Promatix, Standigm and VeraVerse.

AUTHOR CONTRIBUTIONS

131 SR, MM and NH conceived and designed the analysis; SR and MM collected the data, built the model,
132 performed the analysis and wrote the paper; AL, NK, GY, WH and LW contributed data or analysis tools;
133 AL and NH reviewed the paper; NH supervised the project.

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DATA AVAILABILITY STATEMENT

137 The code datasets analysed for this study can be found in the DILI Github. [<https://github.com/sanjaysinghrathi/DILI-Classifier>].
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