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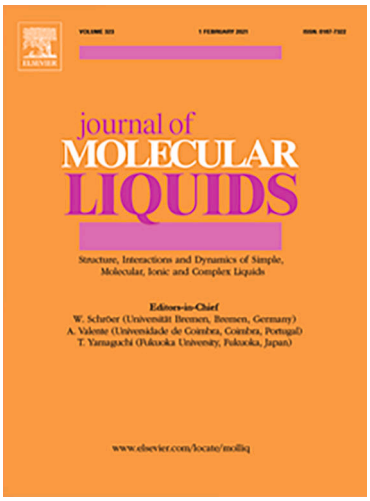

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PII: S0167-7322(22)02652-6
DOI: https://doi.org/10.1016/j.molliq.2022.121113
Reference: MOLLIQ 121113

To appear in: *Journal of Molecular Liquids*

Received Date: 29 November 2022
Revised Date: 13 December 2022
Accepted Date: 18 December 2022

Please cite this article as: Y. Liu, D. Ahmed Smait, A. Yaseen Naser, F. M. A. Altalbawy, H. Bahri, A. Abdul Kadhim Ruhaima, T. Zayad Fathallah, S.K. Hadrawi, R.E. Alsaddon, A. Alshetaili, A.M. Alsubaiyel, Optimization and validation of drug solubility by development of advanced artificial intelligence models, *Journal of Molecular Liquids* (2022), doi: https://doi.org/10.1016/j.molliq.2022.121113

Optimization and validation of drug solubility by development of advanced artificial intelligence models

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Abstract

Over the last ten years, the application of novel mathematical models of Machine Learning employed to model the solubility of drugs especially anticancer drugs, in supercritical carbon dioxide ($ScCO_2$) system has gained remarkable popularity. In this research, three distinct ensemble models have been employed on the data as a novel method for busulfan as anticancer drug for the first time, based on decision trees, including Random Forest (RF), Gradient Boosting Trees (GBRT), and Extremely Randomized Tree (ERT) to predict the solubility of busulfan as an

anticancer drug. The dataset has two input parameters, T=Temperature and P=Pressure, and Y= Solubility is the single output. After implementing and tuning these ensemble models' hyper parameters, the performance has been assessed through several metrics. All three models show R-squared score of more than 0.9, but in terms of RMSE, the error rates are 1.80E-04, 1.72E-04, and 1.03E-04 for RF, ERT, and GBRT models, respectively. Also, MAPE metrics 4.51E-01, 4.87E-01, and 3.62E-01 errors had found for RF, ERT, and GBRT models, respectively. GBRT has been selected as the best model due to the less rate of RMSE and MAPE. An analysis has also been performed to find the optimal amount of solubility, which can be considered the (x1=38.3, x2=333.1, Y=1.36E-03) vector.

Keywords: Anticancer drug; Supercritical fluids; Simulation; Machine learning; Model validation

1 INTRODUCTION

True perception of cancer biology is an important factor towards developing efficacious anticancer therapeutic agent to treat disparate malignant tumors [1, 2]. Apart from acceptable efficiency, manageable toxicity profile of anticancer drugs is an indisputable factor in the new era of oncology drug development due to its significant effect on the quality of life of patients [3, 4]. Therefore, efficient optimization of drug dosage is an important challenge in anticancer drug development.

Supercritical carbon dioxide ($ScCO_2$) has been recently of extensive utilization in biochemical/pharmaceutical industries as a promising solvent because of its remarkable characteristics like near-ambient critical temperatures, safety of operation, inflammability and versatility [5-7]. Drug solubility and materials behavior are two important parameters, which can be achieved by $ScCO_2$ technology for the manufacturing of nano/microparticles of anticancer drugs [8-10] . The prosperous use of $ScCO_2$ relies on the true perception of solute solubility. In recent years, numerous theoretical/experimental investigations have been conducted to predict the solubility of disparate materials in supercritical fluids (SCFs) [11].

Empirical correlations (ECs) are known as one of the promising thermodynamic techniques for predicting the amounts of drug solubility. ECs models have been of paramount attention owing to their simplicity of implementation for the solubility data. These predictive models often possess some fitting parameters, which are able to be specified by means of numerical techniques. Despite noteworthy advantages, ECs do not have sufficient accuracy to be applied for an extensive range of drugs [12-14]. With the goal of enhancing the precision of drug solubility prediction in $ScCO_2$, software-based computational procedures such as machine learning (ML) can be employed. ML-based predictive models, which are based on artificial intelligence (AI), profoundly depend on the

training data. The solubility prediction of drugs in these models take place applying the trained machine [15-19].

There are numerous problems in various scientific fields where there is no clear or linear relationship between input and output values, or the number of available laboratory data is too small or too large to be easily discovered with a human factor. In such situations, machine learning (ML), as the strongest knowledge available in this field, can help to explore these relationships with different tools [20-23].

The decision tree a widely used ML tools. The decision tree (DT) is a structure that generates trees for regression or classification problems. As it generates the associated decision tree, the dataset is gradually segmented into smaller subsets. The output is a tree with both leaf and decision nodes. The decision node may have two or more branches, with each branch representing a possible outcome for the criterion in question. The Leaf node stands [24-26].

Also, Ensemble learning [27] is another popular mixed model that excels in situations where modeling is too difficult to be accomplished with a single approach. They use a variety of learning algorithms to collectively arrive at a more precise estimate. The goal of ensemble models is to decrease bias and variance by combining multiple machine learning or statistical algorithms into a single model [28, 29]. The aim of this research is to model the solubility of busulfan as anticancer drug through machine learning using different models. Boosting and bagging are two types of ensembles learning methods. Boosting is an interdependent base estimator seeking sub-sequential learning algorithm. There will almost certainly be less bias in the overall performance compared to using a single base estimator. Bagging is an approach to parallel learning that averages multiple base estimators in an effort to reduce variance [30-32].

We used three ensemble estimators in this work, all based on DT. Random Forest and Extremely randomized tress are bagging and gradient boosting trees are boosting methods selected for this research.

2 DATA SET

The experimental dataset of this study has two input features P and T and Y= Solubility is the single output that is shown in Table 1. Figure 1 demonstrates the distribution of columns of data set [15].

Table 1- the whole dataset

No.	X1=P	X2=T	y
1	12	308	6.75E-05
2	16	308	1.32E-04
3	20	308	1.77E-04
4	24	308	2.23E-04
5	28	308	2.77E-04
6	32	308	3.41E-04
7	36	308	3.93E-04
8	40	308	4.29E-04
9	12	318	3.46E-05
10	16	318	1.13E-04
11	20	318	1.94E-04
12	24	318	2.70E-04
13	28	318	3.85E-04
14	32	318	5.01E-04
15	36	318	5.67E-04
16	40	318	7.07E-04
17	12	328	2.20E-05
18	16	328	7.65E-05
19	20	328	2.23E-04
20	24	328	3.09E-04
21	28	328	4.88E-04
22	32	328	6.60E-04
23	36	328	8.16E-04
24	40	328	8.81E-04
25	12	338	1.35E-05

26	16	338	6.33E-05
27	20	338	2.07E-04
28	24	338	3.73E-04
29	28	338	6.07E-04
30	32	338	8.20E-04
31	36	338	9.01E-04
32	40	338	1.28E-03

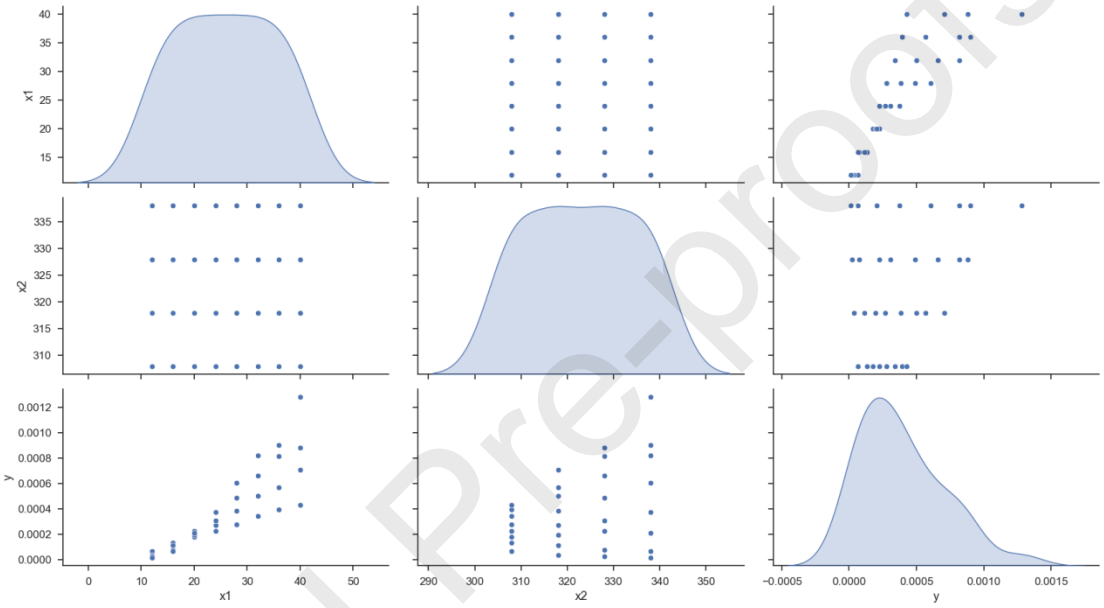

Figure 1- Data Distribution

3 METHODOLOGY

3.1 RANDOM FOREST (RF)

The Random Forest method introduced by Breiman is a form of ensemble methods [33]. In terms of general-purpose learning algorithms, RF is one of the most reliable and efficient. The Random Forest algorithm has been shown to deliver excellent results while utilizing minimal computing power. RF outperforms single-tree algorithms like CART in terms of speed. Compared to more time-consuming and resource-intensive algorithms, this one performs as well as it does [34, 35].

In this regression model, decision tree estimators $h(x,\theta_k)$, k ∈ {1,…,K} take on numerical values according to the random vectors $\{\theta_k\}$. Each piece of data in the training set is randomly selected from a joint distribution of the random vectors *(X,Y)*, where *X* denotes what was observed and *Y* denotes what was expected. The Classification and Regression Trees (CART) [36] algorithm is used to grow individual trees. Listed below is the random forest regression algorithm [37, 38]:

- For *i in {1,...,B}* :
    - Generate a bootstrapped subset Z^* of including *N* data points from training subset.
    - Create a decision T_i with Z^* by iteratively repeat the steps below for every leaf node as late as the node size n_{min} is gained.
        - Choose *m* input variables randomly from *p* input variables.
        - Choose the optimal split point amongst the *m*.
        - Divide the node into multiple Childs.
- Output: the collection of Decision trees $\{T_i\}_1^B$ (Ensemble)
- To estimate an unseen input such as *x*:

$$\bar{f}_{rf}^{B} = \frac{1}{B}\sum_{i=1}^{B} T_i(x)$$

3.2 EXTREMELY RANDOMIZED TREES (ERT)

Extremely randomized trees (ERT) is another Decision Tree based model that develops an ensemble of Decision Trees with no pruning in the traditional top-to-bottom tree growth fashion [39]. ERT, alike other tree-based ensemble models, constructs a group of DTs, but with a heavy focus on randomization to reduce variance without increasing bias too much [40].

The tree growing mechanism introduces randomness by creating split nodes with features and cut-points selected randomly. In this case, the entire learning set is used to build the tree, rather than a bootstrap sample. As a result of the randomization and average of ensembles, DTs' latent variance should be reduced while bias should be avoided by using the original learning sample instead of replicas from bootstraps. Three parameters are important in this regard: the minimum samples for a node-split (n_{min}), the count of randomly selected input features at each node (K). Once the predetermined number of ensemble trees has been generated, a majority vote is used to aggregate their respective predictions, resulting in the final estimated values for the ERT model [41, 42].

3.3 GRADIENT BOOSTING TREES (GBRT)

In the same way that new base estimators learn from older ones, GBRT is another ensemble method. As more weak estimators are added to the model, the error rate decreases. Meanwhile, the GBRT algorithm sets a ratio for base estimators called the learning rate to prevent overfitting. The final prediction from the GBRT model is the sum of the predictions from the weak estimators times the learning rate [43]. The steps involved in the GBRT method are shown in the following algorithm:

Set initial value $F_0(x) = argmin_p \sum_{i-1}^{N} L(y_i, P)$

For $t\ in\ \{1,2,\ldots,M\}$:

1. Determine the negative gradient

$$\overline{y}_i = -\left[\frac{\partial L(y_i, F(x_i))}{\partial F_{x_i}}\right]$$

2. Create a tree model

$$a_t = argmin_{a,\beta} \sum_{i=1}^{N} [\overline{y} - \beta h(x_i, a_t]^2$$

3. Pick a step size for the gradient descent as

$$p_t = argmin_p \sum_{i=1}^{N} L(y_i, Ft-1(x_i) + ph(x_i, a))$$

4. Update the estimation of *F(x)*

$$F_t(x) = F_t - 1(x) + p_t h(x, a_t)$$

Output: $F_t(x)$

4 RESULTS

Standard evaluation criteria were used to fine-tune the hyper-parameters of the three presented models. This section details these requirements.

R^2 (Coefficient of Determination) is a common metric for evaluating the performance of prediction results. It indicates how closely the regression analyses match the observed data's trends [44].

$$R^2 = 1 - \frac{\sum(y_i - x_i)^2}{\sum(x_i - \bar{x}_i)^2}$$

The RMSE is assessed using the sample standard deviation of the separation between the model generated and the actual values. It gives us a way to evaluate how well our predictions are doing [45].

$$RMSE = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (y_i - x_i)^2}$$

Because of its interpretability and scale independence, MAPE is one of the popular metrics. MAPE is a statistical metric for determining how accurate a predictive model is. MAPE discusses the error size as float in the interval of (0 , 1) [46].

$$MAPE = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{x_i - y_i}{x_i}\right|$$

y_i and x_i are model generated and experimental values, respectively. Also, x_i denotes the mean of actual data. n denotes the count of datapoints in the dataset.

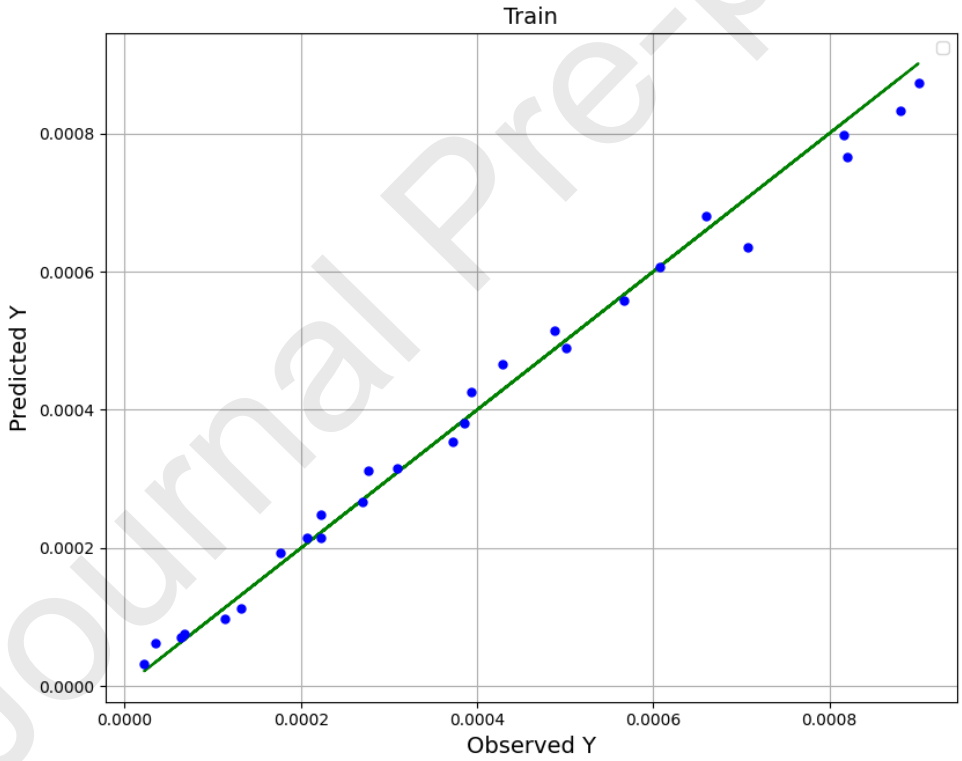

Figure 2- RF training phase

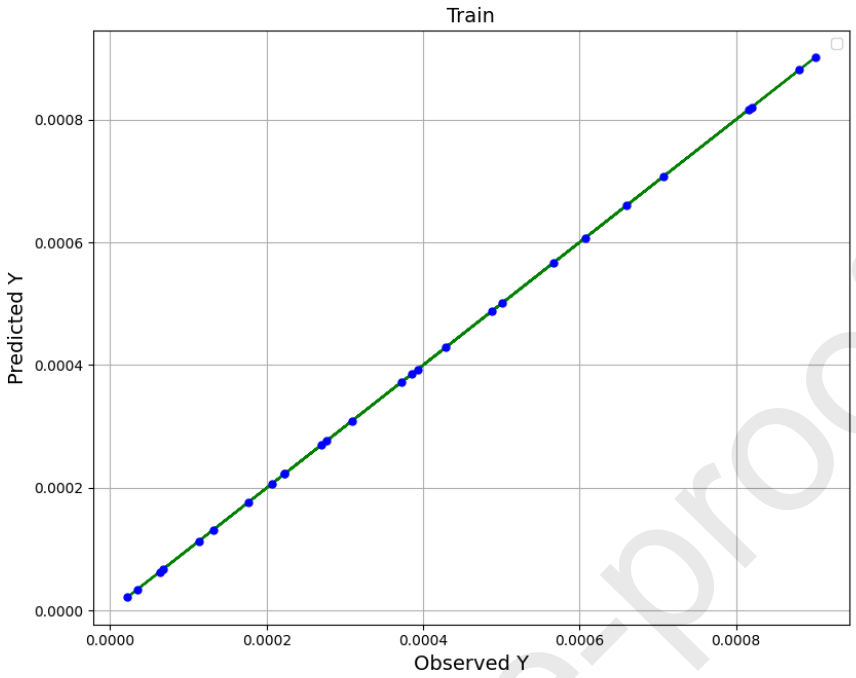

Figure 3- ERT training phase

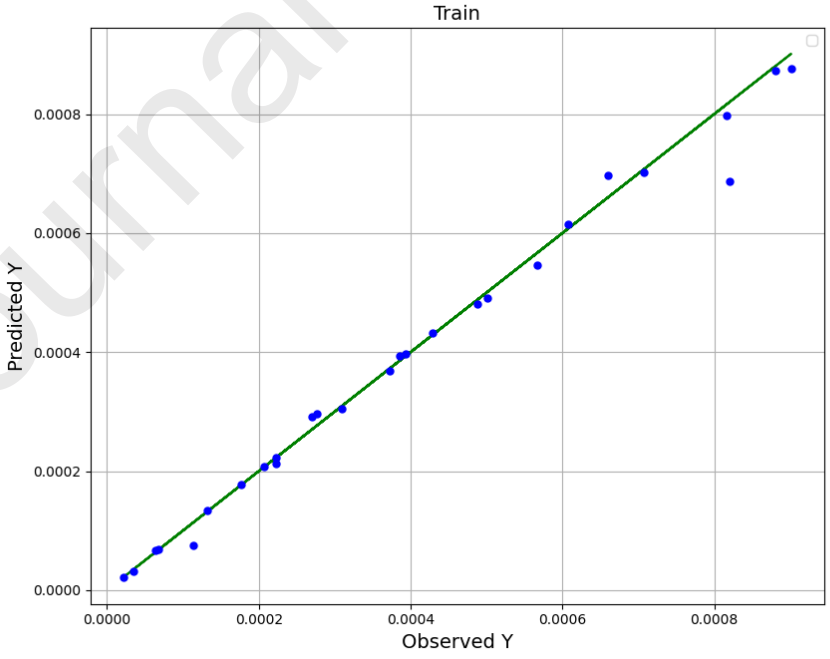

Figure 4- GBRT training phase

In Figure 5, we can see a three-dimensional representation of the inputs being projected onto a single channel of output. Optimal values of X1, X2 confirm this, as they are close to their upper bounds, showing that increasing the value of both features will roughly increase output.

The statistical analysis results of the fitting for three developed models (RF, ERT and GBRT) to prognosticate the busulfan solubility is displayed in Table 2. Evidently, all models have acceptable precision to predict the experimental data. Compared with other predictive models, GBRT model shows greater model validation due to its high R-Squared and RMSE values (0.987 and 1.03E-04).

Table 2- The Performance of final optimized models

Models	R-Squared	RMSE	MAPE
RF	0.988	1.80E-04	4.51E-01
ERT	0.945	1.72E-04	4.87E-01
GBRT	0.987	1.03E-04	3.62E-01

Figures 5, 6 and 7 respectively demonstrate the three-dimensional plot for evaluating the simultaneous effect of X1 (pressure) and X2 (temperature) on the Y (solubility) and the two-dimensional evaluation of temperature and pressure on the busulfan solubility, respectively. Analysis of the figures corroborates that despite the positive impact of pressure on the solubility amounts of busulfan for all evaluated isotherms, its influence improves by increasing the temperature. This reason can be justified due to this fact that the increment of temperature eventuates in a significant reduction in the molecular distance between the CO_2 molecules and modifying the system towards the liquid state. Shifting the system towards the liquid state automatically increases the density of the system, which ultimately causes an enhancement in the solubilizing power of CO_2. Therefore, increment in the solubilizing power of CO_2 eventuates in

improving the dissolution of busulfan in $ScCO_2$. Additionally, stricter evaluation of the predicted busulfan solubility data for all the presented isotherms demonstrate an abnormal manner at the temperature around 20 MPa where the impact of temperature became reversed. At the pressure lower than this point, increasing the temperature reduces the busulfan solubility because of density reduction, while for the pressures more than 20 MPa, the influence of temperature returns to an enhancing trend. Therefore, an important parameter to determine the value of busulfan solubility in $ScCO_2$ is cross-over pressure at the pressure of almost 20 MPa where the temperature influence on the busulfan solubility reverses. It can be concluded form the outcomes that temperature has a paradoxical impact on the busulfan solubility in $ScCO_2$ system. At the pressures lower than 20 MPa, increasing the temperature decreases the busulfan solubility. At these pressures, increase in the temperature reduces the density parameter despite increasing the sublimation pressure. At these pressures, the effect of density decrement is more than increasing the sublimation pressure and thus, increase in the temperature declines the busulfan solubility. At the pressures higher than cross-over pressure (20MPa), the impact of pressure sublimation overcomes the effect of density. Hence, increase in the temperature at these pressures increases the solubility value of busulfan in the $ScCO_2$ system [15]. The optimized values for pressure and temperature to obtain the highest solubility of busulfan is presented in Table 3.

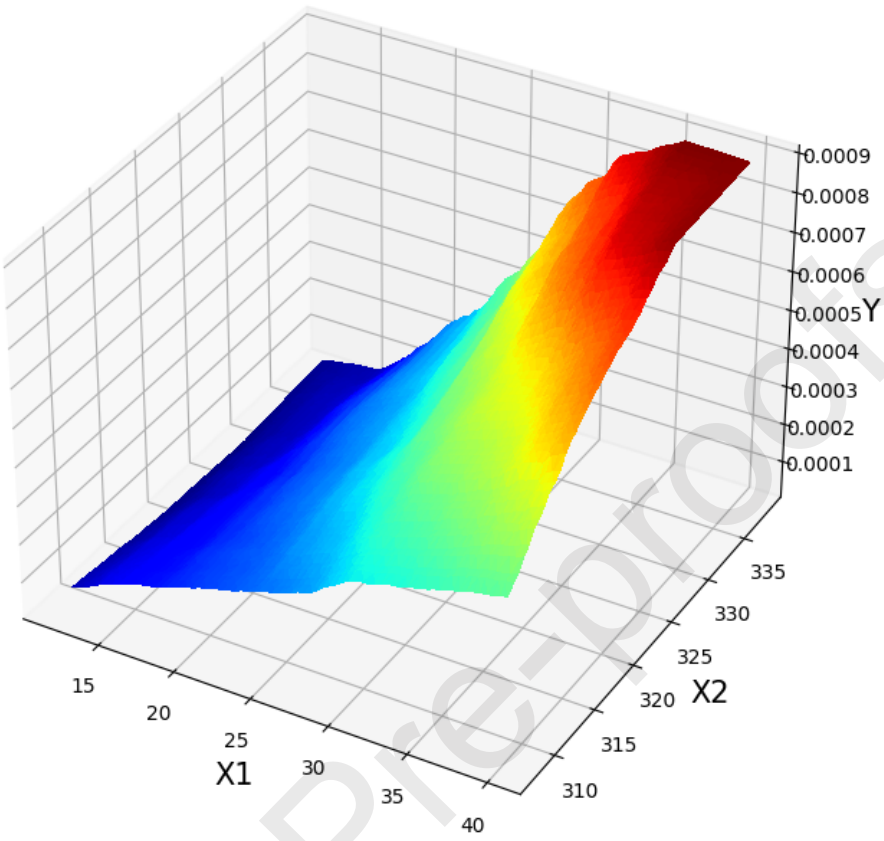

Figure 5- the 3D inputs/outputs projection (GBRT Model)

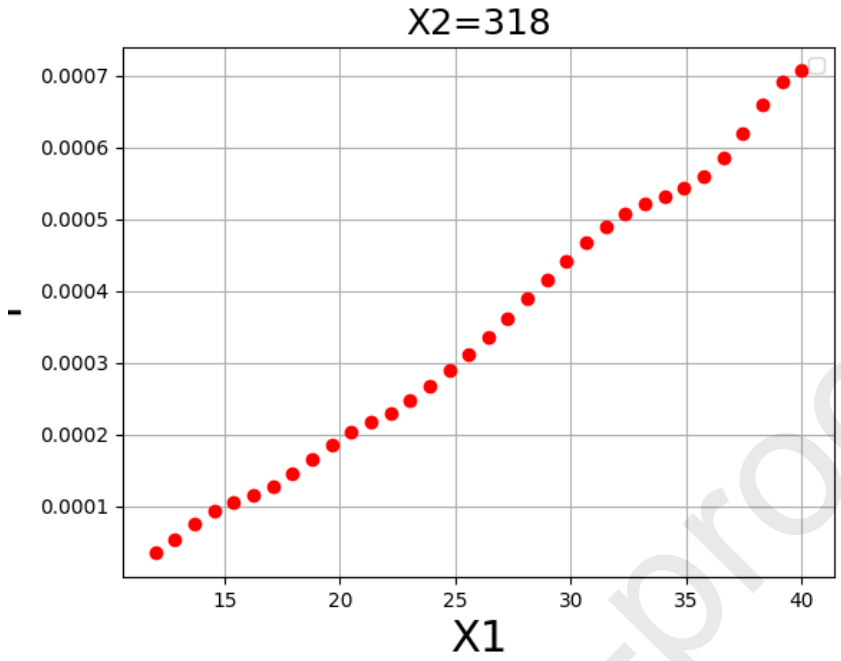

Figure 6- The 2D trends for X1

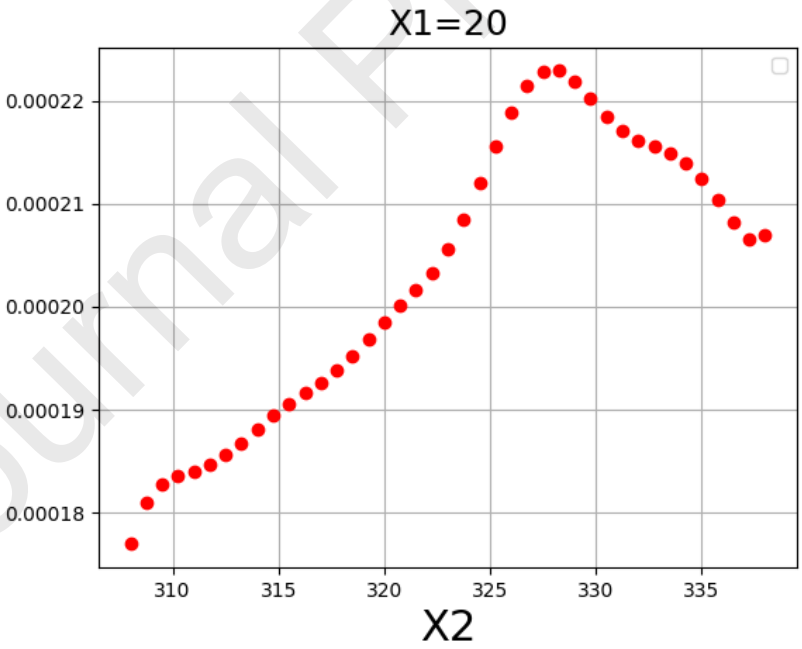

Figure 7- The 2D trends for X2

Table 3- final optimal values of the parameters for maximum solubility

X1=P	X2=T	Y
38.3	333.1	1.36E-03

5 CONCLUSION

In this paper, the optimum value of busulfan solubility in supercritical carbon dioxide ($ScCO_2$) system was aimed to be predicted. For this purpose, three predictive novel models for busulfan based on artificial intelligence and machine learning approach were developed and trained applying the experimental data. This study used different decision tree-based ensemble estimators: RF, ERT, and GBRT. Following the implementation and tuning of these ensemble models' hyper parameters, their overall performance have been evaluated through a variety of criteria. Although all three models show an R-squared score more than 0.9, the RMSE error rates for the RF, ERT, and GBRT models are 1.80E-04, 1.72E-04, and 1.03E-04, respectively, for the RF, ERT, and GBRT models. In addition, MAPE metrics of 4.51E-01, 4.87E-01, and 3.62E-01 errors were obtained for the RF, ERT, and GBRT estimators, respectively, according to the results. GBRT has been selected as the best model due to the less rate of RMSE and MAPE. The optimal solubility amount, expressed by the vector (x1=38.3, x2=333.1, Y=1.36E-03), has also been analyzed.

• Data Availability Statement:

All data are available within the published paper.

• Supplementary information:

No supplementary

• **Ethical approval:**

Not applicable

Author contribution:

Yaoyang Liu: conception, experimental design, carrying out measurements and manuscript composition, writing

Drai Ahmed Smait: writing, investigation, experimental design, carrying out measurements, modelling and analysis

Abbas Yaseen Naser: resources, experimental design, carrying out measurements, writing, analysis

Farag M. A. Altalbawy: investigtaion, experimental design, carrying out measurements and writing, formal analysis

Hala Bahri: writing and editing, investigation, validation

Ali Abdul Kadhim Ruhaima: writing and editing, investigation, validation, resources

Thura Zayad Fathallah: writing and editing, investigation, validation, resources, analysis

Salema K. Hadrawi: writing and editing, investigation, resources, analysis

Refad E. Alsaddon: writing and editing, investigation, resources, analysis

Abdullah Alshetaili: writing and editing, investigation, resources, analysis

Amal M. Alsubaiyel: writing and editing, investigation, validation, resources, analysis, supervision

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Highlight:

1- Solubility enhancement through advanced artificial intelligence model
2- Applying different modeless of machine learning such as Random Forest, Extremely Random Trees, and Gradient Boosting Trees
3- The GBRT has shown the less error rate and can be used as the best model

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:

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Yaoyang Liu: conception, experimental design, carrying out measurements and manuscript composition, writing

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