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Development of Novel Machine Learning to Optimize the Solubility of Azathioprine as Anticancer Drug in Supercritical Carbon Dioxide

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ABSTRACT

Supercritical carbon dioxide (Sc-CO_2) has thus been proposed as an appropriate solvent for diluting the pharmaceuticals to increase particle size. The use of supercritical fluids (SCFs) in various industrial applications, such as extraction, chromatography, and particle engineering, has attracted considerable interest. Recognizing the solubility behavior of various drugs is an essential step in the pharmaceutical industry's pursuit of the most effective supercritical approach. In this work, four models were used to predict the solubility of Azathioprine in supercritical carbon dioxide, including Ridge regression (RR), Huber regression (HR), Random forest (RF), and Gaussian process regression (GPR). The R-squared scores of all four models are 0.974, 0.6518, 0.966, and 1.0 for Ridge regression (RR), Huber regression (HR), Random forest (RF), and Gaussian process regression (GPR) models, respectively. The RMSE error rates of 2.843 $\times 10^{-13}$, 7.036 $\times 10^{-12}$, 5.673 $\times 10^{-13}$, and 1.054 $\times 10^{-30}$ for the RR, HR, RF, and GPR models, respectively. MAE metrics of 1.205 $\times 10^{-6}$, 2.151 $\times 10^{-6}$, 5.997 $\times 10^{-7}$ and 9.419 $\times 10^{-16}$ errors were also found in the RR, HR, RF, and GPR models, respectively. It was found that Ridge regression (RR), Random forest (RF), and Gaussian process regression (GPR) models can be used to predict any compound's solubility in supercritical carbon dioxide.

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1. INTRODUCTION

In the field of pharmaceutical manufacturing, invention of new medications and innovation of favorable therapeutic approachesare the most significant obstacles [1]. An essential step in the pharmaceutical industry's quest for the most effective supercritical approach is the recognition of the solubility behavior of various therapeutic drugs [2]. In fact, the development of methods of particle engineering that are suitableto regulate particle size is of the utmost importance due to the significance of aspects to take into account include solubility and bioavailability [3][4][5][6][7][8]. Sc-CO_2 is well-liked because of features such as low price, low critical pressure, high diffusivity, low viscosity, and high inertness or toxicity. Sc-CO_2 has thus been proposed as a suitable solvent for increasing the particle size of pharmaceuticals. The use of supercritical fluids (SCFs) in numerous applications within the industrial sector, such as chromatography, extractions, and particle engineering, has attracted considerable interest [9], [10][11]–[16]. There have been a great deal of scientific investigations, both experimental and theoretical, carried out to comprehend the properties of Sc-CO_2 systems, particularly the interactions between individual molecules in supercritical fluid solutions [17][3], [10], [18]. Additionally, advancements have been made in the use of Sc-CO_2 as an alternative solvent system for the processing of materials [19], [20].

Azathioprine is a crystalline solid mercaptopurine derivative with the chemical name 6-[(1-methyl-4-nitro-1H-imidazol-5-yl)thio]-9H-purine. It's a drug used mainly to stop the body from rejecting a transplant by

lowering the immune system's T-lymphocyte borne delayed immune responses [21][22][23]. Rheumatoid arthritis, organ transplantation, Crohn's disease, chronic active hepatitis, systemic lupus erythematosus, polyarteritis nodosa, and other autoimmune disorders are all treated with azathioprine [22][23]. Additionally, Azathioprine is authorized as a medicine for the treatment of particular forms of cancer and inflammatory bowel diseases [24], [25]. Only a very small amount of azathioprine can be dissolved in water and other aqueous solutions, but it is highly soluble in organic solvents such as Dimethyl sulfoxide [21].

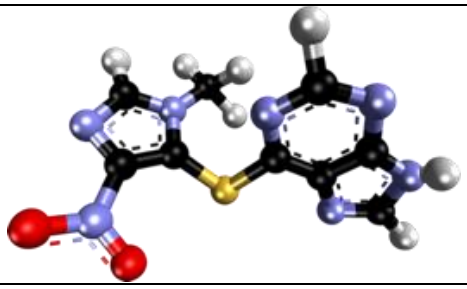
Recently, machine learning (ML) method has become a powerful tool in the scientific disciplines [26]–[34]. In the present work, four models were used to predict the solubility of Azathioprine in supercritical carbon dioxide, including Ridge regression (RR), Huber regression (HR), Random forest (RF), and Gaussian process regression (GPR). Moreover, R^2, RMSE, and MAE were utilized to evaluate the models used. As mentioned previously, the novelty of this study is the application of machine learning to four distinct new models in order to optimize their configurations (hyperparameters) to improve and predict how well a drug will dissolve in water. Thus, the pharmaceutical industry benefits from research, new drugs are developed, and promising therapeutic approaches are advanced.

2. METHODS

2.1. Data Sheet

In this study, 32 data points of solubility on Azathioprine in Sc-CO_2 were used [35]. The chemical structure, formula, molecular weight, and melting temperature of Azathioprine are presented in Table 1. Fig. 1 shows the research diagrams of this study. Y is the solubility output, which has two inputs (temperature = X_1, and pressure = X_2), and it is displayed in Table 2.

Table 1. Azathioprine's molecular form, melting point, and other physical characteristics

Solute	Chemical Form	Structure	Molecular Weight (g/mol)	T_m (K)
Azathioprine	$C_9H_7N_7O_2S$		277.263	526 [36]

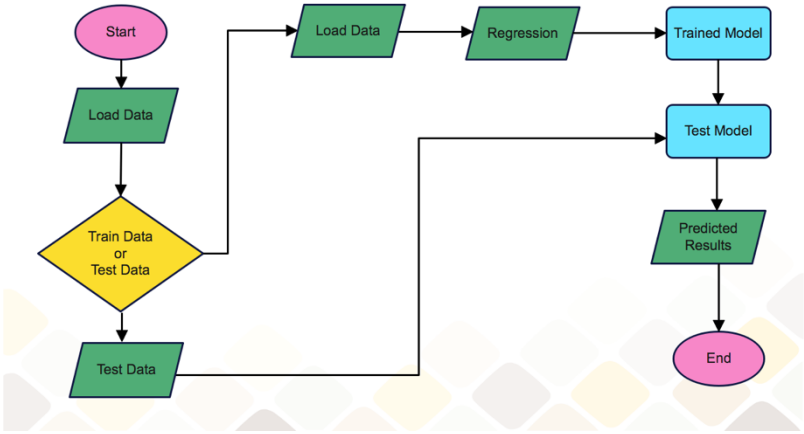


Fig. 1. Research diagrams of Azathioprine predictive solubility in Sc-CO_2

2.2. Ridge Regression (RR)

Ridge regression is a well-known parameter estimation technique that can be applied in multiple linear regression in order to address the frequent collinearity problem. The following is the standard model for performing multiple linear regressions.

$$y = \boldsymbol{x}\beta + \varepsilon, \tag{1}$$

where $E(\varepsilon) = 0$, $E(\varepsilon\varepsilon') = \sigma^2 I_n$, and x is $(n \times p)$ and by bold symbols. The matrix I_n is the identity matrix with dimension n by n [37].

Table 2. Data sheet used in this work

No.	Temperature (K) (X_1)	Pressure (MPa) (X_2)	Y (10^6)
1	308	12	5.1
2	308	15	6.4
3	308	18	6.7
4	308	21	7.4
5	308	24	8.1
6	308	27	8.6
7	318	12	4.0
8	318	15	7.1
9	318	18	7.7
10	318	21	9.4
11	318	24	11.2
12	318	27	12.5
13	328	12	3.4
14	328	15	8.1
15	328	18	9.6
16	328	21	11.9
17	328	24	13.4
18	328	27	15.6
19	338	12	2.7
20	338	15	9.0
21	338	18	12.0
22	338	21	15.0
23	338	24	17.1
24	338	27	18.3
25	308	12	5.1
26	308	15	6.4
27	308	18	6.7
28	308	21	7.4
29	308	24	8.1
30	308	27	8.6
31	318	12	4.0
32	318	15	7.1

2.3. Huber Regression (HR)

Huber regression is an outlier-tolerant regression technique. It is to use a different loss function as opposed to the standard least-squares formula [38]. Definition of the Huber loss as

$$l_\tau(x) = \begin{cases} x^2/2, & \text{if} |x| \leq \tau, \\ \tau|x| - x^2/2, & \text{if} |x| > \tau, \end{cases} \tag{2}$$

where $\tau > 0$ is the robustification parameter that achieves a satisfactory compromise between bias and robustness. $l_\tau(x)$ is the quadratic form of the loss function of x, and when x exceeds some threshold, the graph linearizes τ in magnitude. The τ presides over the blending of quadraticand l_τ losses, which can be considered to be the two polar opposites of the Huber loss with $\tau = \infty$ and $\tau \to 0$, respectively.

2.4. Random Forest (RF)

The steps of bootstrapping and bagging need to be completed before a regression problem can be solved using the random forest (RF) method. A random subset of the training dataset is used in the first step of the process, which generates a set of decision trees based on the growth of each individual tree. After achieving the ensemble, the second stage disassembles the nodes of the decision tree by selecting random subsets of training samples during the initial bagging procedure.The decision is made by selecting the optimal subdivision and its value. The random forest (RF) model can be seen as a collection of decision trees, $G(x, \theta_r)$ is the G^{th} predicting tree, and θ provides a distribution vector that is independent and uniform and that was assigned

before the tree grew [39]. The Breiman (3) is used to construct the forest by combining and average. The RF model is comparable to a collection of decision trees, with G at the cantering the whole trees [39].

$$G(x, \theta_1, \dots \dots \theta_r) = \frac{1}{R}\sum_{r=1}^{R} G(x, \theta_r) \tag{3}$$

2.5. Gaussian Process Regression (GPR)

GPR is a type of nonlinear regression that doesn't use parametric models but uses a probabilistic regression framework [40].

The result variable y in this method can be presented as follows:

$$y = f\big(x(k)\big) + \varepsilon \tag{4}$$

Here (x) is a calculation of data results, f represents the lack of clarity regarding the functional dependence, and ε refers to Gaussian noise (σ_n^2) is the variation that is present in Gaussian noise. Mean and standard deviation are both Gaussian $p\ (y_*|X, y, x_*)$ $c$an be calculated by the following formulas [41].

$$\hat{y}_* = m(x_*) + k_*^T (K + \sigma_n^2 I)^{-1}\big(y - m(x_*)\big), \tag{5}$$

$$\sigma_{y_*}^2 = k_* + \sigma_n^2 - k_*^T (K + \sigma_n^2 I)^{-1} k_*, \tag{6}$$

Here *K* is matrix covariance by using the elements $k_{i,j} = cov\ \big(xi, x_j\big)$, vector *k* as follows

$$[k_*]i = cov\ (xi, x_*)\ and\ k_* = \ cov\ (x_*, x_*) \tag{7}$$

To make reliable predictions, the dataset is used to figure out the mean and covariance function attributes. Because of how the predictive possible distribution functions, the attributes are shown as hyper attributes. The hyper-attributes are made by maximizing $\log p(y|X)$.

$$\log p(y|X) = -\frac{1}{2} y^T (K + \sigma_n^2 I)^{-1} y - \frac{1}{2}\log\left(|K + \sigma_n^2 I|\right) - \frac{n}{2}\log\left(2\pi\right) \tag{8}$$

Here *n* is the quantity of training subset.

2.6. Model evaluation metrics

To evaluate the models selected performance, we used three metrics: the root mean square error, also known as RMSE, the mean absolute error, also known as MAE, and the coefficient of determination, R2, are calculated as follows:

$$R^2 = 1 - \frac{\sum_i (\hat{y}_i - y_i)^2}{\sum_i (y_i - \mu)^2} \tag{9}$$

$$MAE = \frac{1}{n}\sum_{i=1}^{n} |\hat{y}_i - y_i| \tag{10}$$

$$RMSE = \left[\frac{1}{n}\sum_{i=1}^{n} (\hat{y}_i - y_i)^2\right]^{1/2} \tag{11}$$

where y_i is the measured solubility, $\hat{y}_i$ is the predicted solubility, and n is the quantity of data.

3. RESULTS AND DISCUSSION

In this study, 32 data points on Azathioprine solubility in Sc-CO_2 were used. Table 1 presents the chemical structure, formula, molecular weight, and melting temperature of Azathioprine. *Y* is the solubility output, which has two input (temperature = X_1, and pressure = X_2) and it is displayed in Table 2. Scikit-learn [42] is a widely used Python package for conventional machine learning algorithms on which we train all of the models.

Fig. 2 shows the comparison of predicted solubility and real measured of Azathioprine using the Ridge Regression (RR). Fig. 3 presents the comparison of predicted solubility and real measured of Azathioprine

using the Huber Regression (HR). Moreover, the comparison of predicted solubility and real measured of Azathioprine using the Random Forest (RF) are presented in Fig. 4. Additionally, Fig. 5 shows the comparison of predicted solubility and real measured of Azathioprine using the Gaussian Process (GPR). Table 3 summarized performance of Ridge regression (RR), Huber regression (HR), Random forest (RF), and Gaussian process regression (GPR) models for the prediction of Azathioprine solubility in Sc-CO_2, respectively. It was found that the Gaussian Process (GPR) model prediction accuracy was better than three other developed regression machines as presented in Table 3 and Fig. 2- Fig. 5. Fig. 6 displays a 3D results of the input to the single output.

Table 3. Performance of various models (RR, HR, RF, and GPR) for Solubility prediction of Azathioprine in Sc-CO2

Models	R^2	RMSE	MAE
Ridge Regression (RR)	0.974	2.843×10^{-13}	1.205×10^{-6}
Huber Regression (HR)	0.6518	7.036×10^{-12}	2.151×10^{-6}
Random Forest (RF)	0.966	5.673×10^{-13}	5.997×10^{-7}
Gaussian Process (GPR)	1.0	1.054×10^{-30}	9.419×10^{-16}

The Ridge Regression, Huber Regression, Random Forest, and Gaussian Process models each have a RMSE error of 2.843×10^{-13}, 7.036×10^{-12}, 5.673×10^{-13}, and 1.054×10^{-30}, respectively. The MAE values for the RR, HR, RF, and GPR were also found to have 1.205×10^{-6}, 2.151×10^{-6}, $5.997 \times 10^{-7}$and 9.419×10^{-16}, respectively. Additionally, the R^2 values of the RR, HR, RF, and GPR were found 0.974, 0.6518, 0.966, and 1.0, respectively.

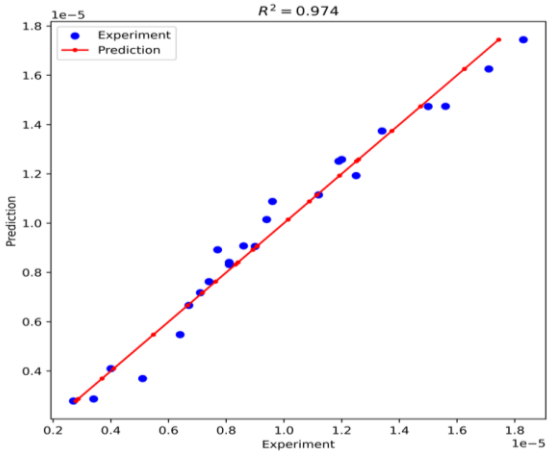


Fig. 2. Ridge Regression plot of predicted solubility of Azathioprine versus experiment

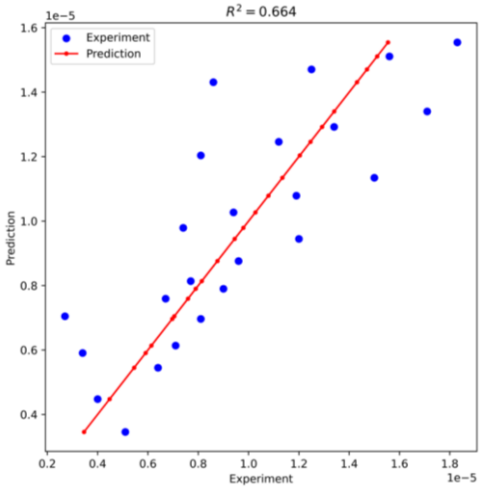


Fig. 3. Huber Regression plot of predicted solubility of Azathioprine versus experiment

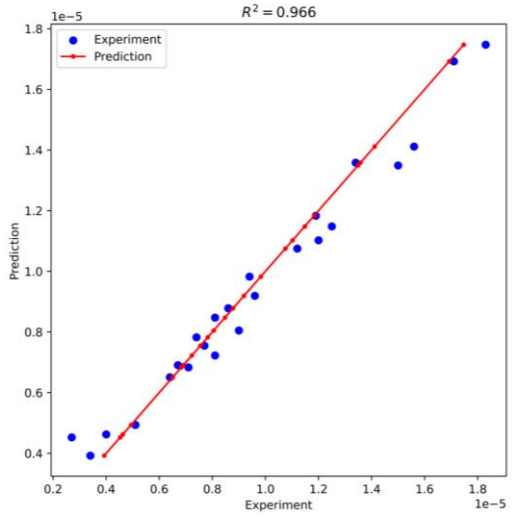


Fig. 4. Random Forest Regression plot of predicted solubility of Azathioprine versus experiment

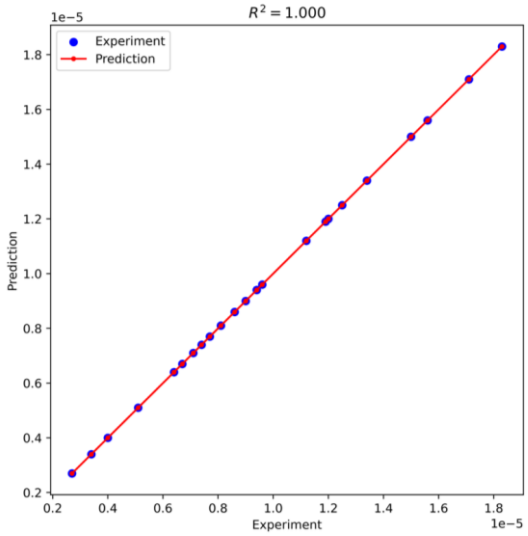


Fig. 5. Gaussian Regression plot of predicted solubility of Azathioprine versus experimental data

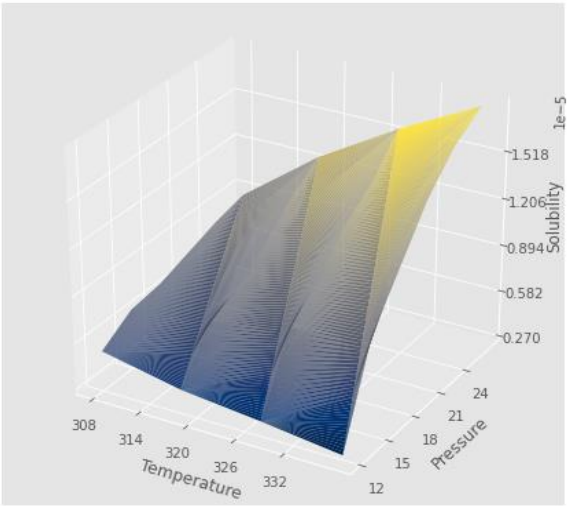


Fig. 6. Gaussian Regression 3D for the solubility of Azathioprine

4. CONCLUSION

In the pharmaceutical industry, optimizing the solubility of various drugs in Sc-CO_2 over a broad temperature and pressure range is a desirable endeavor. The primary objective of this study is to use four machine learning regression algorithms to predict the optimal solubility of anticancer and an immunosuppressive drug in Sc-CO_2. In this regard, four machine learning regression algorithms methods were used in this study to look at the data of solubility of Azathioprine in Sc-CO_2: Ridge regression (RR), Huber regression (HR), Random forest (RF), and Gaussian process regression (GPR). The RR, HR, RF, and GPR models each have a RMSE error rate of 2.843×10^{-13}, 7.036×10^{-12}, 5.673×10^{-13}, and 1.054×10^{-30}. The MAE metrics for the RR, HR, RF, and GPR were also found to have 1.205×10^{-6}, 2.151×10^{-6}, 5.997×10^{-7} and 9.419×10^{-16}. Additionally, the R^2 values of the RR, HR, RF, and GPR were found 0.974, 0.6518, 0.966, and 1.0. It was found that Ridge regression (RR), Random forest (RF), and Gaussian process regression (GPR) models can be used to predict the solubility of any compounds in supercritical carbon dioxide. Finally, this work can be used to optimize and predict the drug solubility. So, research helps the pharmaceutical industry, leads to the creation of new drugs, and moves forward promising therapeutic approaches.

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