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Research Article

Cognitive Enhancement in Mice: a Data Driven Predictive Model for Evaluating Anxiolytic Effects of Diazepam using Supervised Machinelearning Approach

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Abstract:

In the discipline of pharmacology, where it is vital to investigate natural substances for therapeutic benefits, this study investigates the topic of cognitive enhancement in mice with a focus on the anxiolytic characteristics of diazepam. We present a novel approach to predict and assess the anxiolytic potential of diazepam by combining pharmacology with supervised machine learning and making use of the power of modern data analysis techniques.Machine learning is frequently used to build mathematical models that explain or predict data driven based on previous observations. The support vector regressor, Linear Regression, and naïve Bayesian classifier are perhaps among the most popular supervised algorithms. Behavioral pharmacology, which assesses the behavior of experimental subjects after being injected with various chemicals to see if they have positive or negative effects, is an area of possible application. Diazepam (0.5 and 2 mg/kg) was tested in the elevated plus maze (EPM) in the current investigation to determine its effects. Machine learning techniques (SVR Algorithm) was applied. The results showed an effective anxiolytic effect of the 2 mg/kg dose of diazepam when compared with the control group. The findings of the research using conventional statistical methods indicate that progesterone, at a dose of 2 mg/kg, has an impact that is similar to anxiolytics. The variables that provide additional information to distinguish the experimental groups are automatically identified via machine learning.

Introduction

Anxiety is a common experience throughout life. It is a normal and frequent emotion characterised by a sense of unease, trepidation, worry, and self-doubt that may or may not be linked to actual stressors in daily life. Fear is a common response to danger from the outside. Similar to how terror manifests physiologically, anxiety does too. Anxiety is unconscious symptom formation in response to stress. It is commonly seen in population by 4- 6% in chronic form that may disrupt the routine life functions. It mainly involves cognitive, physical and behavioral changes. During real or perceived danger adrenaline rushes, which is a hormone released by the adrenal gland which further triggers anxiety reactions- the

process is called fight and flight response. It may cause other symptoms to develop like increase in blood pressure and nausea. The feeling of anxiety may interrupt daily functions and may take a form of anxiety disorder over a period of time. Anxiety consists of three types: generalized anxiety disorder (GAD), social anxiety disorder (SAD) and panic disorder. Common signs of anxiety include feeling tense, restless, fear or a sense of impending danger, hyperventilating, shaking, sweating, lethargy, sleep apnea, and GI trouble. As a result, anxiolytic medications are still often recommended.

For the clinical treatment of anxiety disorders Benzodiazepines are preferably used, the first patented and marketed drug Diazepam is used. It is fast and long acting BZD, it is approved by FDA for the treatment of anxiety disorders and short term treatment of anxiety symptoms. There are abundant of models for the evaluation of anxiolytic drugs. Behavioral models for anxiety depend on the introduction of a stimulus to create a novel state within the organism. To know the efficacy of the anxiolytic drug, it has to be compared with the control group using animals in a specific model like mirror chamber apparatus, elevated plus maze (EPM), open field apparatus, light-dark model etc. In 1986, the elevated plus maze was developed by Pellow & File and the same was modified by Kulkarni in 1991. The principle of this model is based on the exposure of animals to elevated (open) arm evokes an approach-avoidance conflict that is stronger than that evoked by exposure to an open maze alley. On the basis of behavior of the animal in the given model we can evaluate the anxiolytic drug before and after its administration in animals.

The average body weight of mice for experimental purpose is 18-25 gm. The dose given to experimental animal must be according to their body weight otherwise result affects. The data collected by using elevated plus maze, as it is most simple, accurate and reliable model. Major advantage of this test procedure is- it is fast and less time consuming, no prior training is required, no noxious stimuli (sound, light & current) is required, it is predictable and reliable procedure for studying anxiety response. All of these models are frequently utilized, using a new technology called machine learning (ML) to assess the provided medicine. It is a cutting-edge pharmacy technique that provides precise results in graphical form.

Review of Literature

Marina Padua et al (2021) has presentedthat Diazepam is recommended for the management of recurrent convulsive seizures, sedation and short term treatment for anxiety. Diazepam causes marked depression after binding with GABA to its receptors. Cognitive impairment, lethargy, dependence are commonly seen side effects after administration of the drug. It is used as positive control in behavioral experiments with rodents [6].

Drugs: Diazepam dose (2 mg/kg i.p.), it is suspended in 1% gum acacia or carboxy-methyl-cellulose and inject 1ml/100 g of body weight of mice.

Uma Bhosale et al (2011). As per the study, EEAA (ethanolic extract of AchyranthesAspera) possess anxiolytic and CNS depressant activity. It has also strong analgesic activity and may complement each other, thus, used in painful and excitatory conditions.

Methodology: Exposure of the animalto novel maze alley (arm) induces approach-avoidance conflict which is stronger in open arm compared to closed arm. Mice preferred closed arm and hate to explore open arm due to anxiety. Therefore, mice used to spend

more time in enclosed arm as it is saferin case of control group. The plus maze apparatus comprises two open arms having dimensions (16×5 cm) and two closed arms (16×5×12 cm) for mice, with the entire maze elevated (25 cm) for mice from the ground floor. At the center of EPM, the animals are placed one by one to each facing towards open arm. Noted following parameters: First preference of mouse to open arm, no. of entries in both arms (entry is considered with four paws into the arm) and average time spent by the animal in each arm of maze are recorded. No animal can be used twice and the test should be carried out during a fixed time of the day. The open arm is more fearful for the animal and the number of entries in closed arms reflects the safety comparatively open arms. Anxiolytic drug would be expected to increase the number of entries in open arms. After giving the drug Diazepam, the animal used to spend more time in open arm, hence, shows the potential effect of drug. Freezing, immobility and defecation are also the anxiety related behavior shown by animals. The drug provides valid and reliable measures of anxiety in animals on the basis of behavior and for the evaluation of anxiolytics.

Experimental Output:

As six animals were taken for the experimental purpose, parameters to be tested are- percent preference to open arm, no. of entries in open arm and average time spent by the animal in open arm. The average value of number of entries in open arm is found to be 9.00 in treatment group when compared with control group i.e. 6.833 and the mean value of time spent in open arm was 12.00 in diazepam group comparatively vehicle group i.e. 9.166. This clearly reveals that the drug is highly potent and has strong anxiolytic effect. These results are validated by machine learning tool.Manually experimental values have been noted as shown in Table 1(When no drug is given to animal) and Table2(When drug is given to animal).

Table 1: Dataset:Activity 11 CSV-Control Group

S.No.	Body Weight	Treatment	% Preference to open arm	No. of entries in open arm	Average time spent in open arm (sec)
1	21	Control Group	51	6	8
2	20		46	7	9
3	22		43	6	9
4	21		47	8	10
5	23		48	8	11
6	22		46	6	8

Table 2: Dataset:Activity12 CSV-Drug Treated Group

S. No.	Body weight	Treatment	% Preference to open arm	No. of entries in open arm	Average time spent in open arm
1	20	Treatment Group (Diazepam)	83	9	11
2	22		85	8	12
3	23		89	8	11
4	21		87	10	11
5	20		90	10	13
6	22		91	9	12

Role of Machine Learning

Analyzing the anxiolytic effect of diazepam in mice requires the use of machine learning (ML) techniques. A popular anxiolytic medicine used to treat anxiety disorders and related illnesses is called diazepam. Analyzing the effects of diazepam on mice through trials requires a complicated interplay of many different components. ML methods provide useful tools to improve comprehension of these effects and speed up the evaluation procedure. Machine learning can help in Data Analysis and Feature Extraction,PatternRecognition,Predictive modelling.

Result and Discussion

Dataset Used

Experimental data namely Activity11.csv and Activity12.csv dataset, which consists of one dependent variable (Result) and three independent variables. This study tries to reveal the underlying patterns, relationships, and prediction potential hidden within the information by utilizing modern data analysis techniques. The findings may provide important information for decision-making, predictive modelling, and potential real-world applications by illuminating the complex interplay between various variables.

Supervised Machine Learning –SVR Algorithm

Case 1:

A Dataset "Activity11.csv," having four columns: x11, x22, x33 (independent variables)where x11 is the **Body weight, x22 is the % Preference to open arm,x33 is the No. of entries in open arm**, and result (dependent variable) as **Average time spent in open arm (sec).The Input Values is given as shown in figure 1.**

```
Enter the value:21
Enter the value:51
Enter the value:6
[8.10051023]
[8.]
8
```

Figure 1: Input values given to model to predict the Average time spent in open arm (sec).

The SVR algorithm is applied which produce the same predicted value as shown in the actual value in the dataset as shown in the figure 2.

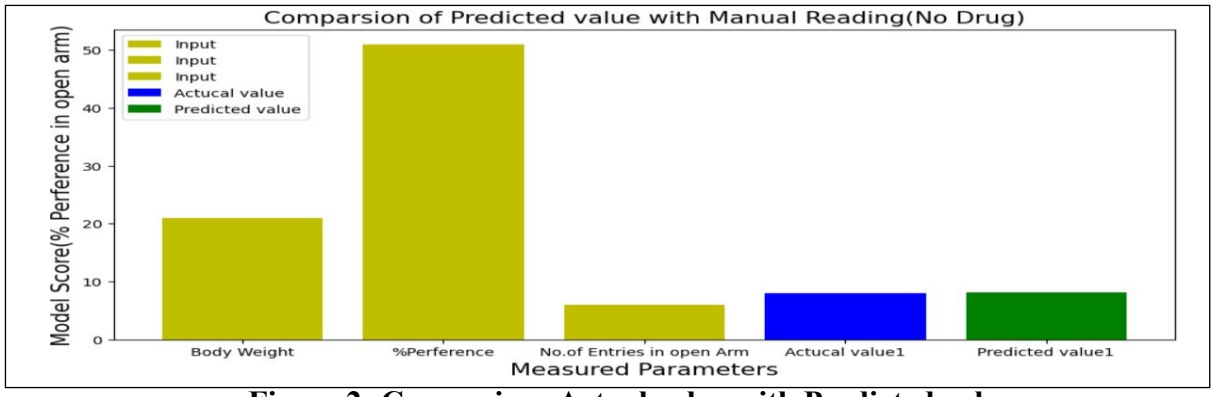

Figure 2: Comparison Actual value with Predicted value

For the same collection of input variables (x11=21, x22=51, x33=6), the SVR method predicted a value of 8 for the dependent variable, and this prediction matches the actual value found in dataset.This shows that the fundamental relationship between the independent variables and the dependent variable has been successfully learned by your SVR model. From the training data, it was able to extrapolate and produce a precise forecast for the input.

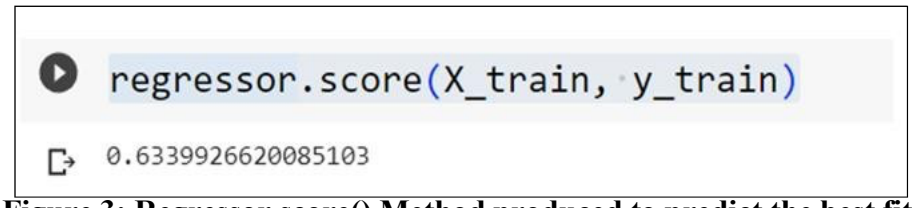

Figure 3: Regressor.score() Method produced to predict the best fit.

The result generated from the regressor.score (X_train, y_train) method as shown in figure 3 has significant significance for the prediction capability of the machine learning (ML) model when evaluating the anxiolytic effect of diazepam in mice. This rating, which is also known as the coefficient of determination or R-squared score, offers information on how well the ML model fits the training data and captures the variability in the dependent variable (anxiolytic effect) explained by the independent variables (model features).The anxiolytic effect (dependent variable) as shown in figure 3 has a score of roughly 0.634 (or 63.4%), which represents the percentage of variation that is accounted for by the independent variables (features) used in the ML model. An R-squared value of roughly 0.6339 indicates that the regression model can use the supplied independent variables (features) to explain roughly 63.39% of the variability in the anxiolytic effect of diazepam in mice. This suggests that the features chosen capture a sizable amount of the underlying patterns in the anxiolytic response, indicating a considerable level of predictive power.

Case 2:

The goal is to forecast values for the dependent variable based on the values of the independent variables using the Support Vector Regression (SVR) algorithm. In regression assignments where the objective is to predict a continuous output variable, SVR is a machine-learning algorithm that is particularly applied.We used the provided dataset to train the SVR method, which meant that the algorithm picked up on the dataset's correlations between the independent variables (x1, x2, and x3) and the dependent variable (result) where x1 is the **Body weight, x2 is the % Preference to open arm,x3 is the No. of entries in open arm**, and result (dependent variable) as **Average time spent in open arm (sec)**. During its training phase, it recognized the patterns and correlations found in the data.

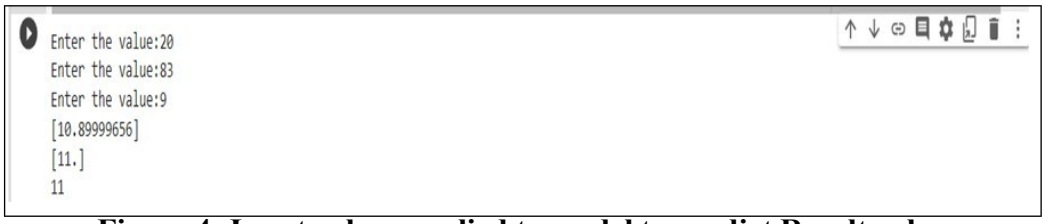

Figure 4: Input values applied to model to predict Result value

When the trained SVR model is applied to input values (x1=20, x2=83, and x3=9) as shown in figure 4, it makes predictions about the associated value of the dependent variable using the learnt patterns. In this instance, the dependent variable's predicted value of 11 from the SVR method matches the actual number found in the dataset.The SVR method has effectively captured and generalized the underlying relationships between the independent variables and the dependent variable if the predicted value matches the actual value. The correlation between the predicted and actual values implies that the SVR model has been successfully trained and is able to predict values accurately for input combinations with similar characteristics. A testimonial to the SVR algorithm's effectiveness in this regression task and its successful use for producing predictions based on the dataset's attributes is its ability to forecast the proper value for the supplied input.

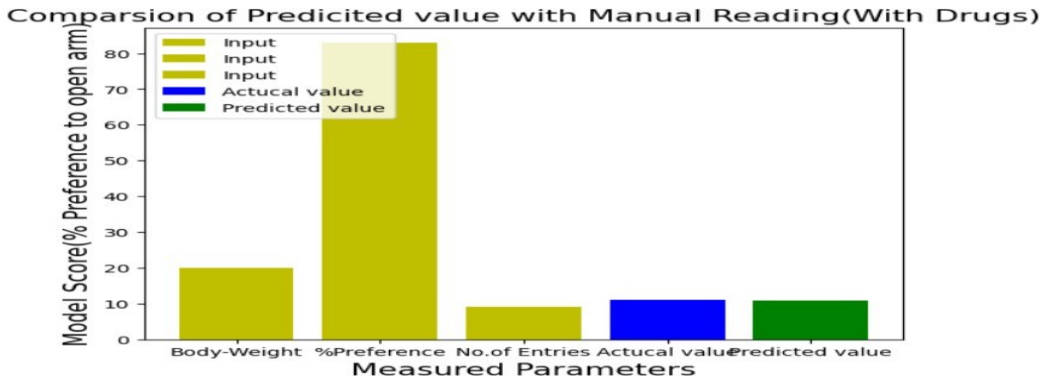

Figure 5: Compare Predicted values using Model with Actual values in the Dataset

In the graphical representation as shown in figure5, the input values (x1=20, x2=83, and x3=9) are given while the axes for each of their respective variables are highlighted in a distinctive mustard colour. The dataset's real value, 11, is represented by the relaxing colour blue. Surprisingly, the forecast made by the SVR algorithm, shown in a dark green hue, matches the real value exactly. The accuracy of the SVR algorithm in this situation is highlighted by this graphic representation. Indicating the algorithm's capacity to generalize and forecast precisely based on the provided input features, both the actual and predicted values converge at the same point on the graph. The SVR model's ability to accurately predict outcomes based on the presented dataset is further increased by the congruence between the predicted and actual values.

The application of ML approaches becomes crucial as researchers set out to determine Diazepam's anxiolytic effects. These methods provide a thorough examination of the diverse data produced by experimental observations and measurements. In this situation, the questioned graph acts as ML approach's effectiveness. The mustard colour effectively represents the inputs (x1, x2, and x3) that are essential for understanding Diazepam's effects. When these inputs are exposed to machine learning (ML) analysis, complicated linkages are revealed that could otherwise escape traditional approaches. The actual value of 11 is presented in calm blue to create a reference point based on empirical facts and indicative of the experimental findings from the study.

Figure 6: Regressor.score() method produced to predict the best fit

The percentage of the dependent variable's variation that can be predicted from the model's independent variables is expressed statistically by the R-squared statistic as shown in figure 6. It shows the degree to which the regression model adequately accounts for the real data points.The regression model can explain around 99.35% of the variance in the target variable (y1_train) using the characteristics in X1_train, according to an R-squared value of roughly 0.9935. This high R-squared value shows that the model is accurately capturing the underlying patterns and relationships in the training data.

Conclusion

Based on the R2 scores derived from two different datasets, the use of machine learning algorithms to assess the anxiolytic impact of diazepam in mice demonstrates various degrees of predictive effectiveness. The activity12.csv dataset's exceptional high R2 score indicates a significant and distinct connection between input features, which probably include diazepam medication and other pertinent parameters, and the measured outcome pertaining to anxiety levels or behavior in mice. On the other hand, the activity11.csv dataset's moderate R2 score shows a discernible but weaker link, presumably as a result of different experimental settings or other variables.In conclusion, applying machine learning algorithm SVR, to predict the anxiolytic effect of diazepam in mice offers significant advantages over manual calculations. It provides a more accurate, data-driven, and automated approach that can handle complex relationships, generalize to new data, and offer quantitative predictions, ultimately enhancing the understanding and application of the anxiolytic effect in a scientific context.

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