Abstract— **The Blood-Brain Barrier (BBB) acts as a protective physiological shield between the bloodstream and brain tissue, blocking harmful substances like toxins, phatogens and certain drugs from entering the brain and potentially causing damage or disrupting its function. Predicting BBB penetration presents a significant challenge due to the complex nature of the BBB's structure and function. Factors such as the size, polarity, and biological activity of drug candidates play a crucial role in determining their ability to cross this barrier. BBB penetration is typically evaluated using conventional in vitro experiments, which encompass a range of methods and artificial membrane penetration tests. While effective, these tests are often expensive, time-consuming, and impractical for large-scale drug screening. Alternatively, computational machine learning approaches offer a more efficient means of assessing BBB penetration. The aim of this study is to predicting BBB penetration for early-stage screening of drug candidates based on their ability to penetrate the BBB. It introduces an innovative approach to predicting BBB penetration using the Cuckoo Search-Ensemble Method. Rigorous testing, which encompassed thorough cross-validation and comparisons with experimental data, provided robust confirmation of the model's reliability. Among the ensemble of models utilized, the Random Forest model notably emerged with the best result, achieving the highest F1-score of 0.914 and accuracy 0.865.**

Keywords*— *Blood-Brain Barrier (BBB), Cuckoo Search, Ensemble Methods, AdaBoost, XGBoost, RandomForest, Feature Selection, Hyperparameter Tuning