THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

Can AI-based Models Serve As An Alternative To Experimental High-throughput Screening?

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Background: Experimental high-throughput screening (HTS) is essential for rapid medical countermeasure discovery but remains a resource-intensive and time-consuming process, typically limited to a few chemical libraries. AI-based approaches offer a promising alternative. However, before AI models can be deployed effectively, their utility must be validated in real-time countermeasure discovery projects. In this study, we evaluated such models, with a focus on muscarinic receptor M1, a critical target for developing nerve agent countermeasures.

Objective: Develop an AI-based model for muscarinic receptor M1 and evaluate its performance against experimental HTS.

Methods: We collected publicly available data for muscarinic receptor M1 and employed novel approaches, such as generative modeling, to address the data imbalance problem associated with these datasets. We trained deep neural network models to predict whether chemicals would potentially interact with M1 and finally compared the models' ability to predict the independent experimental HTS data of 365,000 chemicals against M1.

Results: We developed deep neural network models based on public M1 activity data. Our initial results based on an imbalanced dataset were poor, with a very low Matthews correlation coefficient (MCC). To counter this problem, we examined multiple oversampling strategies on the minority inactive class, including using recurrent neural networks to generate artificial compounds from our existing dataset. This improved model performance, especially when we tested it on HTS data, although overall prediction was still poor. We then examined altering the activity boundary of actives/inactives to create a balanced dataset, and this improved performance, with a final model MCC of 0.27.

Conclusion: We successfully employed AI techniques to identify new muscarinic receptor antagonists, providing a faster alternative to traditional HTS. We believe that further optimization of the top hits from the HTS could provide newer strategies to counter nerve agent exposures. Our work also highlights some challenges and possible solutions in utilizing AI models as an alternative to experimental HTS.