A002 · BBB-Nuke: Transport-Aware Prediction of Blood-Brain Barrier Penetration in Small Molecules

Presenter: Noah Abasciano — Attention Labs

Authors: Noah Abasciano, Hamid Hadipour, Abhishek Poddar, Jack Rudrum, Temitope Sobodu

Session: Day 2 · Fri Oct 2, 2026 · 2:15–4:15 PM

Predicting blood-brain barrier (BBB) penetration remains a central challenge in CNS drug discovery. Existing computational models rely on physicochemical descriptors and are blind to active transport biology; the efflux pumps and carrier proteins that dominate drug exclusion at the BBB in vivo. We present BBB-Nuke, a modular prediction pipeline that integrates physicochemical scoring with explicit efflux transporter substrate modeling. The system computes ten molecular descriptors, predicts ionization state via a graph convolutional network, scores CNS-MPO desirability, and estimates substrate probability for seven efflux transporters (P-gp/MDR1, BCRP/ABCG2, MRP1, MRP2, MRP4, MATE1, OAT3) using Random Forest classifiers trained on curated ChEMBL bioactivity data. A gradient-boosted classifier trained on 67 features; ten physicochemical, seven efflux transporter probabilities, and fifty fingerprint-derived principal components ;achieves an area under the receiver operating characteristic curve (AUROC) of 0.933 +/- 0.006 under five-fold cross-validation on 9,262 labeled compounds, and 0.810 on a fully held-out benchmark of 470 clinically validated compounds. In head-to-head comparisons, BBB-Nuke outperforms CNS-MPO, LightBBB, ADMETlab 2.0, and BBB-Score on both cross-validation and external test sets. We apply the pipeline to screen over one billion commercially available compounds from the Enamine REAL library and PubChem, identifying enriched regions of BBB-penetrant chemical space and characterizing the structural features that distinguish permeable from excluded molecules. BBB-Nuke is freely available as a Python package, REST API, and Model Context Protocol server.

BBB-Nuke: Transport-Aware Prediction of Blood-Brain Barrier Penetration in Small Molecules

Noah Abasciano[1], Hamid Hadipour[1], Abhishek Poddar[2,3], Jack Rudrum[1,4], and Temitope Sobodu[1,*]
[1]Attention Labs, Boston, MA, USA
[2]Department of Molecular Biology, Massachusetts General Hospital, Boston, MA, USA
[3]Department of Genetics, Harvard Medical School, Boston, MA, USA
[4]Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA
*Correspondence: temi@attentionlab.ai

Abstract

Predicting blood-brain barrier (BBB) penetration remains a central challenge in CNS drug discovery. Existing computational models rely on physicochemical descriptors and are blind to active transport biology, including the efflux pumps and carrier proteins that dominate drug exclusion at the BBB in vivo. We present BBB-Nuke, a modular prediction pipeline that integrates physicochemical scoring with explicit efflux transporter substrate modeling. The system computes ten molecular descriptors, predicts ionization state via a graph convolutional network, scores CNS-MPO desirability, and estimates substrate probability for seven efflux transporters (P-gp/MDR1, BCRP/ABCG2, MRP1, MRP2, MRP4, MATE1, and OAT3) using Random Forest classifiers trained on curated ChEMBL bioactivity data.

A gradient-boosted classifier trained on 67 features consisting of ten physicochemical descriptors, seven efflux transporter probabilities, and fifty fingerprint-derived principal components achieves an area under the receiver operating characteristic curve (AUROC) of 0.933 +/- 0.006 under five-fold cross-validation on 9,262 labeled compounds, and 0.810 on a fully held-out benchmark of 470 clinically validated compounds. In head-to-head comparisons, BBB-Nuke outperforms CNS-MPO, LightBBB, ADMETlab 2.0, and BBB-Score on both cross-validation and external test sets. We apply the pipeline to screen over one billion commercially available compounds from the Enamine REAL library and PubChem, identifying enriched regions of BBB-penetrant chemical space and characterizing the structural features that distinguish permeable from excluded molecules. BBB-Nuke is freely available as a Python package, REST API, and Model Context Protocol server.