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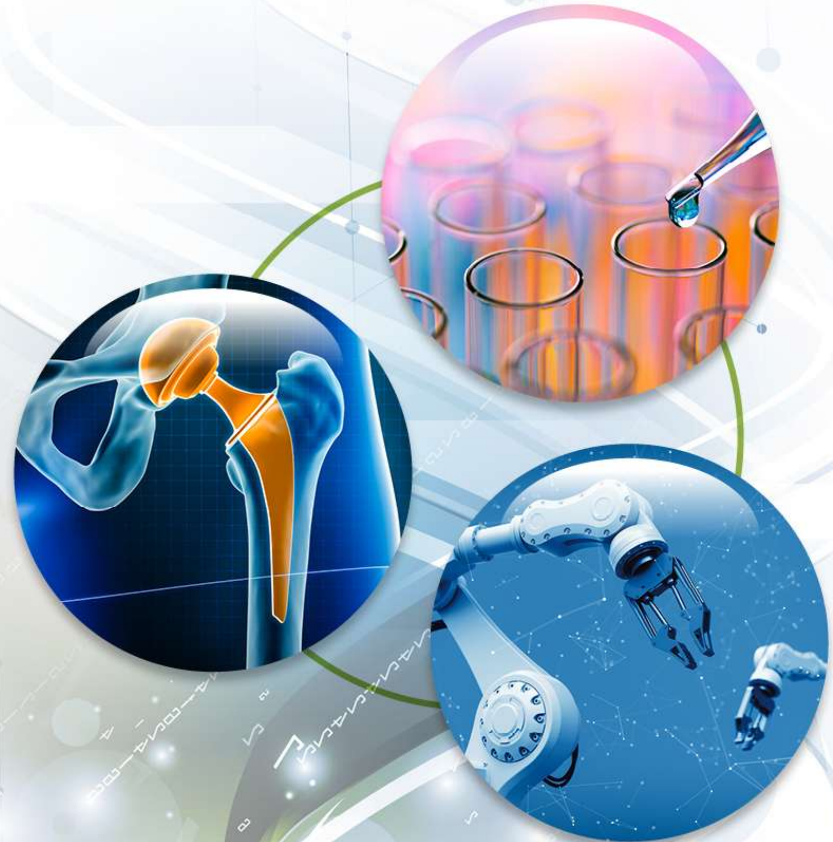

De Novo CNS Drug Generation via Multimodal AI and SHAP-Guided Reinforcement Learning

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Introduction & Motivation

Lab's Interests

Reinforcement Learning

Lab's Ongoing Projects

Blood-Brain Barrier Permeability (BBBP) Classifier

Reading!

Central Nervous System (CNS) Drug Development

Model Interpretability

Generative AI

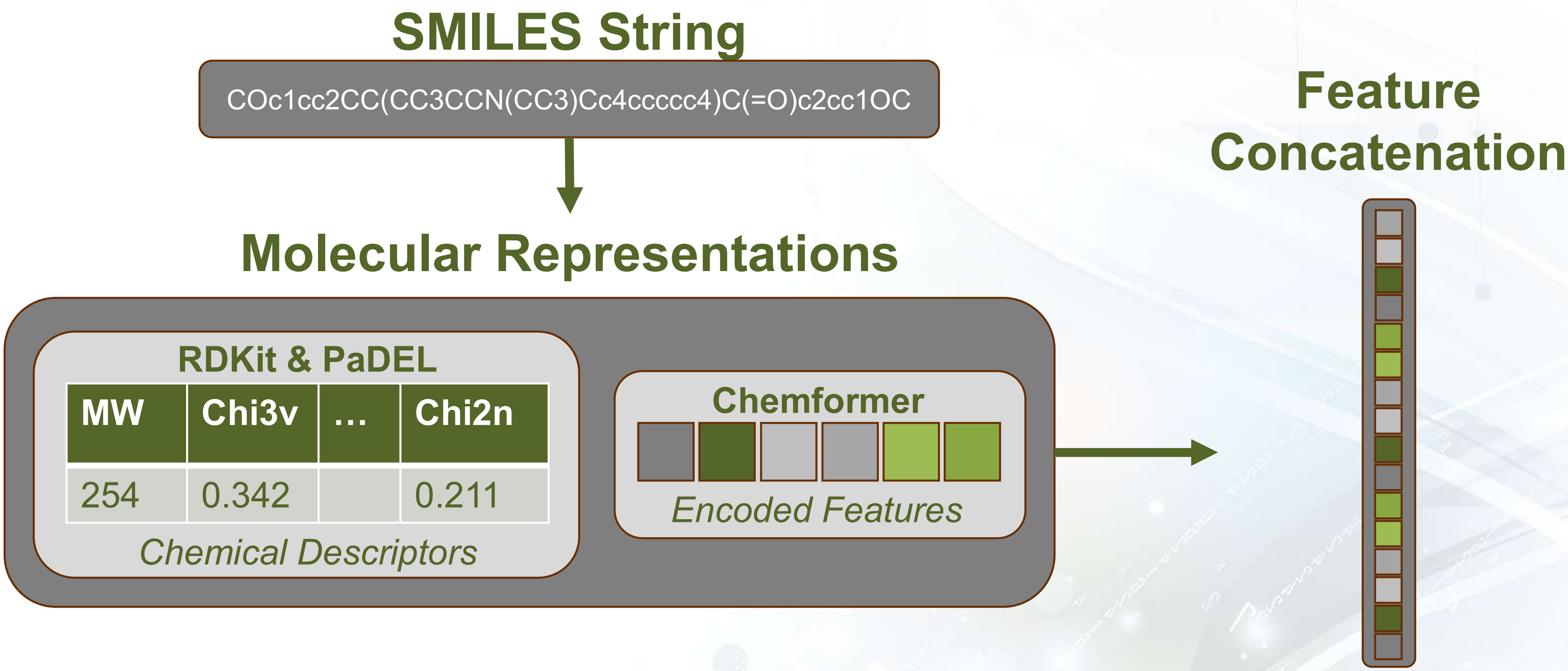
Objectives

- **Generate CNS Optimized SMILES Strings**
  1. Develop Multimodal Classifiers for Key CNS Properties
     - Conduct SHAP Analysis
  2. Design a RL Curriculum
  3. Finetune SMILES Generator

Model Setup

- **Classifiers:** LightGBM
  - **Modals:** PaDEL, RDKit, and Chemformer
- **Generator:** MolGPT (GPT-2 on ZINC-15)
- **Fine Tuning:** Policy Gradient RL
- **Goal:** Valid, Novel, and CNS-Optimized SMILES

I. Feature Extraction

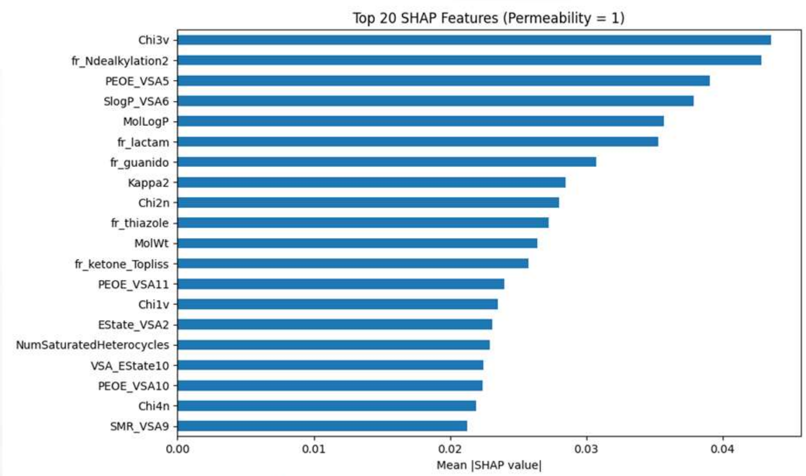


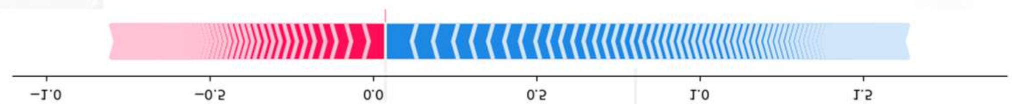
II. Feature Analysis

LightGBM Classifiers

1. Permeability
2. Neuronal cytotoxicity
3. Microelectrode Array–Based Neural Activity
4. Mammalian neurotoxicity

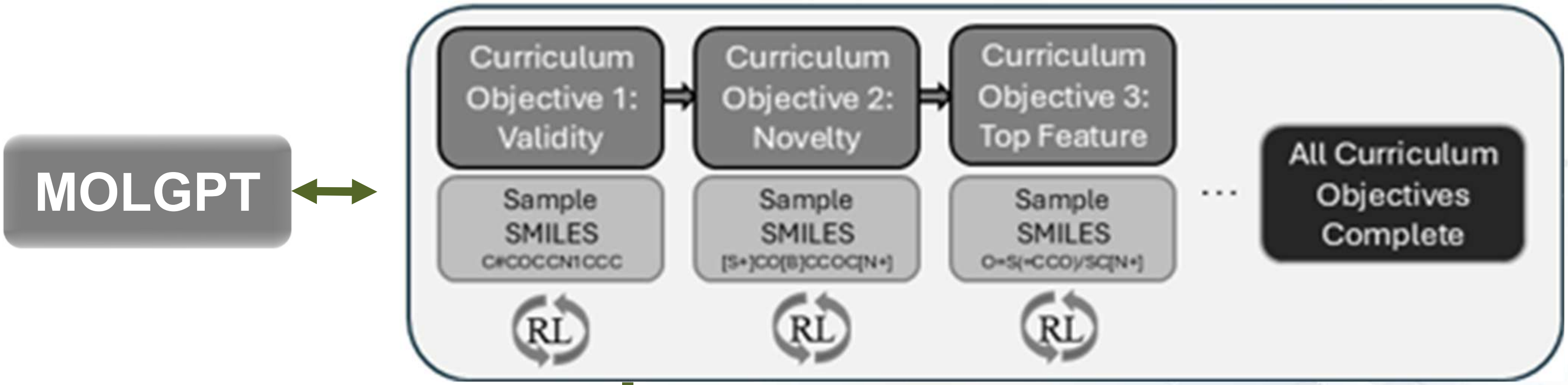
SHAP Analysis





III. Reward Design

SMILES String Generation & RL Curriculum



CNS Optimized SMILES Strings

C[P+](CNCNN)NC(=CCCCC)[B]CSC[N]CCOC=CCS1=CCCC

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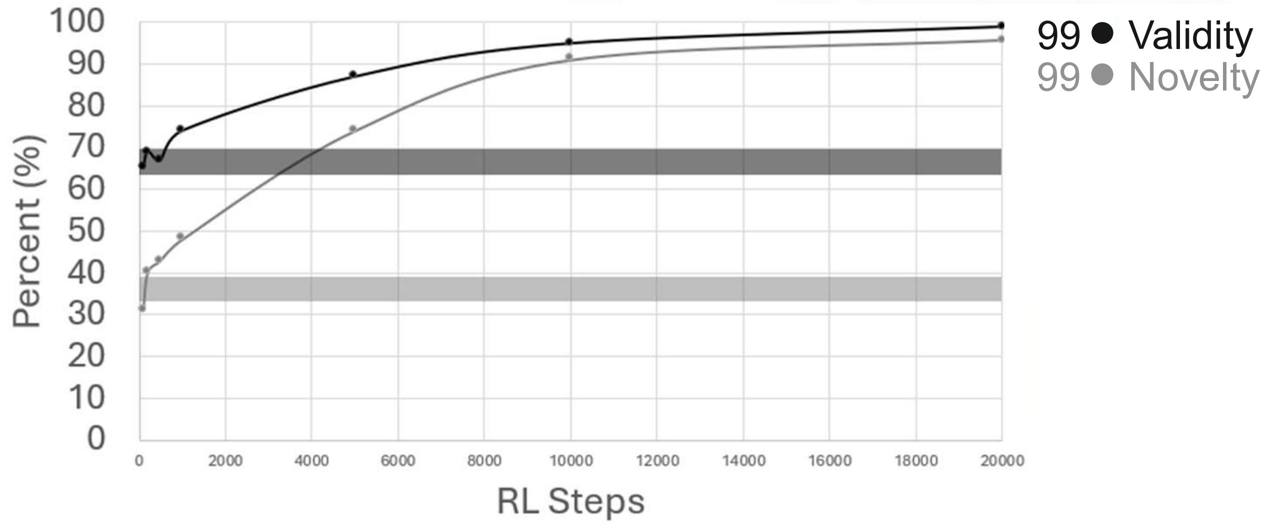
Validation

Generated SMILES Strings Reward During Training



Validation RL → Classifiers → SHAP → Reward Function → Evaluation

Classifiers Performance

Permeability	NA	NT	NC
AUROC: 0.9771	AUROC: 0.7777	AUROC: 0.8178	AUROC: 0.9070
Comparison 0.9745	*Comparison 0.8509*	*Comparison 0.7945*	*Comparison 0.9637*

Pang et al., "NeuTox 2.0," *Environ. Int.*, 2025

Validate RL → **Classifiers** → SHAP → Reward Function → Evaluation

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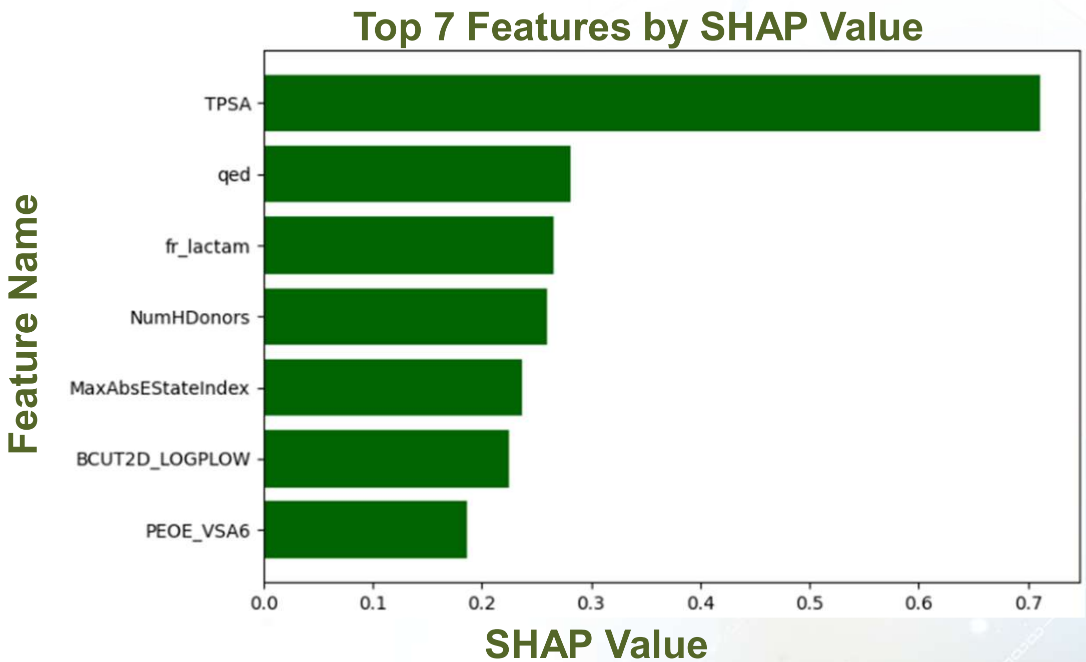
SHAP Analysis



Validate RL → Classifiers → **SHAP** → Reward Function → Evaluation

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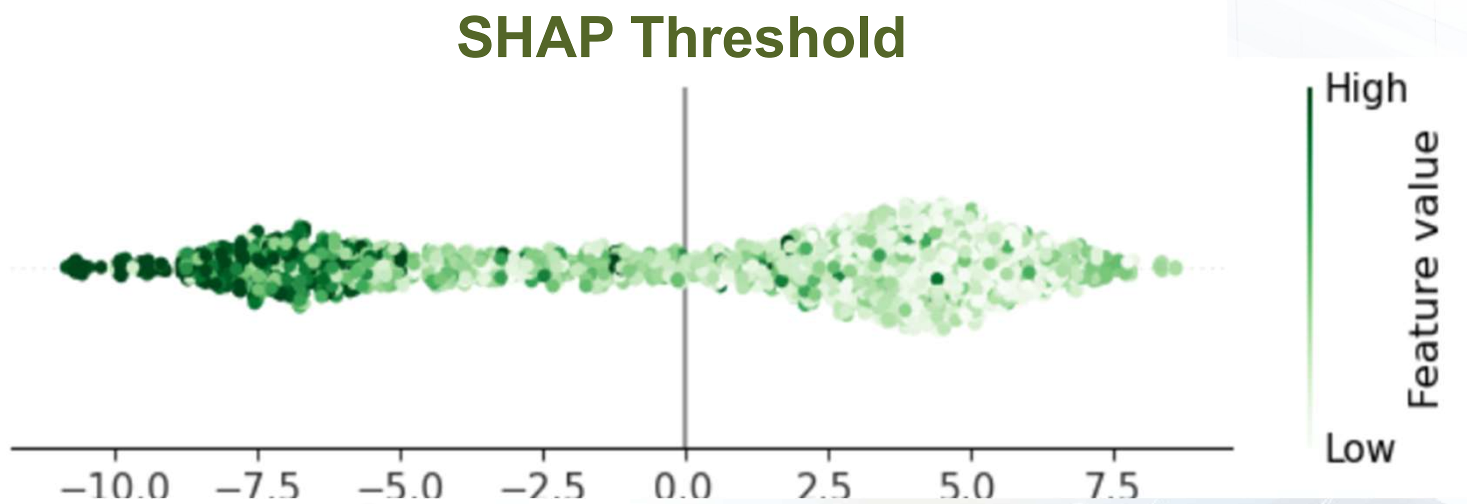
SHAP Analysis



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SHAP Analysis

Feature	Threshold	SHAP Value
fr_Ndealkylation2	0.379	0.0512
Chi3v	-0.170	0.0325
PEOE_VSA5	1.593	0.0321
MolLogP	-0.100	0.0317
SlogP_VSA6	-0.141	0.0309
…continues for all 722 features…		

Validate RL → Classifiers → **SHAP** → Reward Function → Evaluation

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Reward Function Design

Feature	Property	Abs. SHAP Value	Directionality	Threshold
TPSA	Permeability	0.9933	1	60.41
BertzCT	NC	0.6912	1	942.9
MolgLogP	NA	0.6723	1	3.848
…	…	…	…	…

Validate RL → Classifiers → SHAP → **Reward Function** → Evaluation

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Reward Function Design

- **97 Features with Abs. SHAP Value >0.10**
  - Introduce a new feature every 900 steps ~89000 steps

Validity & Novelty | TPSA | BertzCT | MolLogP

⊢ 900 Training Steps ⊣

Validate RL → Classifiers → SHAP → **Reward Function** → Evaluation

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Reward Function Design

Reward Function Components

- **Validity:** +0.1 if SMILES is chemically valid
- **Novelty:** Reward = 1 – max similarity
- **Summary:**

• Starts with validity and novelty

• Gradually adds property-based rewards

Validate RL → Classifiers → SHAP → **Reward Function** → Evaluation

Training Evaluation

Validate RL → Classifiers → SHAP → Reward Function → **Evaluation**

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Future Work

- **Experiment with Curriculum Design**
- **Adapt to a Binding Site**
- **SMILE String Evaluation**

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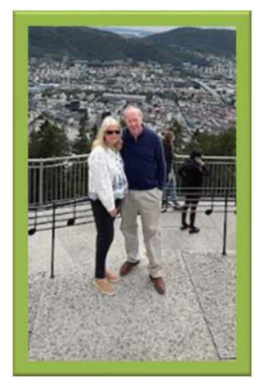


Personal Portfolio

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