Hierarchical H-QSAR Modeling Method that Integrates Binary/Multi Classification and Regression Models for Predicting Acute Oral Systemic Toxicity

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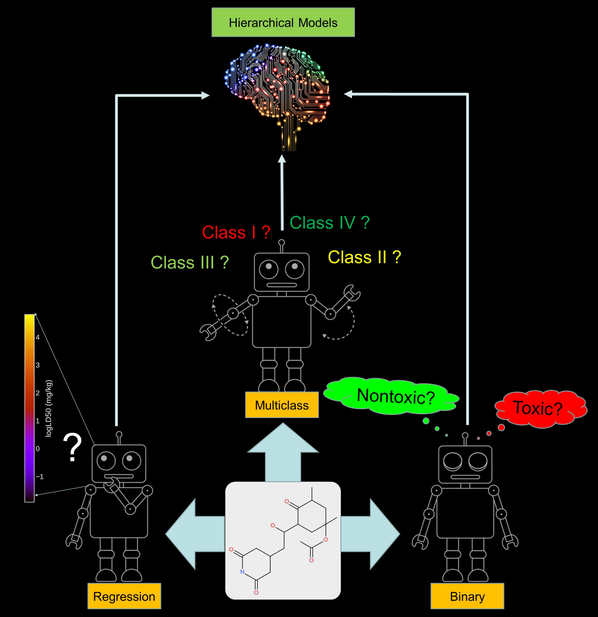
Research Background

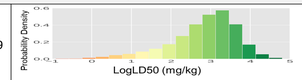
- **Chemical toxicity evaluation is an important step to ensure the environmental and human safety of chemicals.**
- **Due to the increasing number of chemicals requiring toxicological evaluations, there is a high demand for alternatives to replace, reduce, and refine (3Rs) the use of animal testing.**
- ***In silico* methods, such as Quantitative Structure-Activity Relationship (QSAR) modeling are gradually becoming essential and very much complementary to *in vitro* assays to achieve this goal.**

Research Objectives

- **Build robust QSAR models to predict acute oral systemic toxicity.**
- **Conduct hierarchical QSAR modeling that integrates classification and regression models to boost the performance, consistency, and applicability of *in silico* models for chemical risk assessment.**

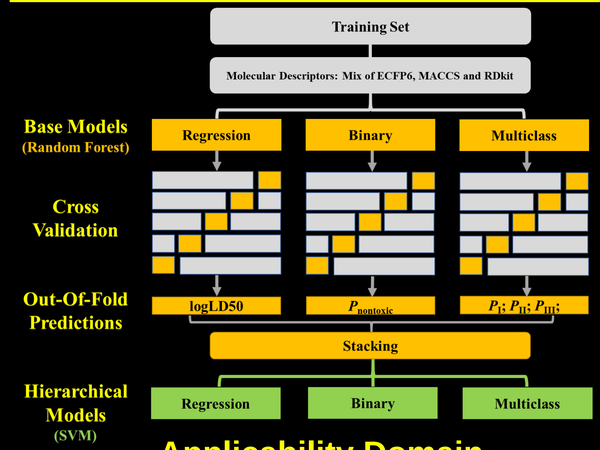


Rat Oral Toxicity Dataset

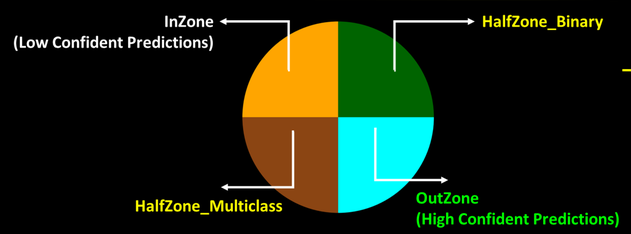
Endpoints	Training Set (75%)					Test Set (25%)
Total	8,944					2,896
LD50 (mg/kg)	6,089					2,144
Toxic/Nontoxic	8,209	Toxic (LD50 < 2,000)		Nontoxic (LD50 > 2,000)		2,820
		4,661		3,548		
EPA Category	8,126	I	II	III	IV	2,842
		<50	50-500	500-5,000	>5,000	
		703	1,767	4,070	1,586	
Mutual	6,089	4,157		1,932		2,144
		683	1,621	2,469	719	

- Comprises 11,992 compounds, covers ***five*** modeling endpoints needed by regulatory agencies.
- Curated following the procedure developed by Fourches et.al. *Nat. Chem. Biol*. **2015**, *11*, 535.

Hierarchical Modeling Workflow



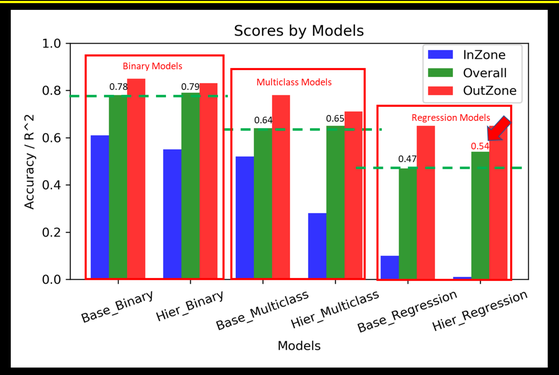
Applicability Domain



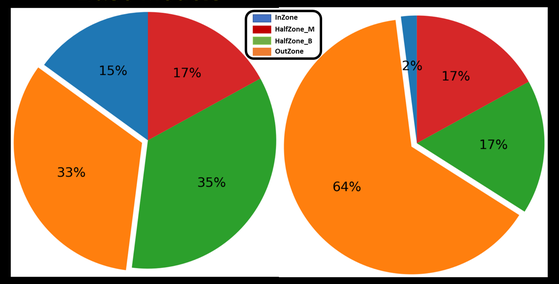
Binary Models:
InZone (low confident) Prediction: Predicted Probabilities ∈ [0.4, 0.6]
OutZone (high confident) Prediction: Predicted Probabilities $outside$ [0.4, 0.6].

Multiclass Models:
InZone Prediction: All four classes predicted probabilities ≤ 0.5
OutZone Prediction: Any of four classes predicted probabilities > 0.5

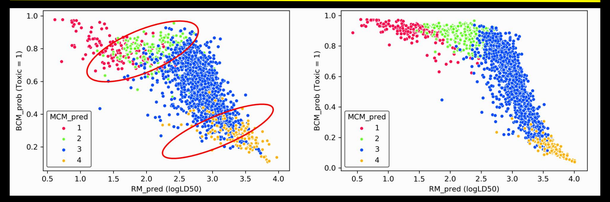
Performances on External Test Set



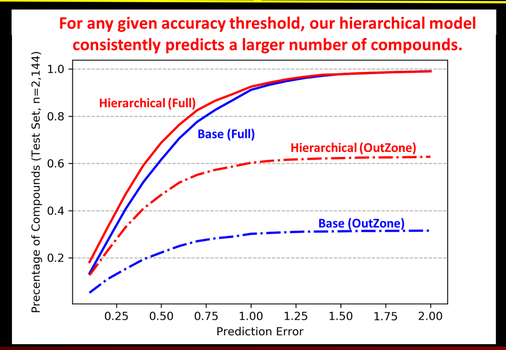
Distributions of Prediction Zones



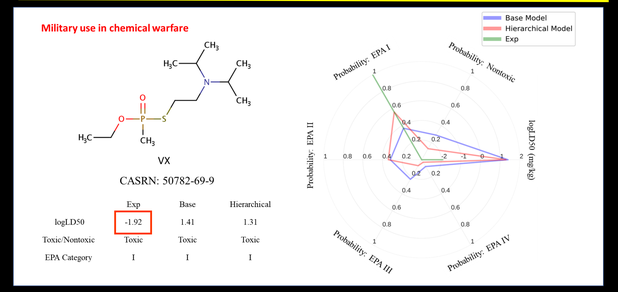
Comparison of Prediction Consistency

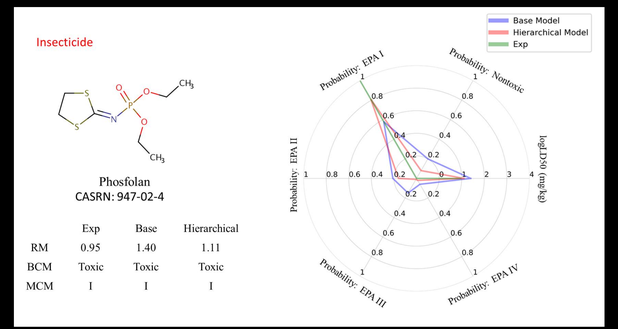


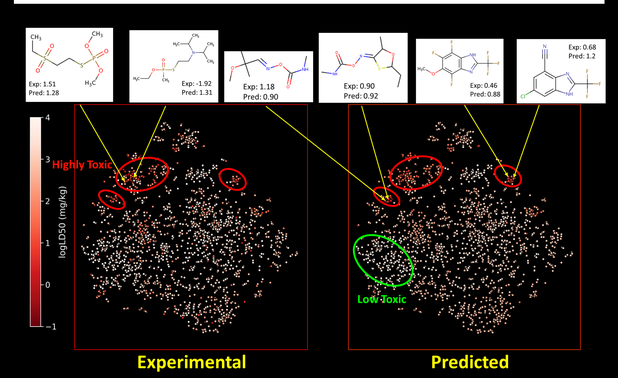
Comparison of Regression Models



Chemicals in Test Set







Conclusions

- **Hierarchical H-QSAR modeling method relying on the full stacking of binary, multiclass, and regression base models represents a promising approach for *in silico* chemical risk assessment and more generally, for blending individual QSAR models into more predictive ensemble models.**
- **Hierarchical H-QSAR models have advantages against base models with respect to the prediction performances, prediction consistency, and broader AD coverage.**

Acknowledgements
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