

Mounika Girireddy*, Suman K. Chakravarti*

*MultiCASE Inc., 5885 Landerbrook Dr., Suite 210, Mayfield Heights, OH, 44124, USA

Introduction

Ecotoxicity QSAR models are traditionally built using various modeling techniques and molecular descriptors, but they often fall short in terms of performance, transparency, interpretability, and maintenance. There is a lack of high-quality physicochemical property models and difficulties in using expert rules. To address these issues, the *FlexFilters* platform was developed. It provides a modular and adaptable computational toxicology solution that combines fragment descriptors, physicochemical properties, and expert knowledge-based alerts to create hybrid models that offer both interpretability and good performance. These models have shown promising results in various ecotoxicity endpoints, including Daphnia toxicity.

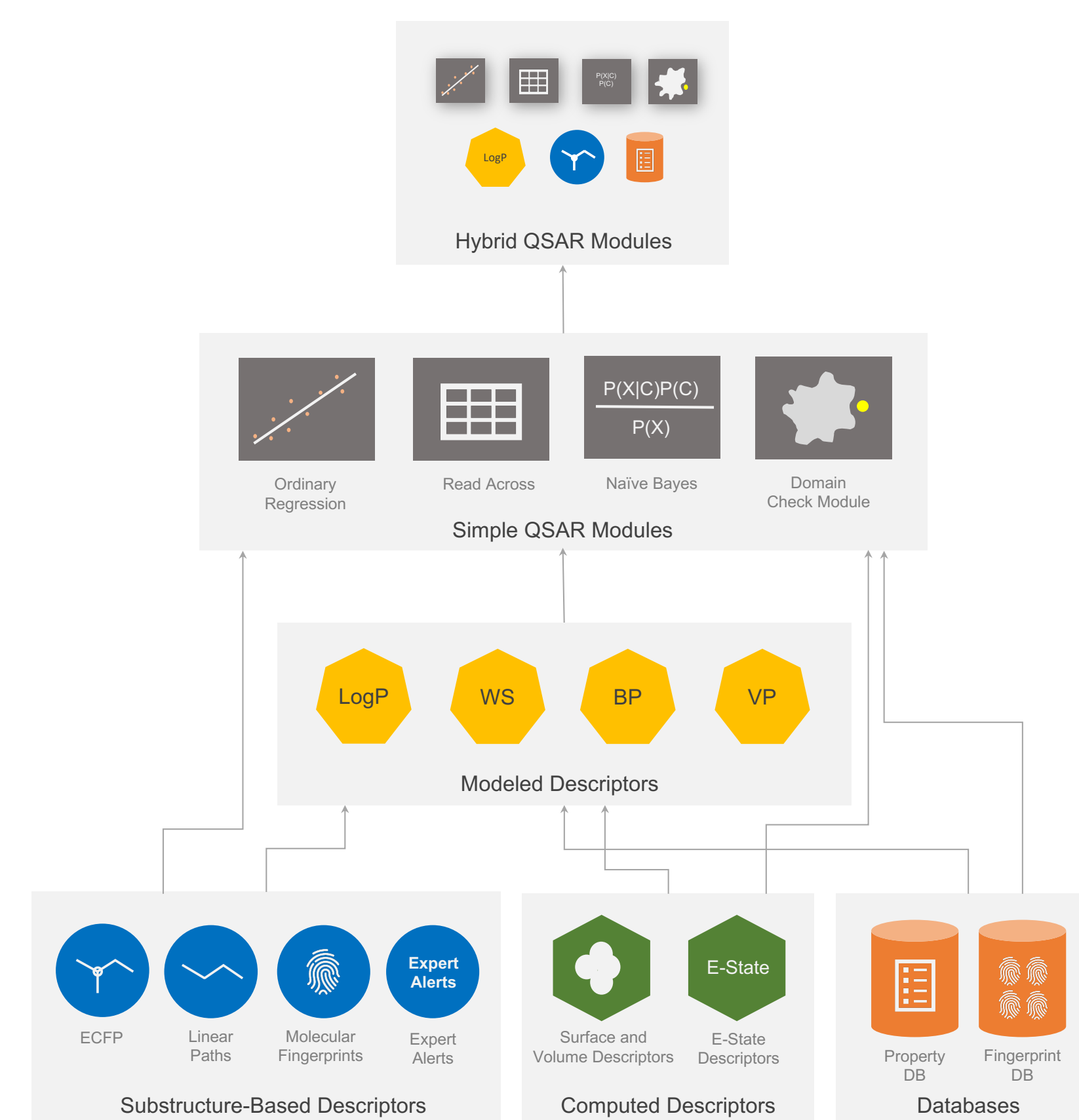
Objectives

- To develop *in-silico* ecotoxicity models with good predictive power and interpretability.
- To create models that are scalable, flexible, upgradable, and modular.
- To integrate descriptor calculators, fragment detectors, QSAR/QSPR models, databases, expert knowledge-based alerts, domain applicability checkers, data curators and other modules.

Materials and Methods

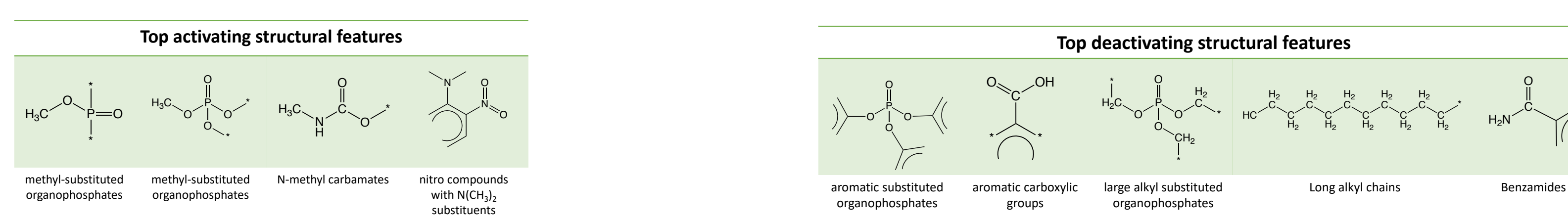
- The *FlexFilters* platform integrated in *QSAR Flex* was used for molecular fragment handling, descriptor calculations, QSAR modeling, and predictions.
- Databases were built for daphnia, fathead minnow, tetrahymena, bio concentration factor (BCF), ready biodegradability, algae, soil adsorption and multiple physicochemical properties.
- Logistic regression was as the model building algorithm and 'R' package *glmnet* was used for descriptor selection.
- Leave-many-out CV method (10%-out-10-times) was used for measuring the predictive robustness of the models.

Hierarchical and Modular FlexFilters Platform



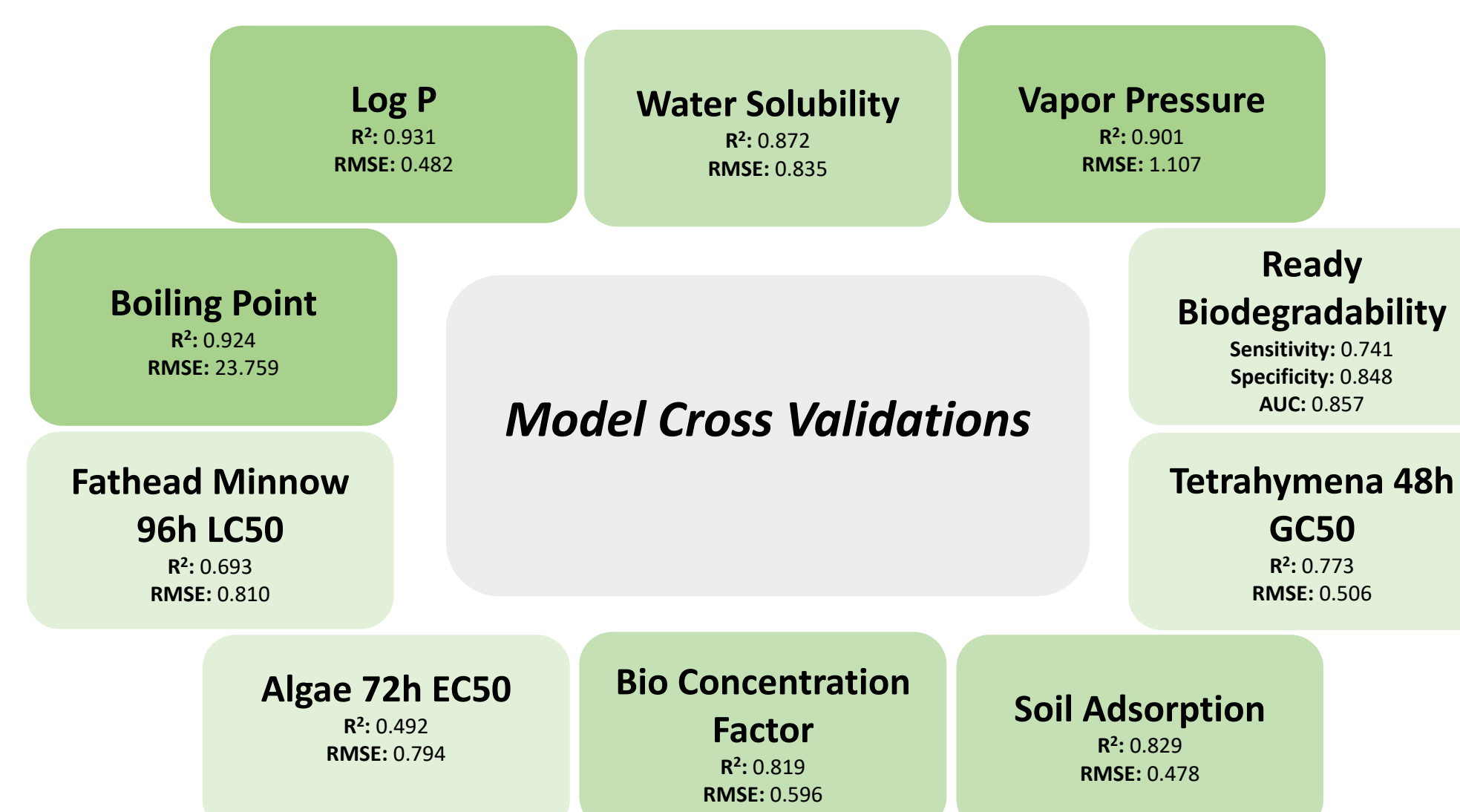
Results and Discussion

Identifying modulators improves predictive performance of expert alerts



Hybrid QSAR models showed superior predictive performance compared to statistically mined fragments or expert alerts alone

Model	Training set size: 2125 External set size: 232	10x CV		External test	
		R ²	RMSE	R ²	RMSE
Log P + Expert Alerts		0.520	1.049	0.471	0.992
Log P + Statistically mined fragments		0.617	0.938	0.576	0.891
Log P + Expert Alerts + Statistically mined fragments		0.633	0.915	0.599	0.871



Conclusions

- The *FlexFilters* platform provides a flexible and modular solution to address the challenges in the field of ecotoxicity prediction through QSAR models.
- This platform seamlessly incorporates expert alerts, molecular fragments, physicochemical properties, and diverse model building algorithms. Consequently, it generates highly effective and easily understandable hybrid models, thus rendering it an invaluable tool for the *in silico* evaluation of chemical safety.

References

- Chakravarti, S. K., *FlexFilters: A Scalable and Flexible QSAR Platform for Addressing Complex and Diverse Types of in Silico Safety Assessment of Chemicals*, Poster, Society of Toxicology Annual Meeting, Anaheim, 2020.
- Chakravarti, S. "Augmenting Expert Knowledge-Based Toxicity Alerts by Statistically Mined Molecular Fragments." *Chemical Research in Toxicology*, May 19, 2023, DOI: 10.1021/acs.chemrestox.2c00368.

Mounika Girireddy
MultiCASE Inc.
girireddy@multicase.com
6146070418