Hierarchical QSAR Modeling for Predicting Acute Oral Systemic Toxicity

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Background

• Thorough toxicity evaluation is an important step to ensure the environmental safety of chemicals. In vivo procedures are not only costly and time-consuming, but the use of animals raises ethical issues and often has questionable relevance to human biology.

• Reliable in silico approaches to replace, reduce and refine animal testing for the evaluation of potential acute toxic effects are highly demanded by regulatory agencies.

• Quantitative Structure-Activity Relationship (QSAR) modeling is a major in silico approach relying on machine learning techniques and a set of molecular descriptors directly computed from chemical structures.

Visualization of the Chemical Space

Clustering of the full dataset (11,056 molecules) by t-SNE with 2D bit-based ECFP6 (2,048 bits)

Performance on External Test Set

Overall workflow for building hierarchical QSAR models. Base regression, binary and multiclass models are built with diverse combinations of four machine learning algorithms (RF, SVM, kNN and XGBoost) and five chemical descriptors/fingerprints (ECFP6_Bits, ECFP6_Counts, MACCS keys, RDKit descriptors and Mordred descriptors). For each endpoint, a diverse set of 20 models were built at this stage (60 base models total). Out-of-Fold Predictions of base models are generated through 10-fold cross-validation. The out-of-fold predictions are concatenated together and used as input (Meta Features) for building hierarchical regression, binary and multiclass models.

Examples of Chemicals in External Test Set

• A dual-layer hierarchical QSAR modeling protocol was developed and applied to three acute oral systemic toxicity endpoints. The hierarchical models outperform the individual base models on all the three endpoints.

• Hierarchical H-QSAR modeling method relying on the full stacking of binary, multiclass, and regression models represents a promising approach for in silico chemical risk assessment and more generally, for blending individual QSAR models.

Conclusion

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