The applicability domain concept, a must for all NAMs: focus on Machine Learning QSAR models

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INTRODUCTION

In the era of the Replacement, Reduction and Refinement principles, New Alternative Methodologies (NAMs) are promising and powerful approaches to avoid animal testing. However, with great power comes great responsibility and one of them is being able to identify the limits of such new approaches to provide a result with confidence. In this context, Quantitative Structure Activity Relationship (QSAR) models are always related to a specific Applicability Domain (AD). AD is so important that it constitutes the third OECD principle of model validation (OECD, 2007) and the second OECD principle for a prediction validation (OECD, 2023). If defining the AD of models like linear regression may be trivial, challenges arise to define the AD of more complex models like machine learning ones properly to enhance the confidence of QSARs users and regulatory authorities. This poster will present the principle of AD, make an overview of the ways to define it according to model families and discuss how to manage it in the era of machine learning and in the light of the release of the QSAR Assessment Framework (QAF) in late 2023.

WHAT IS AN AD?

Many definitions of AD exist in the literature. The one mentioned in the QAF is: "the response and chemical structure space in which the model makes predictions with a given reliability" (Netzeva et al., 2005). The nature of this space is dependent on the model and the features used as predictors, resulting possibly in a n-multidimensional chemical space where is it more complicated to clearly define the limits. Outside that space, the prediction for a given chemical may not be considered as reliable.

STEP INTO AD CONCEPT FOR REGULATION

- **STEP 1: Assessing the applicability domain**

The QAF requires the following domains and considerations are dealt with, depending on the model:

DESCRIPTOR DOMAIN	STRUCTURAL DOMAIN	RESPONSE DOMAIN	MECHANISTIC CONSIDERATION	METABOLIC CONSIDERATION
Variables used to predict the endpoint	Caracterisation of the compounds in the training set (under the responsability of the model developer)	Range or class of predicted variables in the training set	Understanding the link between the dependent and independent variables	Knowledge of metabolism of the compounds in the medium of interest

- **STEP 2: Assessing the reliability of a prediction**

Applicability domain assessment may be sufficient for simple models such as linear regression, where the domain is easier to define. Moreover, these models provide explicit statistical tools, such as confidence and prediction intervals, to directly estimate uncertainty.

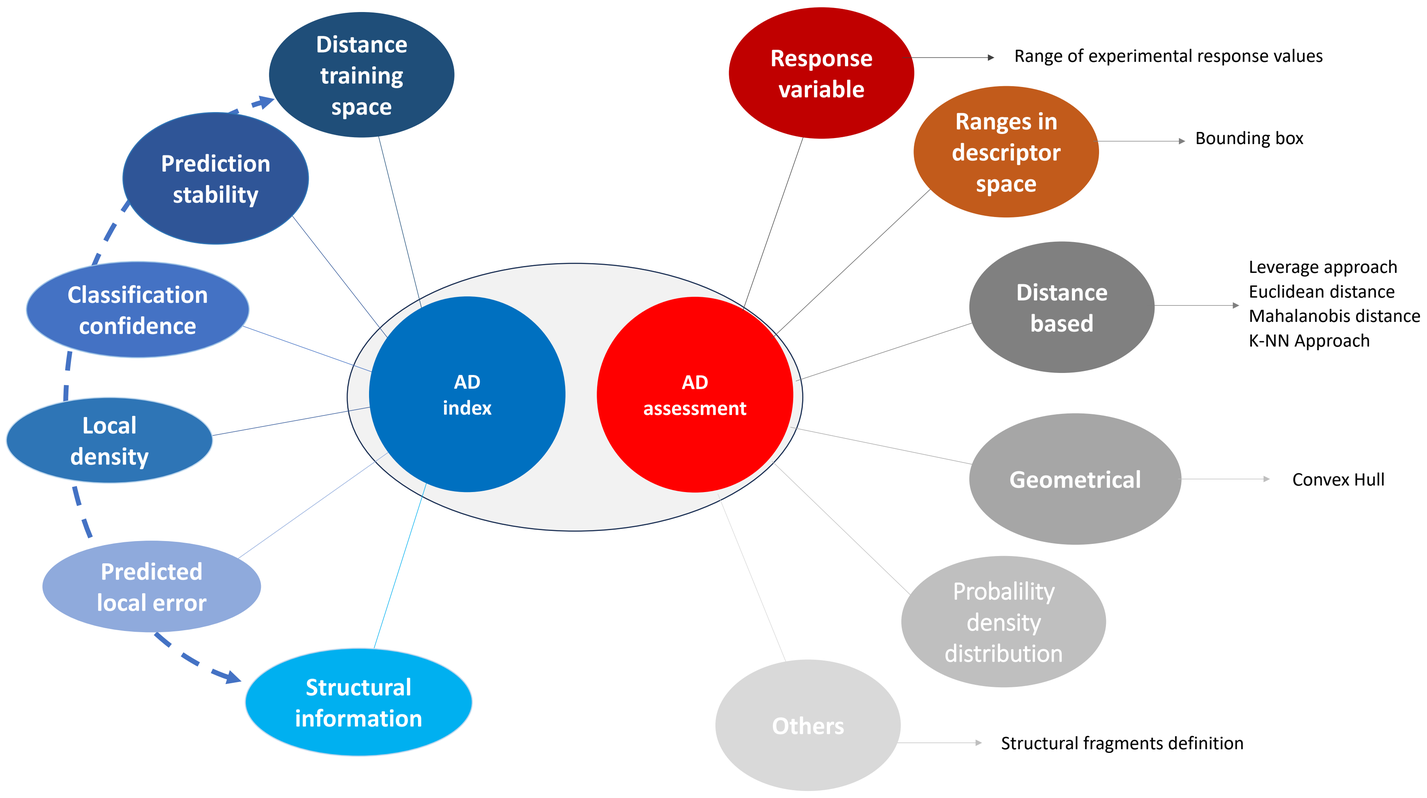
In contrast, **machine learning models, often seen as "black boxes"**, lack such readily accessible indicators. In such cases, a **double approach** relying on both the **AD assessment** and the **AD index** assessing the reliability of the AD is necessary to **enhance the confidence in the prediction**. Even if a given chemical falls "in AD", it may fall in a gap of the domain. Different software like ACD/Labs, VEGA, OPERA and some KREATiS models already adopted this strategy.

The AD index is often built by combining several model- and data-related criteria. Each component reflects a different aspect of prediction reliability that are complementary.

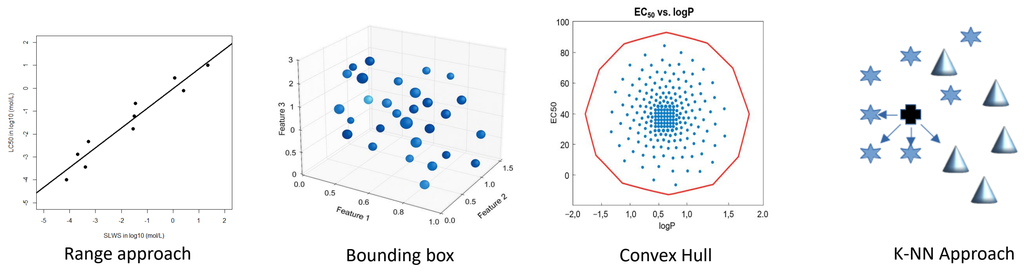
Component	Associated Method	What It Measures
Distance to training space	k-NN, PCA distance	Proximity to known molecules in the descriptor space
Prediction stability	Random Forest, Deep Ensembles	Variance among model outputs (model disagreement)
Classification confidence	Softmax output, RF probabilities	Confidence score for the predicted class
Local density	KDE, local k-NN	Whether the compound lies in a well-populated region
Predicted local error	Error model (e.g., RF trained on residuals)	Expected prediction error in the local neighborhood
Structural information	Tanimoto similarity, known substructures	Presence of chemical motifs already seen in training

Some issues remain. What about:

- Singletons?
- Unbalanced data?
- Relevant similarity algorithm?



A non-exhaustive set of examples of applicability domain approaches



Range approach | Bounding box | Convex Hull | K-NN Approach

CONCLUSION

Although QSAR models are still thought by many scientists to be not trustworthy enough, especially as stand alone, assessing the AD of a model and calculating an AD index relative to a query chemical is a safety barrier that enhances the confidence to the prediction. This is especially true for machine learning methods where it is not always easy to extract information about the chemical space covered by a model. Statisticians has developed an arsenal of tools that can tackle the "black box" appearance of such complex methods helping them to be more interpretable and compliant with OECD guidelines for QSARs prediction acceptance. However, among the QSAR user community, AD is not sufficiently considered as it is time-consuming to properly investigate, especially because it is model-specific. The model users should also be responsible for understanding and correct use and interpretation of the model they are using as some software will provide a predicted value from a QSAR even if it falls outside the AD. NAMs in general are still considered as controversial approaches to replace *in vivo* studies as stand-alone studies. AD assessment is clearly an essential indicator of model accuracy and validity that should be given higher priority to enhance the respect and recognition of NAMs within the scientific community.

REFERENCES

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