Applicability Domain

Towards a more formal definition

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Thierry Hanser

Research Leader
Can we trust a specific individual prediction?

Screening

Risk assessment

83% accuracy
Can we trust a specific individual prediction?

Screening

Risk assessment

83% accuracy

x 1000000
Can we trust a specific individual prediction?

83% accuracy

Screening

Risk assessment

x 1000000
Can we trust a specific individual prediction?

83% accuracy

Screening: $x \times 1000000$

Risk assessment: $x \times 1$
Can we trust a specific individual prediction?

83% accuracy

Screening

Risk assessment

x 1000000

x 1
Can we trust a specific individual prediction?

Screening

83% accuracy

Risk assessment

Global model accuracy estimate

Individual prediction accuracy estimate
Current understanding and definitions

OECD QSAR principles

- A defined endpoint
- An unambiguous algorithm
- **A defined domain of applicability**
- Appropriate measures of goodness-of-fit, robustness and predictivity
- A mechanistic interpretation, if possible

Common definition

“AD is the response and chemical structure space in which the model makes predictions with a given reliability”.


Current understanding and definitions

**QSAR principles**

- A defined endpoint
- An unambiguous algorithm
- **A defined domain of applicability**
- Appropriate measures of goodness-of-fit, robustness and predictivity
- A mechanistic interpretation, if possible

**Common definition**

“AD is the response and chemical structure space in which the model makes predictions with a given reliability”.
A good foundation to build on


Norinder U, Rybacka A, Andersson PL. **Conformal prediction to define applicability domain** – A case study on predicting ER and AR binding. SAR and QSAR in Environmental Research. 2016 Apr 2;27(4):303–16.


And many more...
A good foundation to build on

Full Paper

Structure Modification toward Applicability Domain of a QSAR/QSPR Model Considering Activity/Property

Shoki Ochi, Tomoyuki Miyao, Kimito Funatsu

First published: 16 August 2017 | https://doi.org/10.1002/minf.201700076

Predicting skin sensitizers with confidence — Using conformal prediction to determine applicability domain of GARD

Andy Forreryd, Ulf Norinder, Tim Lindberg, Malin Lindstedt

Conformal Regression for Quantitative Structure–Activity Relationship Modeling—Quantifying Prediction Uncertainty

Fredrik Svensson, Natalia Aniceto, Ulf Norinder, Isidro Cortes-Ciriano, Ola Spjuth, Lars Carlsson, and Andreas Bender

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A strategy on the definition of applicability domain of model based on population analysis

Yong-Huan Yun, Dong-Ming Wu, Guang-Yi Li, Qiao-Yan Zhang, Xia Yang, Qin-Fen Li, Dong-Sheng Cao, Qing-Song Xu
Current common methods

Molecule classes
- Organic-Organometallic-Inorganic
- Class of molecules (Arom. Amines)

Feature representation
- Unseen features

Agreement based
- RF consensus
- kNN

Descriptor ranges
- Box
- Convex hull

Distance based methods
- Distance to data points
- Density

Response domain
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Response domain

No boronic acids in the training set
**Current common methods**

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- Distance to data points
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Response domain

Distance to data

Distance to data points
Current common methods

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- Unseen features

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Distance based methods
- Distance to data points
- Density

Response domain
Mixture of different concepts

Applicability
(can I use this model to make a prediction?)

Reliability
(is the prediction reliable?)

Decidability
(can I make a clear decision)
Mixture of different concepts

**Applicability**
(can I use this model to make a prediction?)

**Reliability**
(is the prediction reliable?)

**Decidability**
(can I make a clear decision)
Mixture of different concepts

Applicability Domain
Towards an extended and more formal framework

Confidence in the prediction if ...

- My model can be applied for this query compound
  Applicability domain
- The prediction is reliable enough for my use case
  Reliability domain
- I can make a clear decision
  Decidability domain
Applicability (of the model)

- Is the class of my query compound supported by the model?  
  e.g. exclude polymers, proteins, inorganic molecules, etc.

- Is my query compound in the range of the descriptor of the training set?  
  e.g. inside convex hull, minimum information density

- Did my model see all the structural features present in the query compound?  
  e.g. not in domain, contains unseen boronic acid functional group
Reliability (of the prediction)

- How close are the nearest neighbours?
- How reliable are these nearest data points? e.g. GLP compliance
- How well did my model predict these data points? e.g. performance during CV

Out of Reliability domain

Can I trust my prediction?

Out of Applicability domain

Can I apply my model?
Decidability (of the outcome)

- Does my evidence converge or conflict? e.g. k Nearest Neighbours distribution
- Is there a consensus between intermediate conclusions? e.g. RF tree distribution
- Is my posterior likelihood strong enough? e.g. Naïve Bayes posterior probability

Can I apply my model?
- Out of applicability domain

Perform the prediction
Can I trust my prediction?
- Out of Reliability domain

Look at the prediction
Can I make a clear call?
- Equivocal or Undecided

Make a statement

Intuitive, non ambiguous and formal decision framework

Can I apply my model?

- Out of applicability domain
- Perform the prediction
  - Is my prediction reliable enough?
    - Out of reliability domain
    - Look at the prediction
      - Can I make a clear call?
        - Equivocal / Undecided
        - Make a statement

Applicability

Reliability

Decidability

Articulation of the method

- Applicability domain is **not a monolithic concept**, there are 3 key layers

- Separation of concern can **help clarify and formalise** the notion of AD

- Purpose: Initiate a constructive discussion among our QSAR community to build a **common understanding** together

- **Harmonize the way we define and present AD** to the end users across models and applications

- **Remove confusion** for the end user and improve the value of our AD model
Collaborators

• Stéphane Werner

• Jean-François Marchaland

• Sébastien Guenes

• Lilia Fisk

• Chris Barber
Thank you for your kind attention