Applicability Domain
Towards a more formal definition

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Presentation aims

- Applicability Domain (AD) is **not a monolithic concept**: there are 3 key layers
- Separation of concerns can **help clarify and formalise** the notion of AD
- Purpose: Initiate a constructive discussion among the (Q)SAR community to build a **common understanding** together
- **Harmonize the way we define and present AD** to the end user across models and applications
- **Remove confusion** for the end user and improve the value of AD model


**Current understanding and definitions**

**OECD (Q)SAR 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.”

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(Q)SAR principles

- A defined endpoint
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Common definition²

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

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**Boundaries**

**Reliability**

**Likelihood ?**

**Applicability**
A good foundation on which to build


And many more...
Current common methods

Molecule classes
- Organic-Organometallic-Inorganic
- Class of molecules (e.g. Aromatic 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
Current common methods

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Response domain

No boronic acids in the training set
Current common methods

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Response domain

Random forest

Nearest Neighbours
Current common methods

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Response domain
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Response domain

Distance to data

Distance to data points
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Current common methods

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Distance based methods
- Distance to data points
- Density

Response domain
Mixture of different concepts

Reliability
(is the prediction reliable?)

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

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 decision if ...

My model can be applied for this query compound

The prediction is reliable enough for my use case

I can make a clear decision

Applicability domain

Reliability domain

Decidability domain
Applicability (of the model)

Can I apply my model?

- Out of Applicability Domain
- Perform the prediction

Applicability
Model boundaries (Designer’s specifications)

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

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

- Has my model seen all the structural features present in the query compound?
  e.g. 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 the nearest neighbours? e.g. performance during cross-validation
‘Decidability’ (of the outcome)

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 / Undecided

Decidability
Likelihood boundaries
(User defined)

- Does my evidence converge or conflict? e.g. 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

Make a statement
3-step process (separation of concerns)

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 / Undecided

Applicability

Reliability

Decidability

Make a statement
Intuitive, non ambiguous and formal decision framework

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 / Undecided
        - Make a statement

Decision domain
Decision Domain

Proposal: Extend and refine the Applicability Domain into a Decision Domain

Decision Domain

“The Decision Domain (DD) is the scope within which it is possible to apply the model to make a non equivocal decision based on a reliable prediction”.
Confidence

- Confidence (subjective)
- Reliability
- Decidability
- Applicability

Confidence
Confidence in the decision

Low reliability

High reliability
Confidence in the decision

Low decidability

High decidability
Confidence in the decision

Can I trust my prediction?

We can't trust this high likelihood!
Confidence in the decision

Can I make a clear call?

Outside the Reliability Domain

Equivocal / Undecided

Outside the Reliability Domain

Confident call

Difficult call (activity cliff)
Reliability and Likelihood are not compensatory

Reliability and Likelihood are not interconvertible
They can't compensate each other
(e.g. low likelihood can't be compensated by high reliability)
Transparent decision process

- My model can be applied for this query compound: Applicability
- The prediction is reliable enough for my use case: Reliability
- I can make a clear decision: Decidability
Transparent decision process

- **Applicability**: My model can be applied for this query compound
- **Reliability**: The prediction is reliable enough for my use case
- **Decidability**: I can make a clear decision
- **Interpretation**: I understand which assumptions the model has used in its reasoning
- **Evidence**: I know which data (examples) support the model’s conclusion
Transparent decision process

- My model can be applied for this query compound
  - Applicability
- The prediction is reliable enough for my use case
  - Reliability
- I can make a clear decision
  - Decidability
- I understand which assumptions the model has used in its reasoning
  - Interpretation
- I know which data (examples) support the model's conclusion
  - Evidence

Decision domain

Decision support
TARDIS principle

Requirements to usefully support a decision process:

- **Transparency** (of the method)
- **Applicability** (of the model)
- **Reliability** (of the prediction)
- **Decidability** (non equivocal conclusion)
- **Interpretability** (of the conclusion)
- **Support** (evidence supporting the conclusion)
Conclusion

• Confidence in a decision can be assessed in 3 steps corresponding to 3 separate concerns.

• Separation of concerns offers clarity, transparency and can be more easily formalised.

• In the context of risk assessment models should provide transparent, interpretable, reliable and non equivocal conclusions that can be easily assessed by human experts using their own knowledge.

• It is the human experts that make the final decision based on their knowledge and the helpful information provided by the tools.
Thank you for your contribution and attention!