Applicability Domain

Towards a more formal definition

thierry.hanser@lhasalimited.org

Thierry Hanser

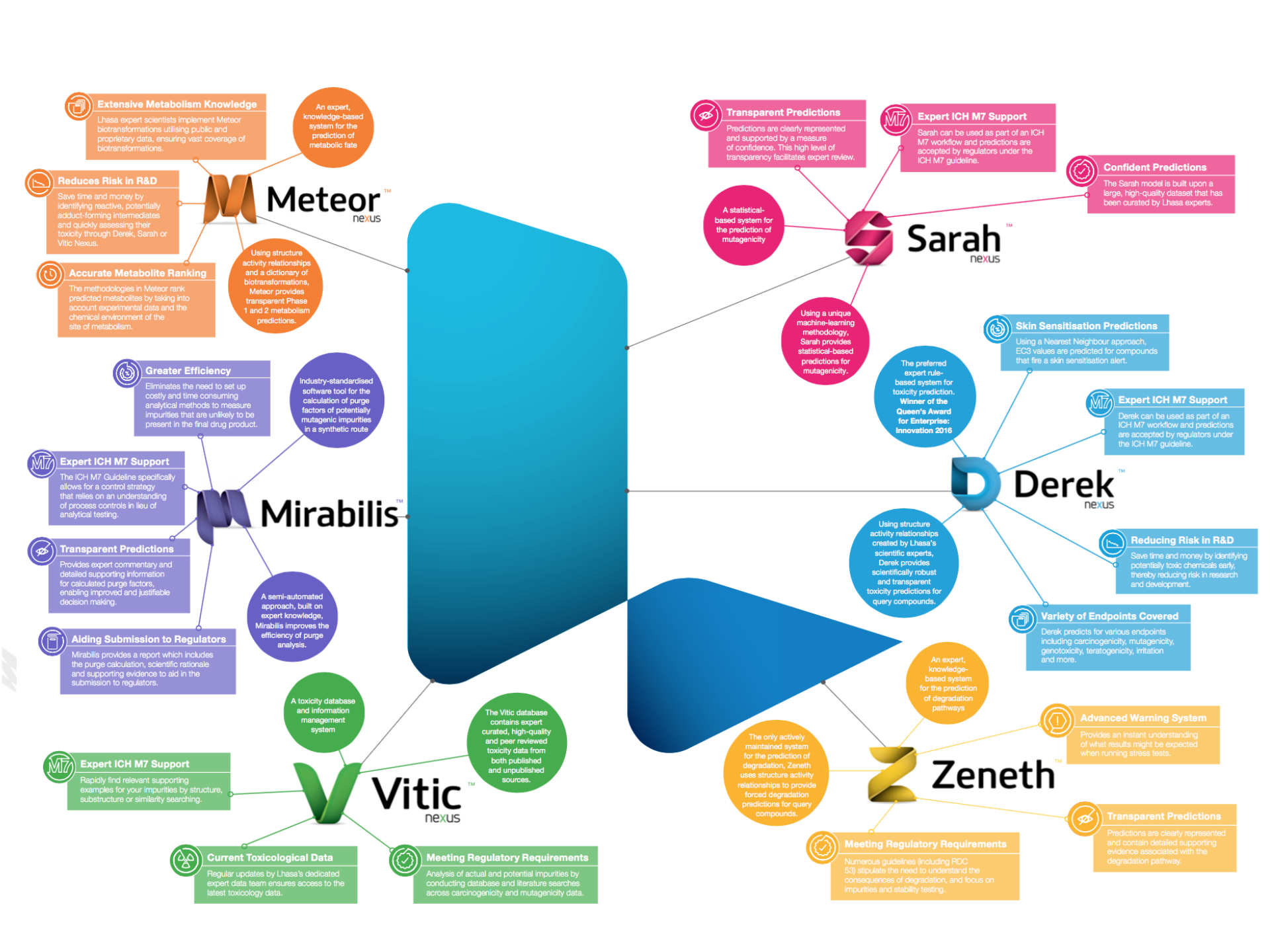
Research Leader

Lhasa Limited

shared **knowledge** • shared **progress**

Lhasa Limited Registered Office
Granary Wharf House, 2 Canal Wharf, Leeds LS11 5PS
Registered Charity (290866)

+44 (0)113 394 6020
info@lhasalimited.org
www.lhasalimited.org


Extensive Metabolism Knowledge
Lhasa expert scientists implement Meteor biotransformations utilising public and proprietary data, ensuring vast coverage of biotransformations.
An expert, knowledge-based system for the prediction of metabolic fate
Reduces Risk in R&D
Save time and money by identifying reactive, potentially adduct-forming intermediates and quickly assessing their toxicity through Derek, Sarah or Vitic Nexus.
Meteor nexus
Using structure activity relationships and a dictionary of biotransformations, Meteor provides transparent Phase 1 and 2 metabolism predictions.
Accurate Metabolite Ranking
The methodologies in Meteor rank predicted metabolites by taking into account experimental data and the chemical environment of the site of metabolism.
Transparent Predictions
Predictions are clearly represented and supported by a measure of confidence. This high level of transparency facilitates expert review.
Expert ICH M7 Support
Sarah can be used as part of an ICH M7 workflow and predictions are accepted by regulators under the ICH M7 guideline.
Confident Predictions
The Sarah model is built upon a large, high-quality dataset that has been curated by Lhasa experts.
A statistical-based system for the prediction of mutagenicity
Sarah nexus
Using a unique machine-learning methodology, Sarah provides statistical-based predictions for mutagenicity.
Skin Sensitisation Predictions
Using a Nearest Neighbour approach, EC3 values are predicted for compounds that fire a skin sensitisation alert.
The preferred expert rule-based system for toxicity prediction. Winner of the Queen's Award for Enterprise: Innovation 2016
Expert ICH M7 Support
Derek can be used as part of an ICH M7 workflow and predictions are accepted by regulators under the ICH M7 guideline.
Derek nexus
Using structure activity relationships created by Lhasa's scientific experts, Derek provides scientifically robust and transparent toxicity predictions for query compounds.
Reducing Risk in R&D
Save time and money by identifying potentially toxic chemicals early, thereby reducing risk in research and development.
Variety of Endpoints Covered
Derek predicts for various endpoints including carcinogenicity, mutagenicity, genotoxicity, teratogenicity, irritation and more.
Greater Efficiency
Eliminates the need to set up costly and time consuming analytical methods to measure impurities that are unlikely to be present in the final drug product.
Industry-standardised software tool for the calculation of purge factors of potentially mutagenic impurities in a synthetic route
Expert ICH M7 Support
The ICH M7 Guideline specifically allows for a control strategy that relies on an understanding of process controls in lieu of analytical testing.
Mirabilis
Transparent Predictions
Provides expert commentary and detailed supporting information for calculated purge factors, enabling improved and justifiable decision making.
A semi-automated approach, built on expert knowledge, Mirabilis improves the efficiency of purge analysis.
Aiding Submission to Regulators
Mirabilis provides a report which includes the purge calculation, scientific rationale and supporting evidence to aid in the submission to regulators.
A toxicity database and information management system
The Vitic database contains expert curated, high-quality and peer reviewed toxicity data from both published and unpublished sources.
Expert ICH M7 Support
Rapidly find relevant supporting examples for your impurities by structure, substructure or similarity searching.
Vitic nexus
Current Toxicological Data
Regular updates by Lhasa's dedicated expert data team ensures access to the latest toxicology data.
Meeting Regulatory Requirements
Analysis of actual and potential impurities by conducting database and literature searches across carcinogenicity and mutagenicity data.
An expert, knowledge-based system for the prediction of degradation pathways
Advanced Warning System
Provides an instant understanding of what results might be expected when running stress tests.
The only actively maintained system for the prediction of degradation, Zeneth uses structure activity relationships to provide forced degradation predictions for query compounds.
Zeneth
Transparent Predictions
Predictions are clearly represented and contain detailed supporting evidence associated with the degradation pathway.
Meeting Regulatory Requirements
Numerous guidelines (including RDC 53) stipulate the need to understand the consequences of degradation, and focus on impurities and stability testing.

Can we trust a specific individual prediction?

83%
accuracy

Screening

Risk assement

Can we trust a specific individual prediction?

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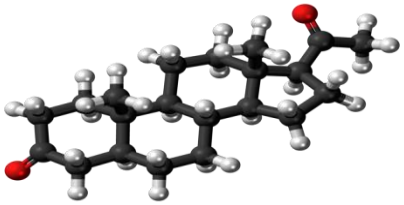
accuracy

Screening



x 1000000

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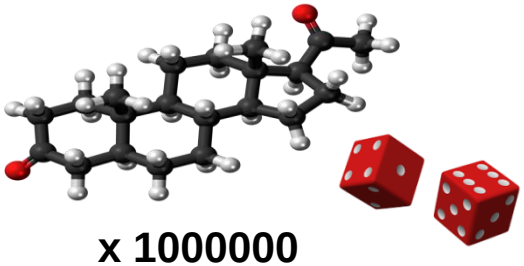

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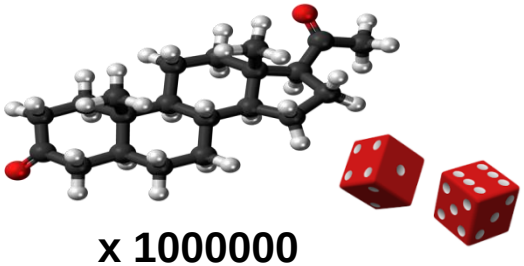
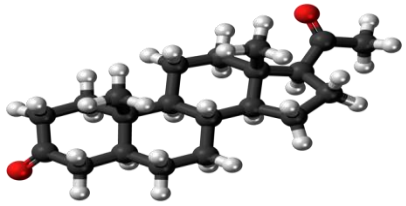


x 1000000

Risk assement



x 1

Can we trust a specific individual prediction?

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accuracy

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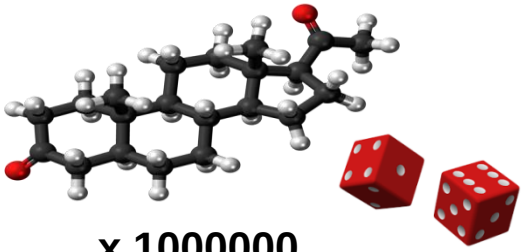
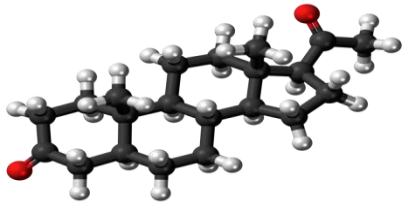


x 1000000

Risk assement



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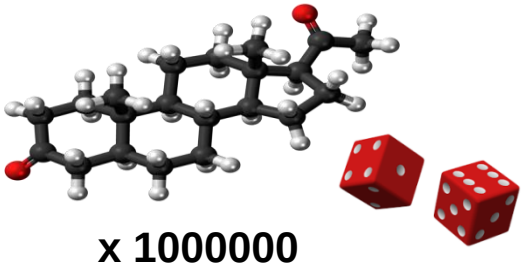
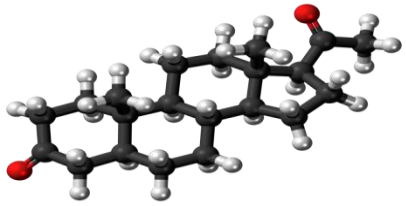


x 1000000

Global **model accuracy** estimate

Risk assement



x 1

Indivitual **prediction accuracy** estimate

Current understanding and definitions

OECD QSAR principles[1]

- 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[2]

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

Guidance Document on the Validation of (Quantitative) Structure− Activity Relationship QSAR Models; OECD Series on Testing and Assessment No.69; OECD Environment Directorate, Environment, Health and Safety Division: Paris, 2007

Setubal workshop report : Jaworska, J. S.; Comber, M.; Auer, C.; Van Leeuwen, C. Environ. Health Perspect. 2003, 111, 1358−1360

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Boundaries

Likelihood ?

Applicability

Reliability

A good fundation to build on

- Mathea M, Klingspohn W, Baumann K. **Chemoinformatic Classification Methods and their Applicability Domain**. Mol Inf. 2016 May 1;35(5):160–80.
- Gadaleta D, Mangiatordi GF, Catto M, Carotti A, Nicolotti O. **Applicability Domain for QSAR Models:: Where Theory Meets Reality**. International Journal of Quantitative Structure-Property Relationships. 2016 Jan;1(1):45–63.
- 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.
- Toccacheli P, Nouretdinov I, Gammerman A. **Conformal Predictors for Compound Activity Prediction**. arXiv:160304506 [cs] [Internet]. 2016 Mar 14 [cited 2016 May 11]; Available from: http://arxiv.org/abs/1603.04506
- Roy K, Kar S, Ambure P. **On a simple approach for determining applicability domain of QSAR models. Chemometrics and Intelligent Laboratory Systems**. 2015 Jul 15;145:22–9.
- Sheridan RP. **The Relative Importance of Domain Applicability Metrics for Estimating Prediction Errors in QSAR Varies with Training Set Diversity**. J Chem Inf Model. 2015 Jun 22;55(6):1098–107.
- Cherkasov A, Muratov EN, Fourches D, Varnek A, Baskin II, Cronin M, et al. **QSAR Modeling: Where have you been? Where are you going to?** J Med Chem. 2014 Jun 26;57(12):4977–5010.
- Carrió P, Pinto M, Ecker G, Sanz F, Pastor M. Applicability Domain Analysis (ADAN): **A Robust Method for Assessing the Reliability of Drug Property Predictions**. J Chem Inf Model. 2014 May 27;54(5):1500–11.
- Toplak M, Močnik R, Polajnar M, Bosnić Z, Carlsson L, Hasselgren C, et al. **Assessment of Machine Learning Reliability Methods for Quantifying the Applicability Domain of QSAR Regression Models**. J Chem Inf Model. 2014 Feb 24;54(2):431–41.
- Dragos H, Gilles M, Alexandre V. Predicting the Predictability: **A Unified Approach to the Applicability Domain Problem of QSAR Models.** J Chem Inf Model. 2009 Jul 27;49(7):1762–76.

And many more...

A good fundation to build on

molecular informatics
models – molecules – systems

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

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Volu

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

Andy Forreryd [a], Ulf Norinder [b, c], Tim Lindberg [a], Malin Lindstedt [a]

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

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

Fredrik Svensson*†‡, Natalia Aniceto†, Ulf Norinder§ı, Isidro Cortes-Ciriano†, Ola Spjuth⊥, Lars Carlsson#∇, and Andreas Bender†

† Centre for Molecular Informatics, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U.K.
‡ IOTA Pharmaceuticals, St Johns Innovation Centre, Cowley Road, Cambridge CB4 0WS, U.K.
§ Swetox, Unit of Toxicology Sciences, Karolinska Institutet, Forskargatan 20, SE-151 36 Södertälje, Sweden
ı Department of Computer and Systems Sciences, Stockholm University, Box 7003, SE-164 07 Kista, Sweden
⊥ Department of Pharmaceutical Biosciences, Uppsala University, Box 591, SE-75124, Uppsala Sweden
Quantitative Biology, Discovery Sciences, IMED Biotech Unit, AstraZeneca, SE-43183, Mölndal, Sweden
∇ Department of Computer Science, Royal Holloway, University of London, Egham Hill, Surrey, U.K.

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Chemometrics and Intelligent Laboratory Systems
Volume 170, 15 November 2017, Pages 77-83

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

Yong-Huan Yun [a, b, c], Dong-Ming Wu [a, c], Guang-Yi Li [a, c], Qiao-Yan Zhang [a], Xia Yang [a], Qin-Fen Li [a, c], Dong-Sheng Cao [d], Qing-Song Xu [e]

Current common methods

Molecule classes

- Organic-Organometalic-Inorganic
- Class of molecules (Arom. Amines)

Feature representation

- Unseen features

Agreement based

- RF consensus
- kNN

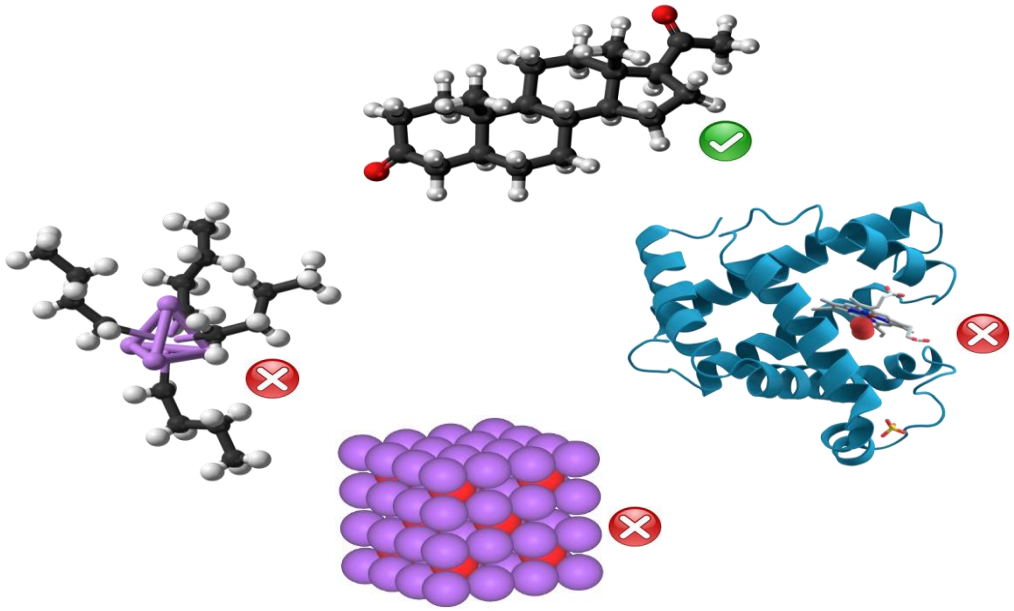
Descriptor ranges

- Box
- Convex hull

Distance based methods

- Distance to data points
- Density

Response domain



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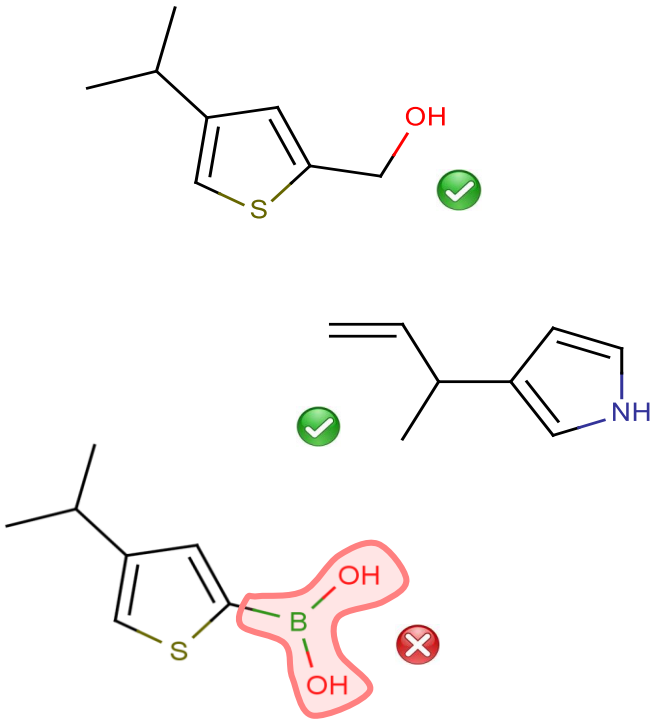

No boronic acids in the training set

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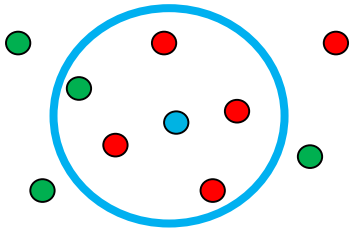
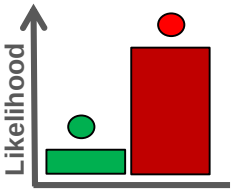
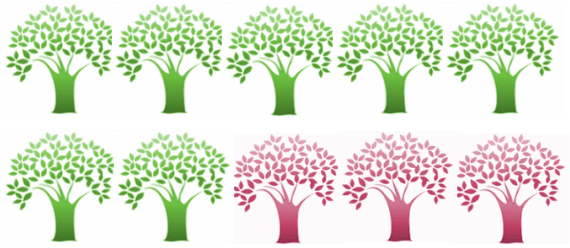
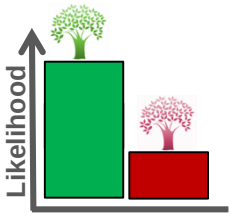




Nearest Neighbours





Random forest

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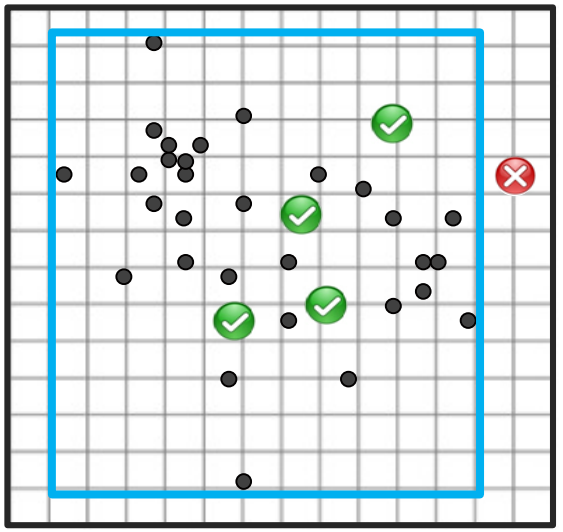

Box

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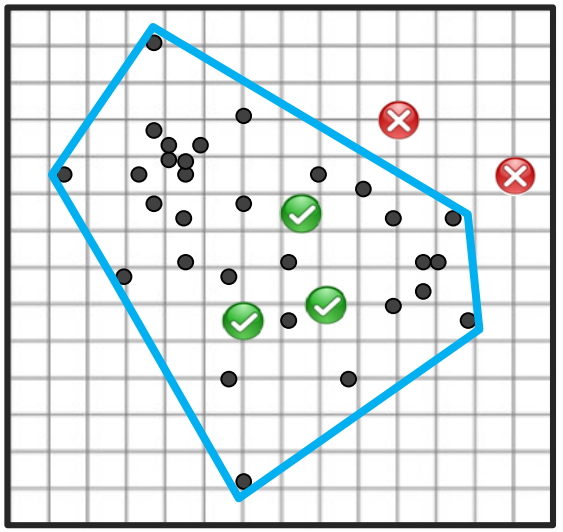

Convex hull

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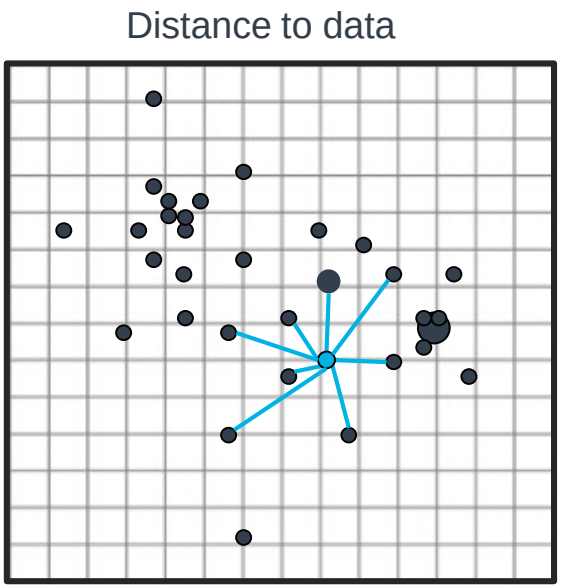

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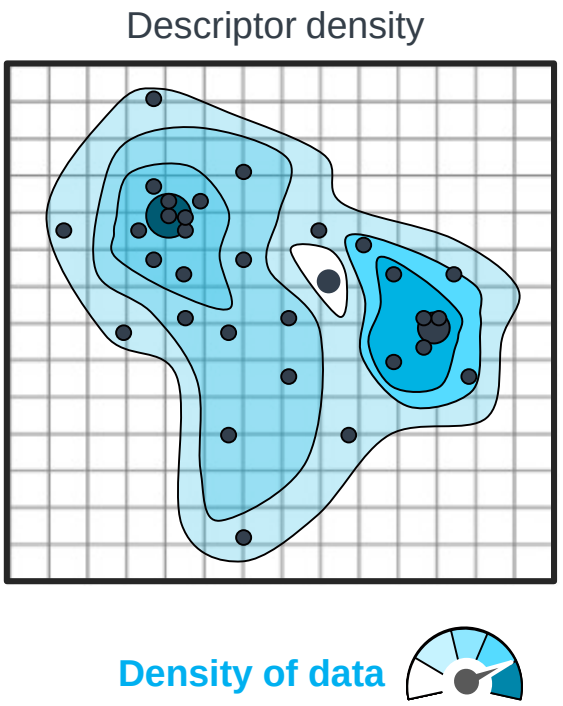
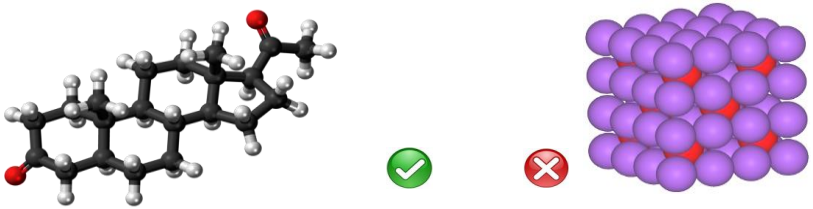
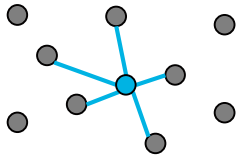


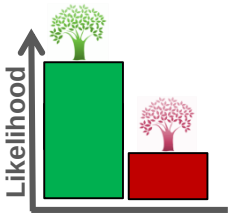
Mixture of different concepts



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

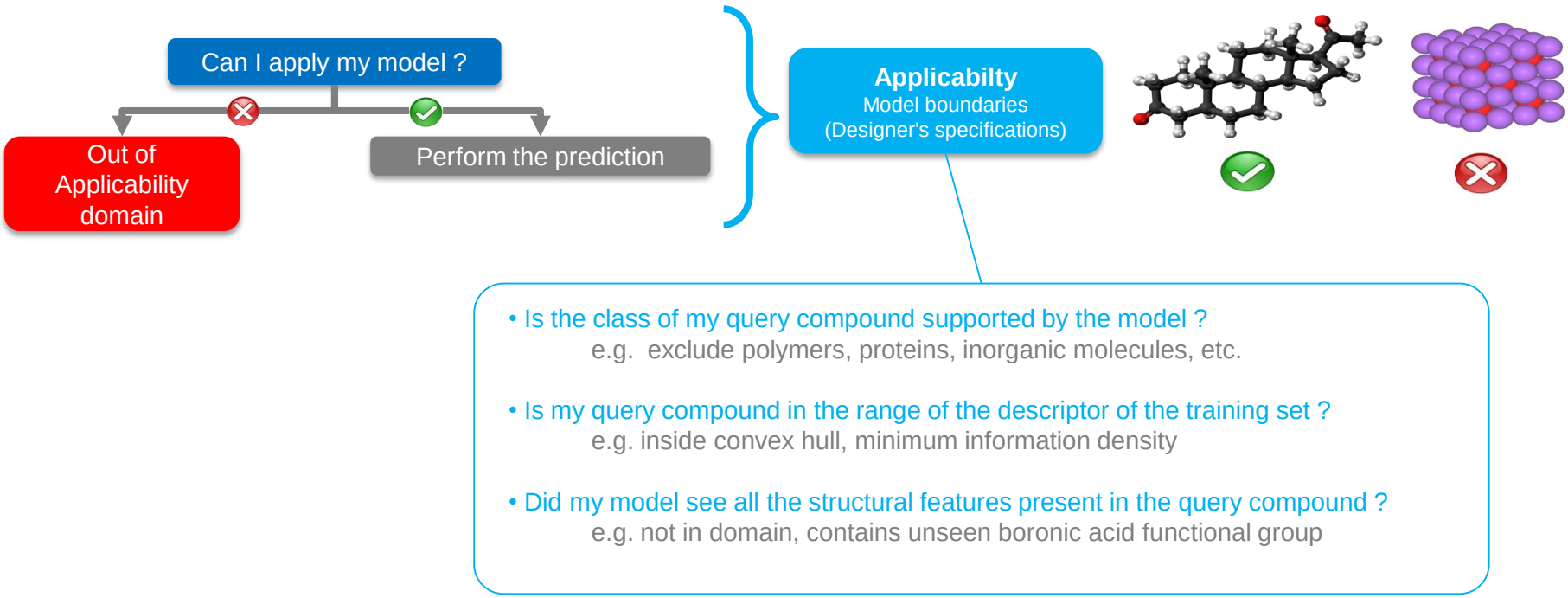
The prediction is reliable enough for my use case

Reliability domain

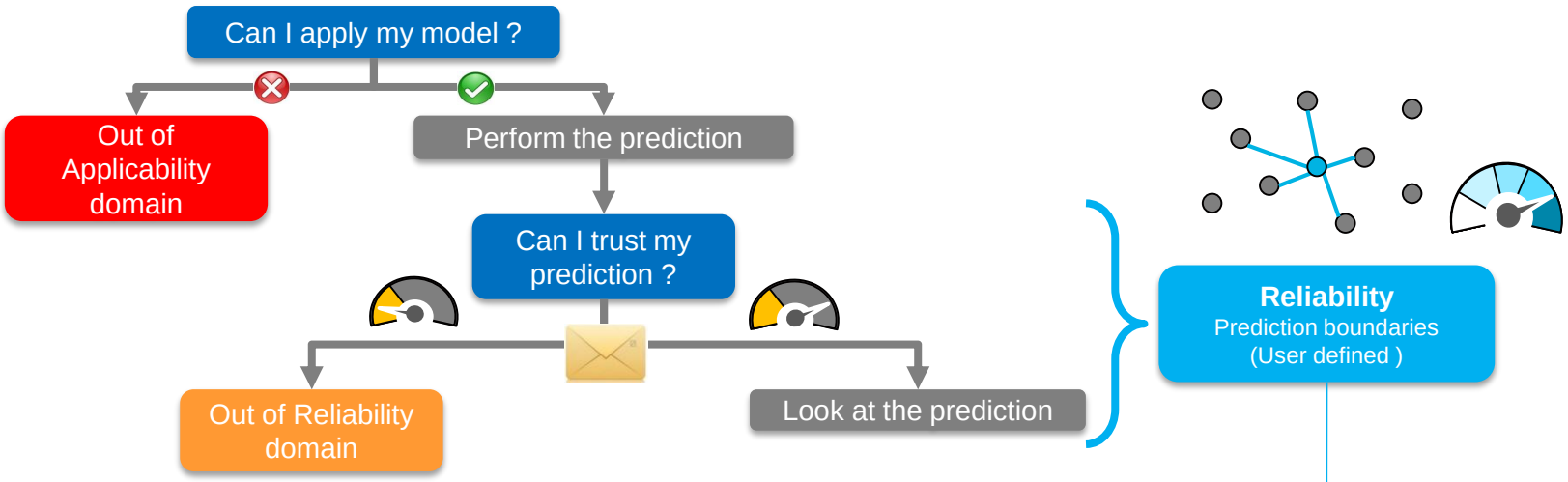
I can make a clear decision

Decidabiity domain

Applicability (of the model)



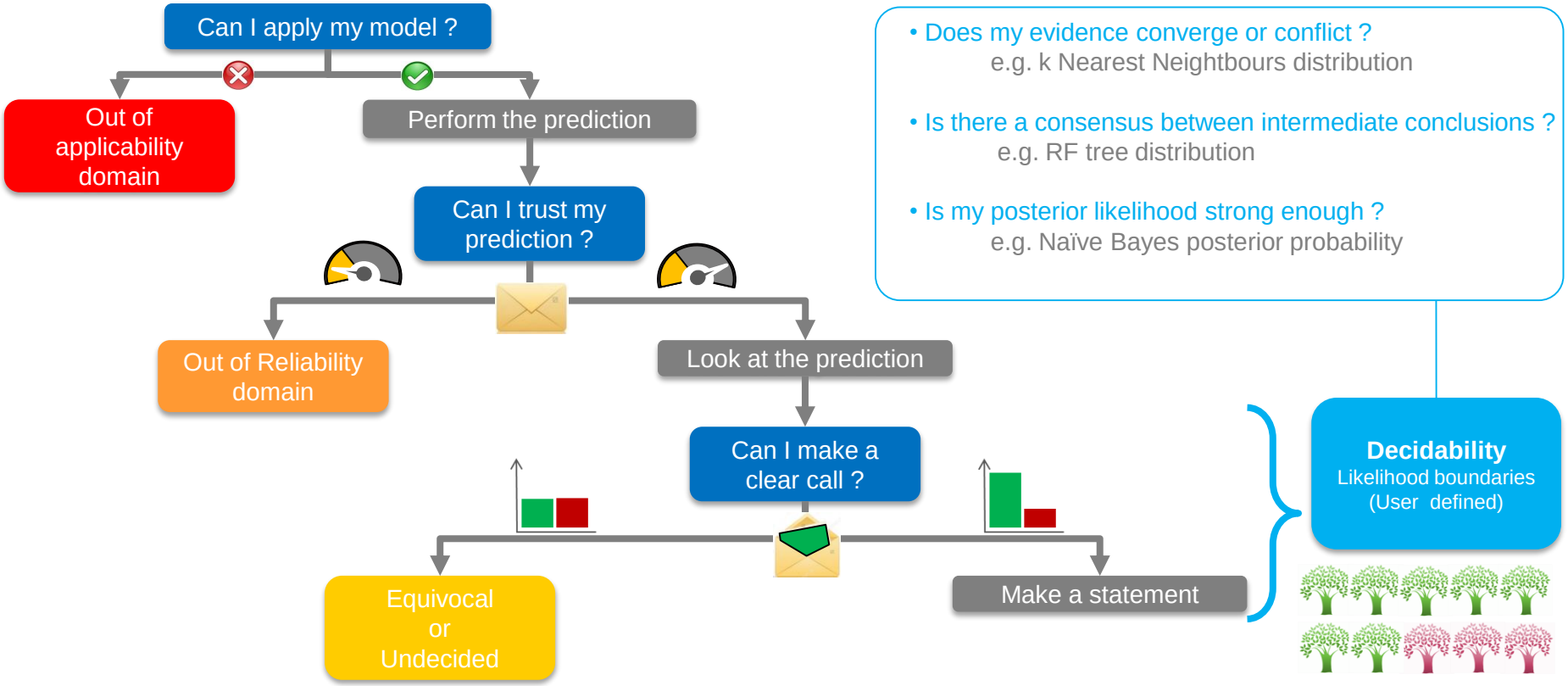
Reliability (of the prediction)



- 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

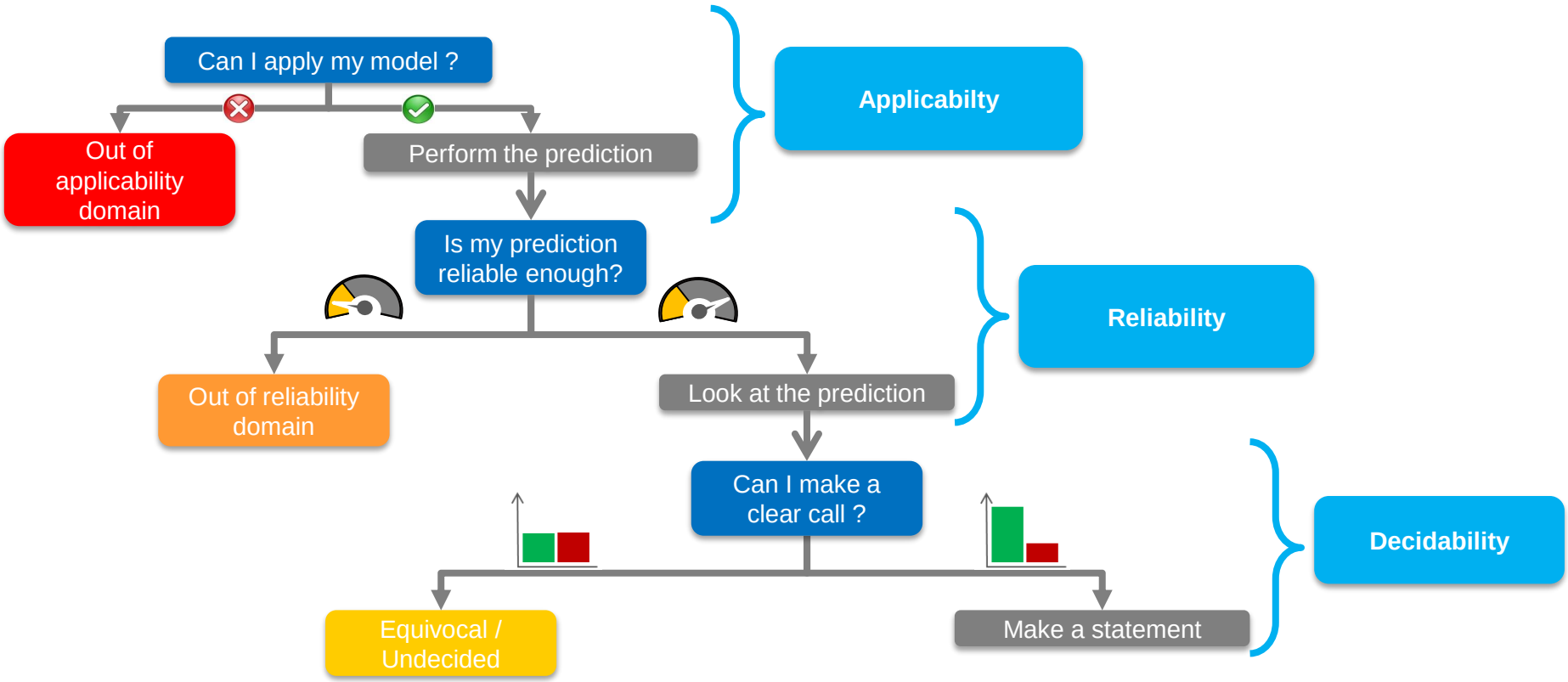
Aniceto, N., Freitas, A.A., Bender, A. et al. J Cheminform (2016) 8: 69. https://doi.org/10.1186/s13321-016-0182-y

Decidability (of the outcome)



Introducing Conformal Prediction in Predictive Modeling. A Transparent and Flexible Alternative to Applicability Domain Determination Ulf Norinder, Lars Carlsson, Scott Boyer, and Martin Eklund J. Chem. Inf. Model., 2014, 54 (6), pp 1596–1603

Intuitive, non ambigous and formal decision framework



Applicability domain: towards a more formal definition. Hanser T, Barber C, Marchaland JF, Werner S.
SAR QSAR Environ Res. 2016 Nov;27(11):893-909. Epub 2016 Nov 9.

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

shared **knowledge** • shared **progress**

Lhasa Limited

Granary Wharf House, 2 Canal Wharf

Leeds, LS11 5PS

Registered Charity (290866)

Company Registration Number 01765239

+44(0)113 394 6020

info@lhasalimited.org

www.lhasalimited.org