Filling knowledge gaps in Nanotoxicology with Read Across Predictions, Practice & Requirements

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ENM
eNanoMapper

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`lazar` read across framework

A reproducible version of the read across procedure commonly used in toxicological risk assessment (based on the k-nearest-neighbor algorithm)

- Search in a database for similar nanoparticles (*neighbors*)
- Build a local QSAR model with these neighbors
- Use this model to predict the activity of the query substance

`lazar` was originally designed for small molecules with a defined chemical structure. The nanoparticle extension was developed and validated within the eNanoMapper project.

Similarity calculation

Requirements

Descriptors (features) for the query substance and the neighbor candidate

Observation

A large number of irrelevant features can lead do meaningless similarity estimates

Relevant features

Features that correlate significantly with toxicity (Pearson correlation p-value < 0.05)

Weighted cosine similarity

- Scaled and centered *relevant feature* vectors
- Feature contributions weighted by Pearson correlation coefficient
- Similarity threshold: $sim > 0.5$

Local regression algorithms

- Weighted average
- Weighted partial least squares regression
- Weighted random forests

Partial least squares and random forest models use the `caret` R package with default settings

Prediction intervals: 1.96*RMSE of `carets` bootstrapped model predictions

If PLS/RF modelling or prediction fails, `lazar` resorts to using the weighted average method.

Validation

- 3 repeated 10-fold crossvalidations with independent training/test set splits
- *No* fixed random seed for training/test set splits, to avoid overfitting and to demonstrate the variability of validation results due to random training/test splits.
- Separate feature selection for each training dataset to avoid overfitting

Data requirements

- At least 100 examples per toxicity endpoint for statistically meaningful validation results
- At least non-empty intersection of descriptors for calculation of similarities

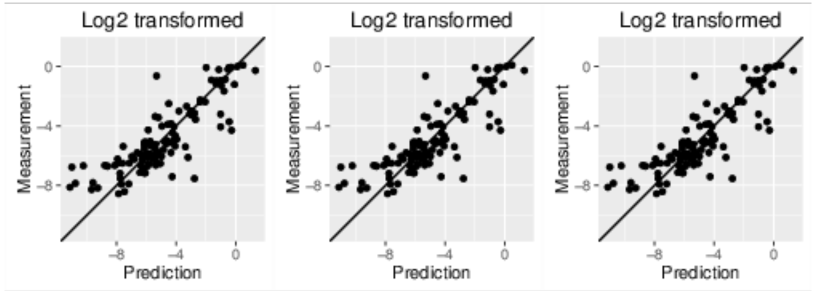
Net cell association endpoint of the *Protein corona* dataset (121 gold and silver particles)

10-fold crossvalidations

Descriptors	**Algorithm**	r^2	**RMSE**
Physchem	WA	0.42, 0.46, 0.48	2.02, 1.94, 1.92
Physchem	PLS	0.53, 0.54, 0.49	1.83, 1.8, 1.9
Physchem	RF	0.53, 0.52, 0.54	1.82, 1.84, 1.79
Proteomics	WA	0.66, 0.63, 0.63 *	1.58, 1.62, 1.66 *
Proteomics	PLS	0.59, 0.66, 0.63 *	1.74, 1.56, 1.65 *
Proteomics	RF	0.66, 0.65, 0.63 *	1.56, 1.59, 1.64 *
All	WA	0.73, 0.66, 0.66 *	1.41, 1.57, 1.58 *
All	PLS	0.67, 0.64, 0.69 *	1.53, 1.63, 1.5 *
All	RF	0.69, 0.69, 0.7 **	1.51, 1.5, 1.46 **

Gold *and* silver particles included!

Correlation plot



Correlation of log2 transformed net cell association measurements with random forest predictions using physchem properties and protein corona data.

Links

Nano-lazar GUI

https://nano-lazar.in-silico.ch

Lazar (source code)

https://github.com/opentox/lazar

Presentation (source code)

https://github.com/opentox/nano-lazar-paper

Docker image

https://hub.docker.com/r/insilicotox/nano-lazar-paper/

Nano-lazar development version

https://nano-lazar-dev.in-silico.ch/predict

Exercises

Try the nano-lazar versions at

Old (stable) version (physchem only)

https://nano-lazar.in-silico.ch

Next release

https://nano-lazar-dev.in-silico.ch/predict

Questions

- Do you think that nanoparticle predictions based on physchem parameters are a *practical* approach
- Do you think that nanoparticle predictions based on proteomics measurements are a *practical* approach
- What would you expect from a nanoparticle read-across application
  - *User input*
  - *Prediction output*
- Comments, bug reports and feature suggestions