Clinical predictions in CNS drug discovery based on in vivo systems response profiles and non-linear machine learning methodology

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Background

- The Integrative screening Process, ISP, uses linear dimensionality reducing methods, such as partial least squares regression (PLS), to analyze and compare systems response profiles capturing pharmacological effects on neurochemistry, behavior and gene expression (1). This approach is useful to understand multivariate dose response profiles for different compounds, and can be further applied for classification and prediction of clinical effect profiles. In this work, which was part of (2), we wanted to explore if nonlinear methods could improve such translational models and predictions.

Method

- Nonlinear methodology was applied for multidimensional in vivo pharmacological dose-response data (postmortem neurochemistry in several brain regions, behavioral patterns) on a broad array of CNS therapeutics and exploratory compounds.
- t-distributed stochastic neighbor embedding (t-SNE) and kernel PLS were applied for dimensionality reduction and visualization on a data set of 850 observations/55 compounds (n=4-5 observations/dose group).
- Classification of compounds into clinical classes based on therapeutic usage was performed using linear logistic regression as well as nonlinear random forest and multilayer perceptron networks. The clinical classes in the investigated data were antidepressants (AD), drugs for attention deficit hyperactivity disorder (ADHD), cognitive/drugs for dementia (cogn), drugs for Parkinson, antipsychotics (AP), atypical antipsychotics (AP2) and drugs of abuse. The data set consisted of 2880 observations and was divided, using stratified sampling, into one set used for training and validation (87%) in the k-fold cross-validation technique, and another set for testing (13%).
- Based on performance metrics (precision, recall, F1 score), the best performing classifier was applied on a separate data set of 85 exploratory compounds.

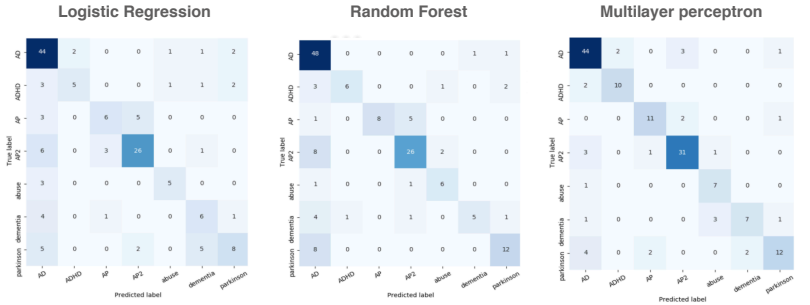

Figure 1. Confusion matrices showing number of predictions in different classes for the classifier yielding best F1 score for the investigated methods.

Classifier performance metrics per class

$$\text{Precision} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Positive}}$$

$$\text{Recall} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}}$$

Figure 2. Performance metrics where true positives are correct predictions, false positives are predictions to a class that are not of this class and false negatives are predictions of a class that are falsely classified to another class. The F1 score is the harmonic mean of Precision and Recall.

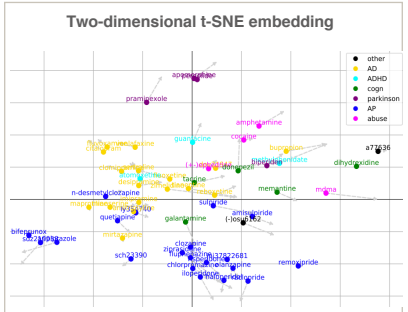

Figure 3. t-SNE embedding. Dots are in the average of all observations for one compound. From each dot, there is an arrow pointing in the direction of increasing dose-level of the test compound.

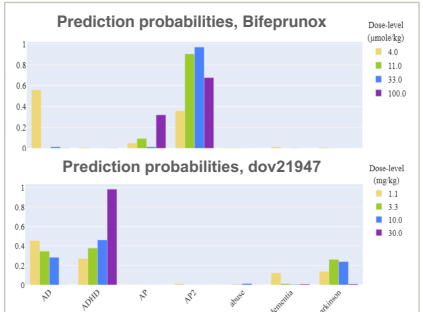

Figure 4. Average prediction probabilities of two compounds using a perceptron network. Bifeprunox, showing reasonable classification (AD/AP2/AP) and dov21947, showing potentially unknown effects, i.e., the ADHD classification, especially at larger dose levels.

Results and conclusion

- Results from nonlinear dimensionality reduction methods yielded similar results, compared to linear methods (1). However, in particular, t-SNE modelling resulted in somewhat different clustering and appears promising to build upon in further applications.
- The best performing classification method, the perceptron network, shows results corresponding to well-known effects for 71% of the exploratory compounds.
- Moreover, classifications of 12% of the compounds indicate potentially unknown effects, which are interesting and could be a springboard for further analysis.
- One important advantage with these nonlinear classifications is that they handle bell-shaped and other nonlinear dose responses and compounds displaying different mode of action at different doses.
- Based on in vivo phenotypic response profiles, the conclusion is that nonlinear classification methods, in particular multilayer perceptron networks, performed well in terms of correct classifications. This further indicated potential new classes of interest in several cases, suggesting use for e.g. drug repurposing purposes.

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Acknowledgments:

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