chemmodlab

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Abstract An abstract of less than 150 words.

Introduction

[TODO this text was written for JCIM and needs to be made less specific to cheminformatics for r journal]

In the recent years, virtual screening technologies have become an integral part of the discovery pipeline. In this pipeline, fast and accurate virtual screening methods are necessary to reduce a pool of compounds on the order of 10 million to a few thousand that are enriched for potential actives and can be tested experimentally. While only one approach to virtual screening, QSAR-based methods have become pervasive in the recent years. Cherkasov et al have recently reviewed [REF] numerous recent examples of QSAR-based virtual screening leading to the experimental identification of novel, highly active compounds. For example, Zhang et al [REF] have recently used QSAR models to virtually screen the ChemBridge library for novel antimalarials. They confirmed 25 of these predictions experimentally, some of which had novel scaffolds, opening up new avenues for lead optimization and further exploration of new antimalarial chemical structures. However QSAR model performance can vary dramatically and it is often unclear which modeling method and/or descriptor set will have the best performance for a particular data set [Hopfinger REF]. Therefore, it is often necessary to use multiple modeling routines and compare their performance with measures of prediction accuracy for held out data.

- Importance of QSAR based virtual screening methods
  - Need highly accurate models to screen large databases and locate only a few actives
  - Example of how QSAR predictions have been experimentally confirmed and identified novel, highly active compounds
- Difficulties with QSAR models
  - High dimensional data with many predictors and few observations. Non-linear relationships between predictors and response. Models must have enough flexibility to adequately capture complex relationships.
  - Often unclear which model will have the best performance - need to try many
  - However, in Cheminformatics literature only a few modeling strategies are typically compared
  - Variability of model accuracy measures with different splits is often ignored
- ChemModLab
  - State there was previously a webserver and now is an R-package
  - Can now analyze any set of descriptors and can take advantage of several nice packages for computing chemical descriptors like RDkit.
  - Goal: Streamline fitting and assessing many QSAR models
  - Implements 12 machine learning models in R (svm, neural nets, random forests, etc)
  - Requires little user intervention – fits all models with one command
  - Provides sensible defaults for tuning parameters
  - Users can tune and set parameters manually if they like
  - Fits any subset of these models to any number of descriptor sets the user provides
  - Performs repeated k-fold cross-validation to assess model accuracy
- Mention specifically new features that have been implemented
  - Implemented many new accuracy measures
  - Users can now customize tuning parameters
  - Parallel processing

chemmodlab implementation

Overview

chemmodlab takes advantage of the numerous machine learning models already implemented in the R environment. Its primary aim is to streamline the process of model fitting so that users do not have

to learn the syntax and best practices for fitting each model separately. **chemmodlab** is organized into two successive components: (1) model fitting and (2) model assessment.

An illustrative example

We will use a cheminformatics data set to illustrate a typical analysis pipeline in **chemmodlab**. In cheminformatics, chemists often build machine learning models that relate a chemical compound's structure to an observed endpoint. These models are collectively referred to as quantitative structure activity relationship (QSAR) models. See [REF] for an excellent review of the ways in which these models have played a crucial role in the drug discovery process. Often the "endpoint" (or response variable) is a measure of a compound's biological activity, which may be either binary, indicating active/inactive, or a continuous measure of binding affinity for a target protein. Chemical "descriptors" (also known as predictors, features, or covariates) represent various levels of organization of a chemical's structure. See [REF] for an overview of commonly used chemical descriptors.

The data we will analyze is from a cytotoxicity assay conducted by the Scripps Research Institute Molecular Screening Center. There are 3,286 compounds, 50 of which are active. Visit http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=364 for more details.

For completeness, the preprocessing of the data set analyzed will be shown. First, the response variable and molecule ID's are read in from file.

```
data <- read.csv("AID_364_response.csv")
head(data)
```

```
#>        CID Outcome
#> 1  5388992       1
#> 2  5388983       1
#> 3   663143       1
#> 4    10607       1
#> 5  5388972       1
#> 6 11970251       1
```

Next, two descriptor sets are added to the data frame. Both of these sets were computed using the software, PowerMV - see [REF] for more information. The first set of continuous descriptors are a modification of the Burden number descriptors [REF].

```
desc.lengths <- c()
d <- read.csv("BurdenNumbers.csv")
head(d[, 1:5])
```

```
#>        Row WBN_GC_L_0.25 WBN_GC_H_0.25 WBN_GC_L_0.50 WBN_GC_H_0.50
#> 1  5388992      -2.40010       1.98339      -2.52864       2.50835
#> 2  5388983      -2.40010       1.98240      -2.52868       2.50398
#> 3   663143      -2.41650       1.32890      -2.53910       2.05778
#> 4    10607      -2.38337       2.17677      -2.52643       2.33232
#> 5  5388972      -2.29039       1.97468      -2.41743       2.46177
#> 6 11970251      -2.29039       2.22488      -2.41748       2.56161
```

```
data <- cbind(data, d[-1])
desc.lengths <- c(desc.lengths, ncol(d[-1]))
```

The number of descriptors in each descriptor set are also stored, as this information will be used to parse the data frame later on. The second set contains binary descriptors, indicating the presence/absence of "pharmacophore" features, described in more detail in [REF].

```
d <- read.csv("Pharmacophores.csv")
head(d[, 1:6])
```

```
#>        Row NEG_01_NEG NEG_02_NEG NEG_03_NEG NEG_04_NEG NEG_05_NEG
#> 1  5388992          0          0          0          0          0
#> 2  5388983          0          0          0          0          0
#> 3   663143          0          0          0          0          0
#> 4    10607          0          0          0          0          0
#> 5  5388972          0          0          0          0          0
#> 6 11970251          0          0          0          0          0
```

```
data <- cbind(data, d[-1])
desc.lengths <- c(desc.lengths, ncol(d[-1]))

dim(data)

#> [1] 3311  173

aid364 <- data
```

Model fitting: The ModelTrain function

For the model fitting component of **chemmodlab**, the primary function is **ModelTrain**, which fits a series of classification or regression models to a data set.

The *data* input parameter

This function takes as input a data frame with an (optional) ID column, a response column, and descriptor columns. We have processed the *aid364* data set so that it follows this format. The specification of an ID column allows users to easily match response predictions to their observation IDs in the **chemmodlab** output. **chemmodlab** can currently handle responses that are continuous or binary (represented as a numeric vector with 0 or 1 values). Users can specify which columns in the data frame they would like to consider distinct descriptor sets. At the moment, the response and descriptors may only be binary or continuous, though we are currently working on support for categorical variables of more than two levels.

We previously stored the number of descriptors in each descriptor set in an integer vector named *desc.lengths*, with the ordering of the integers matching the order of the descriptor sets in *aid364*:

```
desc.lengths

#> [1]  24 147
```

Users can also name the descriptor sets by providing a character vector to the *des.names* parameter. If this character vector is specified, all of **ModelTrain** output and downstream **chemmodlab** functions will name the descriptor sets accordingly:

```
des.names = c("BurdenNumbers", "Pharmacophores")
```

The specification of distinct descriptor sets in a data frame is illustrated in the following call to **ModelTrain**:

```
cml <- ModelTrain(aid364, ids = TRUE, xcol.lengths = desc.lengths,
                  des.names = des.names)
```

If the descriptor set columns are not identified by the user, ModelTrain assumes there is one descriptor set, all columns in data except ycol and the optional ID column.

chemmodlab models

Currently, 13 different machine learning models are implemented in **chemmodlab**. The details of each modeling method, including descriptions of the default parameters are provided at https://jrash.github.io/chemmodlab/ (TODO make this into a table and put in Supporting Info). Briefly, the current models are: elastic net, k-nearest neighbors, least angle regression, neural networks, partial least squares linear discriminant analysis, partial least squares, principal components regression, ridge regression, random forest, two implementations of recursive partitioning, and support vector machines.

Some modeling strategies may not be suitable for both binary and continous responses. Six of the models have implementations in R that directly support both binary and continuous responses (both implementations of recursive partitioning, random forest, k-nearest neighbors, neural networks, and support vector machines). However, five methods (least angle regression, ridge regression, elastic net, principal components regression, and partial least squares) assume that responses have equal variances and normal distributions. This assumption is often reasonable for continuous responses, but may be suspect if the response is binary. However, these models can be viewed as a modification to linear discriminant analysis and still may be appropriate for binary responses [TODO This point was made in the former chemmodlab paper, but I am not sure if I follow the arguement]. Binary responses

are treated as continuous, resulting in continuous response predictions that are not restricted to range between 0 and 1. A threshold can then be applied to obtain a binary predicted response. The model assessment functions discussed later allow users to select this threshold. Finally, partial least squares linear discriminant analysis (PLSLDA) cannot be applied to a continous response, but if the user wishes to analyze this type of data, a threshold value may be used to convert a continuous response to a binary one.

In cheminformatics applications, descriptors often show strong multicollinearity. Since this is often problematic for machine learning models, we have specifically included several models in **chemmodlab** that are known to be resilient to multicollinearity (eg. principal components regression and partial least squares regression). However, some methods for which prediction is not considerably affected by multicollinearity do suffer in terms of model interpretability (eg. recursive partitioning and random forests).

chemmodlab has been designed in a way that it is easily extensible to new machine learning modeling methods, and new modeling methods will be added as the authors identify those that have broad utility to our users. Support for other models can be requested here: https://github.ncsu.edu/jrash/chemmodlab/issues.

chemmodlab automatically performs data preprocessing before fitting the models that require it (eg. centering and scaling variables before principal components regression), so the user need not worry about preprocessing of descriptors prior to model fitting.

Specifying model parameters with *user.params*

Sensible default values are selected for each tunable model parameter, however users may set any parameter manually using the *user.params* parameter.

MakeModelDefaults is a convenience function that makes a list containing the default parameters fDor all models implemented in ModelTrain. Users may set any parameter manually by generating a list with this function and modifying the parameters assigned to each modeling method:

```
params <- MakeModelDefaults(n = nrow(aid364),
 p = ncol(aid364[, -c(1, 2)]), classify = TRUE, nfolds = 10)
params[1:3]
```

```
#> $NNet
#>   size decay
#> 1    2     0
#>
#> $PCR
#> NULL
#>
#> $ENet
#>   lambda
#> 1      1
```

```
params$NNet$size <- 10
params[1:3]
```

```
#> $NNet
#>   size decay
#> 1   10     0
#>
#> $PCR
#> NULL
#>
#> $ENet
#>   lambda
#> 1      1
```

This list can then be provided to the *user.params* parameter to assign the tuning parameter values used by **ModelTrain**:

```
cml <- ModelTrain(USArrests, models = "NNet", nsplits = 3,
 user.params = params)
```

Model assessment

Repeated k-fold cross-validation

For each descriptor set, **ModelTrain** performs repeated k-fold cross validation for the selected set of regression and/or classification models.

For each cross-validation split, observations are randomly assigned to one of k folds, splitting the data set into k blocks that are approximately equal in size. The number of cross validation folds (k) is set with the *nfolds* parameter. Users may also use the *seed.in* parameter to set the seed for each split, so that the **ModelTrain** results are reproducible. Each block is iteratively held out as a test set, while the remaining $k-1$ blocks are used to train each descriptor set and modeling method (D-M) combination. Predictions for the held out test set are then made with the resulting models.

Many resampling methods for assessing model performance involve partitioning a data set into a training set and test set. With these methods, predictions are made on observations that are not involved in training. This results in model performance measures that are less likely to reward over-fitting.

Since performance measures can be highly variable (James et al., 2013) depending on which observations are held out and which are involved in training, the repetition of this procedure during k-fold cross validation and the averaging of the performance measures often result in a more accurate estimation of model performance than a one-time split.

Finding the right number of cross-validation folds for the estimation of a performance measure involves consideration of the **bias-variance trade off**. The mean squared error of an estimator, a measure of how accurately an estimator estimates the true value of parameter, can be partitioned into two components, bias and variance:

$$E[\hat{\theta} - \theta] = (E[\hat{\theta}] - \theta)^2 + Var[\theta]$$

Where $\hat{\theta}$ is the estimate of the true performance measure θ. The first component is bias and the second is variance. An increase in either the bias or variance will decrease the quality of an estimator. When a resampling method substantially over- or under-estimates a performance measure on average, it is said to have high **bias**. Bias is often related to size of the data set that is held out as a test set (James et al., 2013). The smaller the number of folds in k-fold cross validation, the more observations are held out in each fold, and the less observations that are used to train a model. Fewer observations in a training set means that a model is likely to perform worse, and model performance tends to be underestimated. Thus, performing k-fold cross validation with 2 folds, where there is 50% of the data in each fold, would likely result in high bias.

In contrast, a performance measure estimator suffers from high **variance** when its estimate varies considerably when there are slight changes made to the training and/or test set. Leave-One-Out-Cross-Validation (LOOV) refers to k-fold cross validation with k equal to n, the number of observations. LOOCV often suffers from high variance (James et al., 2013). This is due to the fact that the training set changes very little with each iteration of LOOCV. Thus, performance measure estimates tend be highly correlated. The mean of a highly correlated variable has higher variance than an uncorrelated one. Decreasing the number of folds tends to decrease the correlation of performance measure estimates and lower the variance. Therefore, the ideal number of folds to use for cross validation is often somewhere between 2 and n. The number of folds often used for k-fold cross validation are 5 and 10, as these values frequently provide a good balance between bias and variance.

Several studies (Molinaro et al., 2005; Kim, 2009; Shen et al., 2011) have shown that repeated cross validation can reduce the variance for a k-fold cross validation procedure with low bias, achieving a more accurate estimation of model performance. When k-fold cross validation is repeated in **chemmodlab**, multiple iterations of random fold assignment, or "splits", are performed. Because the observed performance measures may vary greatly depending on the definition of folds during k-fold cross validation, all models are built using the same fold assignment, thus using fold definition as a "blocking factor" in the assesment investigation. This process is repeated for multiple k-fold cross validation runs. The user may choose the number of these splits with the *nsplit* parameter.

We will see later how, in addition to increased accuracy in estimation of performance measures, repeated cross validation allows one to measure the standard error of model performance measures, quantifying how sensitive performance measures are to fold assignments.

Accumulation curves

plot.chemmodlab takes a **chemmodlab** object output by the **ModelTrain** function and creates a series of accumulation curve plots for assessing model performance.

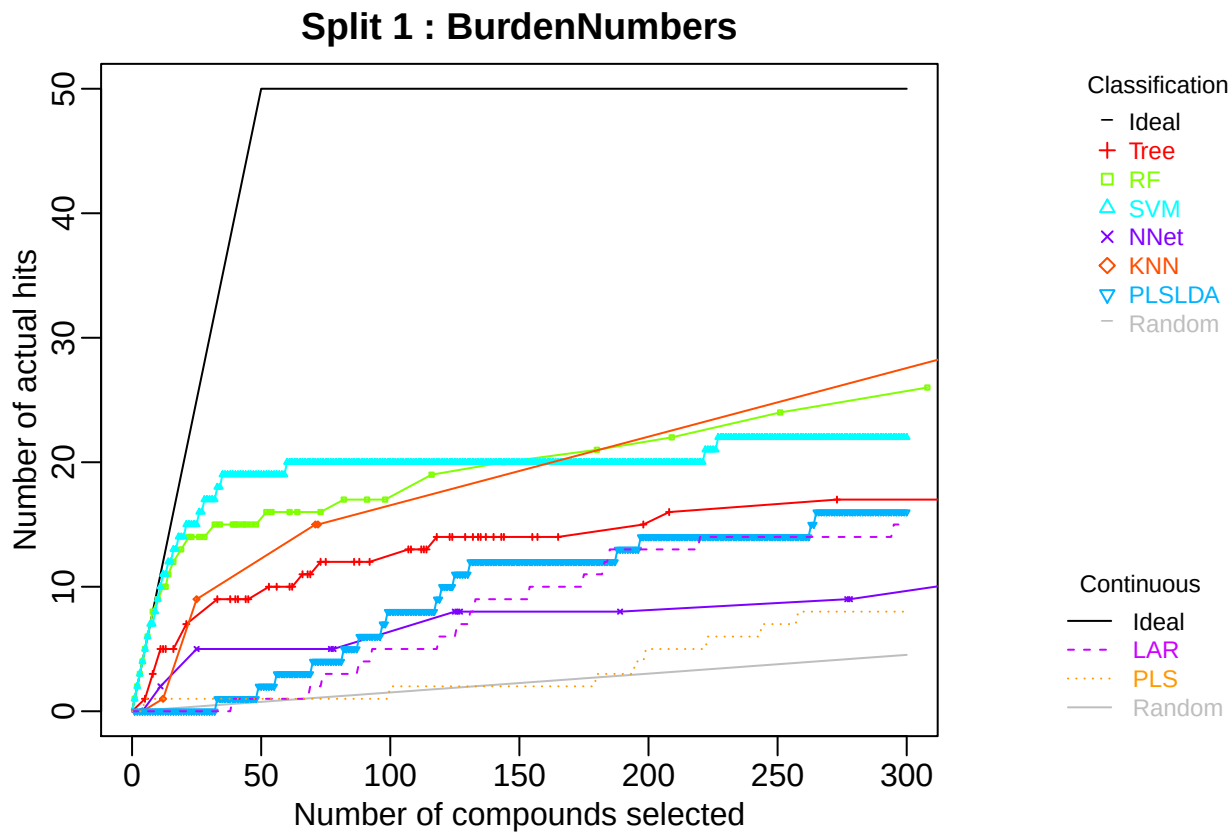
The accumulation curve for binary responses shows the number of positives versus the number of "tests" performed, where testing order is determined by the k-fold cross validated predicted probability of a response being positive.

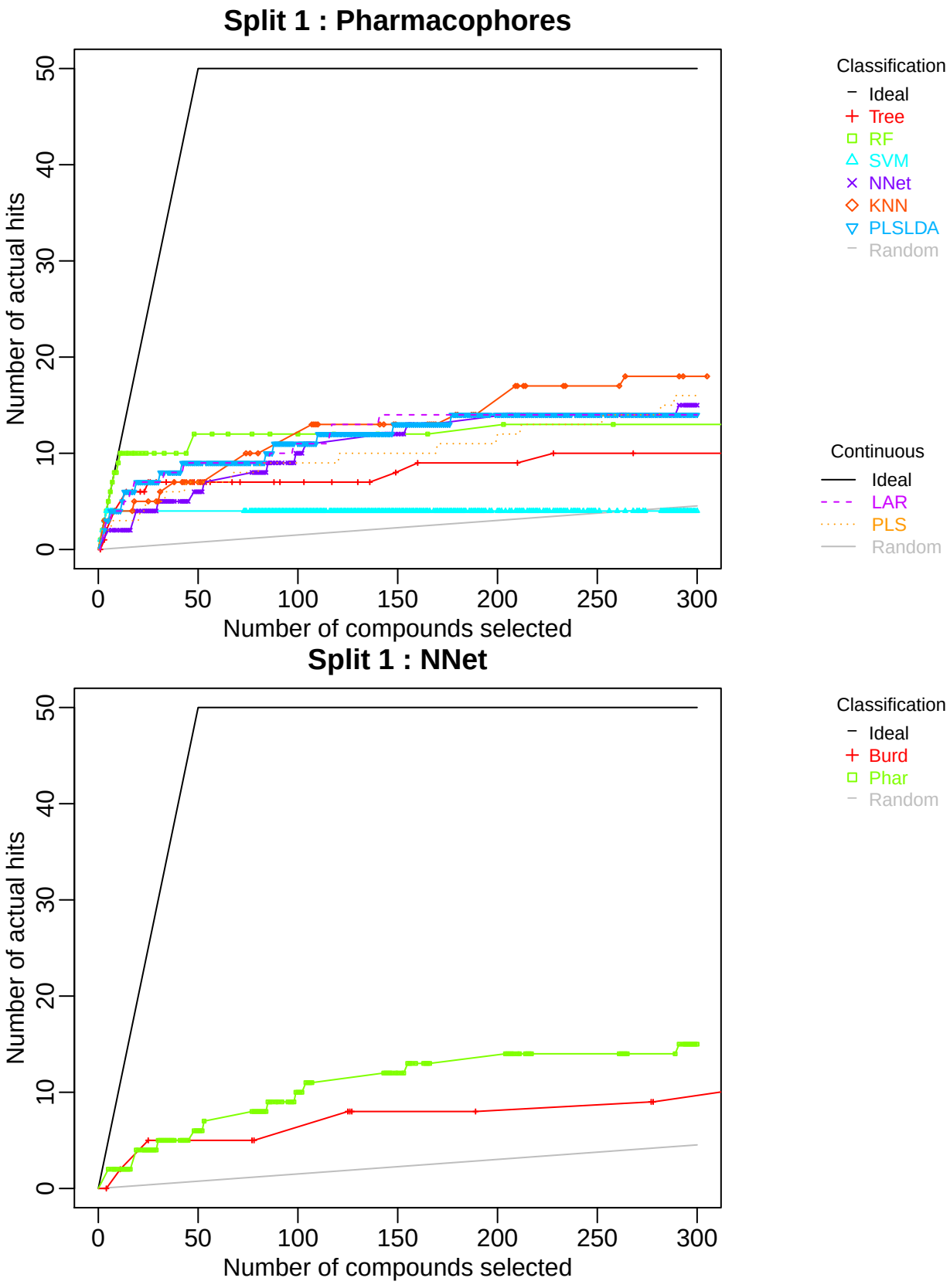
The *max.select* parameter sets the maximum number of tests to plot for the accumulation curves. By default, $\lfloor \min(300, \frac{n}{4}) \rfloor$ is used, where n is the number of observations. This prioritizes finding actives in a relatively small number of tests.

Two series of plots are constructed. In the first series, there is one plot per CV split and descriptor set combination. The accumulation curves for each model are plotted together so that they can be compared. In the second plot series, there is one plot per CV split and model fit. The accumulation curves for each descriptor set are plotted together so that they can be compared.

By default a large number of accumulation curve plots are constructed. The *splits* and *meths* parameters may be used to select a subset of splits and/or methods to plot.

```
plot(cml, splits = 1, meths = c("NNet"))
```





An "ideal" curve is plotted on these graphs to demonstrate the accumulation curve of a model that correctly identifies the p positives in the first p tests. Thus, at n tests, models with accumulation curves that are nearest to the ideal curve are preferable. Also, if an accumulation curve has a slope that is parallel to the ideal curve for an interval of tests, the model has ideal performance for that interval. A "random" curve shows the accumulation curve if the testing order were decided at random. At n tests, models with accumulation curves that are below the random curve have worse performance

than random chance.

The accumulation curve has also been extended to continuous responses. In QSAR models, a continuous response is often a measure of binding affinity (eg. pKi) where a large positive value is preferable. Therefore, observations on the x-axis are in decreasing order according to the response. The response is then accumulated so that $\sum_{i=1}^{m} y_i$ is the sum of the y over the first m tests. The binary response accumulation curve is a special case of this.

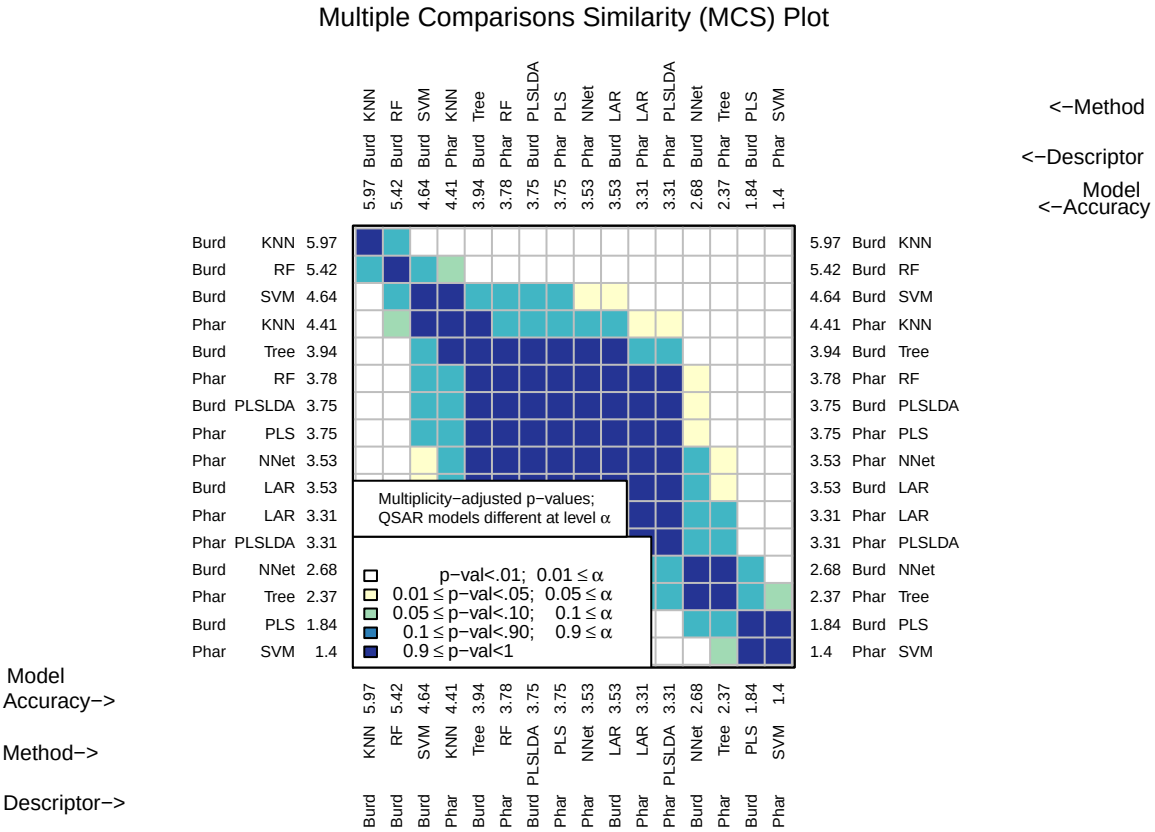
Multiple comparisons plots

Observed performance measures are assessed across all splits using **CombineSplits**. This function assesses how sensitive performance measures are to fold assignments, or small changes to the training and test sets. Multiplicity-adjusted statistical tests are used to determine the best performing D-M combination. Intuitively, this assesses how much a performance measure may change if a slightly different data set is used.

As input, **CombineSplits** takes a **chemmodlab** object produced by the **ModelTrain** function:

```
CombineSplits(cml)
```

```
#>    Analysis of Variance on: 'enhancement'
#>  Using factors: Split and Descriptor/Method combination
#> Source    DF        SS        MS         F   p-value
#> Model     17   65.7202    3.8659   32.3901    <.0001
#> Error     30    3.5806    0.1194
#> Total     47   69.3008
#>       R-Square   Coef Var   Root MSE       Mean
#>         0.9483     9.5895     0.3455     3.6027
#> Source       DF       SS       MS        F   p-value
#> Split         2    1.585    0.792    6.638    0.0046
#> Desc/Meth    15   64.136    4.276   35.824    <.0001
```



By default, **CombineSplits** uses initial enhancement proposed by Kearsley et al. [REF] to assess model performance. Initial enhancement at n tests is the hit rate - the fraction of accumulated positives at n tests - divided by the porportion of positives in the entire data set. This is a measure hit rate improvement for a model relative to random chance. A desirable model will have an initial enhancement much larger than one. A typical number of tests for initial enhancement is $n = 300$.

CombineSplits is a designed experiment with two factors: method (D-M combination) and split (fold assignment). Therefore, we perform an analysis of variance (ANOVA) to identify significant differences between the mean performance measures according to factor levels. The linear model corresponding to this ANOVA is:

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \epsilon_{ijk}$$

Where α_i corresponds to ith level of the split factor α and β_j to the jth level of the method factor β. From the ANOVA table in this example, the split factor is highly significant, indicating that there is a significant difference between mean split performance measures for a fixed method. The difference between mean method performance measures is also highly significant for a fixed split. The "error MS" estimates the variance in the performance measures within the groups corresponding to each combination of factor levels. The "treatment MS" estimates the variance between groups.

[TODO From the ChemModLab paper: 'ChemModLab is a designed study in that we defined "experimental" conditions according to two factors: modeling method (allowed to take 12 "levels") and descriptor set (allowed to take five "levels")....To broaden our range of inference, we include assay as a third factor. Recognizing that the definition of folds in k-fold cross validation may have an impact on observed IE, fold definition is treated as a blocking factor.'

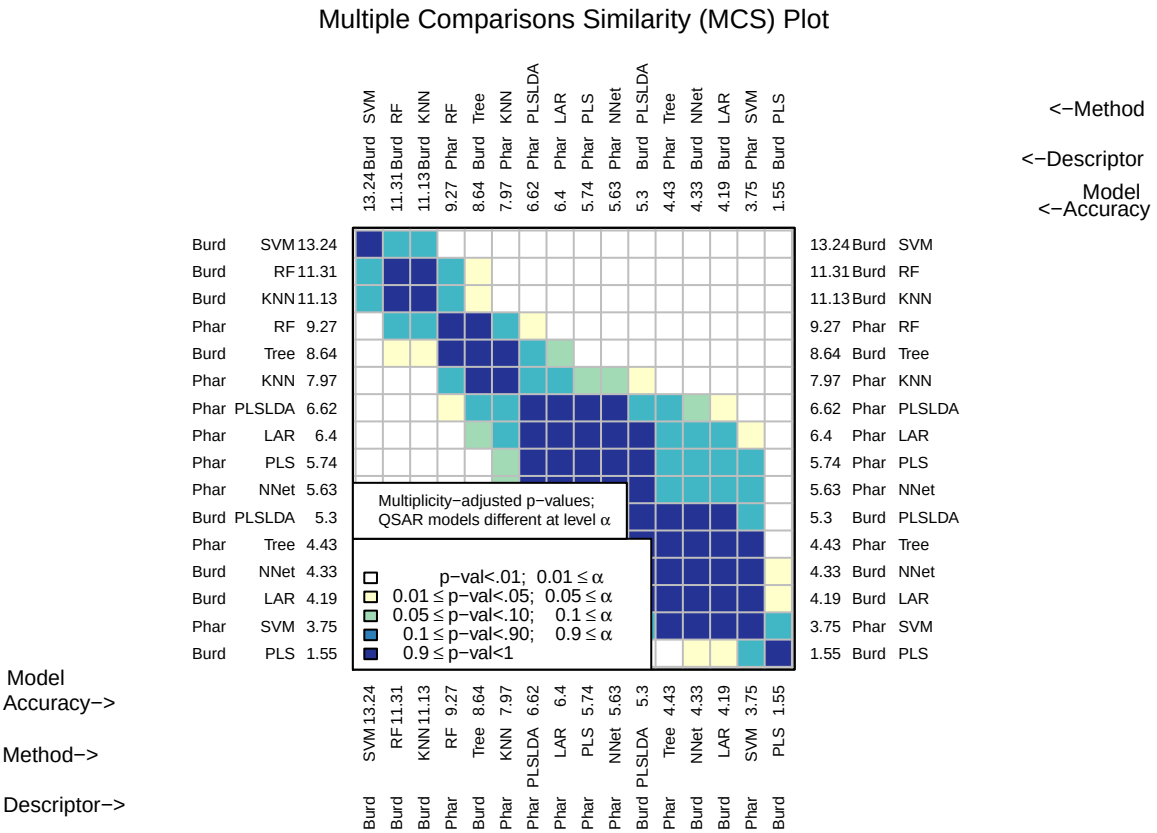
From looking at the code, I believe that there should be two factors, split and D-M combination. Has the definition of the factors changed from the way they were defined in the ChemModLab paper? Also With this data set, we are fitting 16 models, with 2 descriptor sets and 3 splits. So, shouldnt there be 32-1 = 31 df for the D-M combination factor, and 3-1 = 2 df for the split factor? From the ANOVA tables it seems that the two factors are split and method. It seems that the degrees of freedom match this definition of factors (15 for the method factor and 2 for the split factor). Is there a potentially a bug in the code?]

The multiple comparisons plot shows the results for tests for significance in all pairwise differences of mean model performance measures. Because there can be many estimated mean performance measures, an adjustment for multiple testing is necessary. We use the Tukey-Kramer multiple comparison procedure (see Tukey [REF] and Kramer [REF]). If you are having trouble viewing all the components of the plot, make the plotting window larger.

For many applications, user may know the number of tests they would like to perform. This is often the case in drug discovery when chemists have a set number of compounds they would like to assay and the goal is to enrich this set of compounds with as many actives as possible. The number of tests used for initial enhancement may be modified with the *at* parameter:

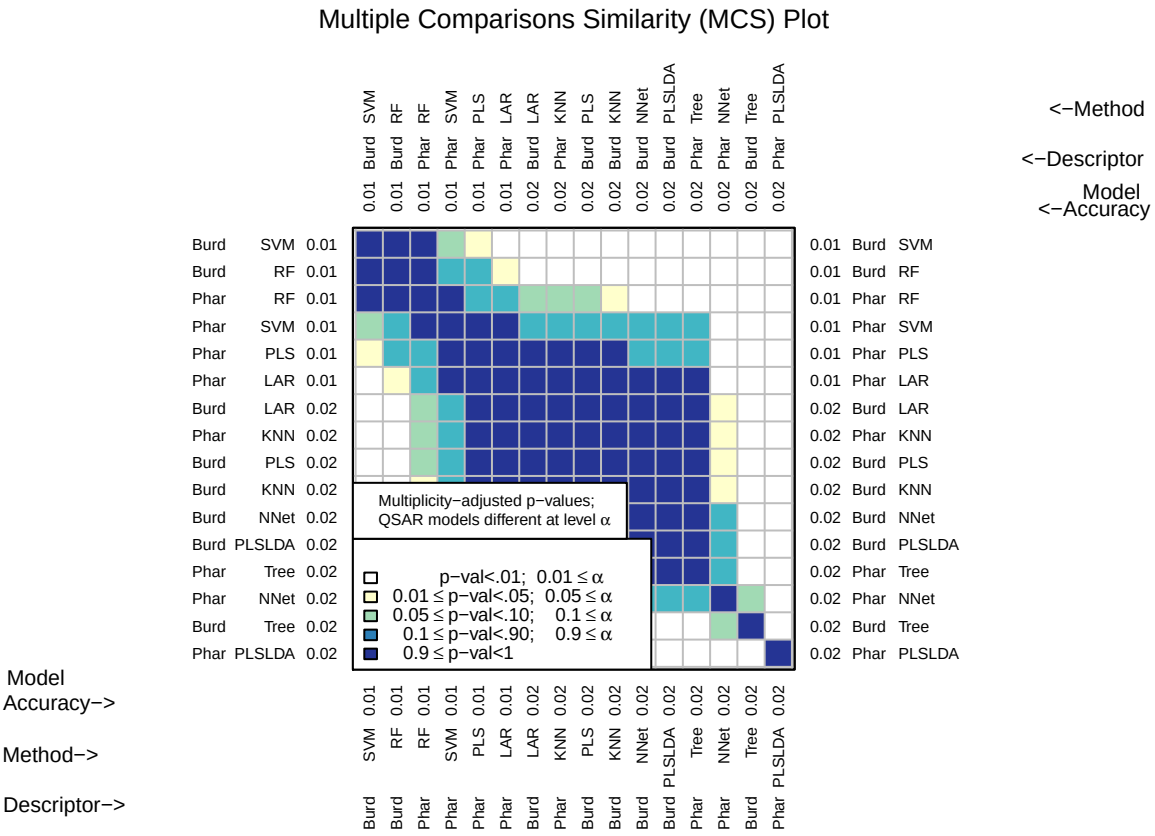
```
CombineSplits(cml, at = 100)
```

```
#>    Analysis of Variance on: 'enhancement'
#>  Using factors: Split and Descriptor/Method combination
#> Source    DF        SS        MS         F   p-value
#> Model     17   460.546    27.091    43.072    <.0001
#> Error     30    18.869     0.629
#> Total     47   479.416
#>       R-Square   Coef Var   Root MSE       Mean
#>         0.9606    11.5877     0.7931     6.8441
#> Source       DF        SS        MS         F   p-value
#> Split         2     5.254     2.627     4.177    0.0232
#> Desc/Meth    15   455.292    30.353    48.258    <.0001
```



For binary responses, model performance may also be assessed with misclassification rate:

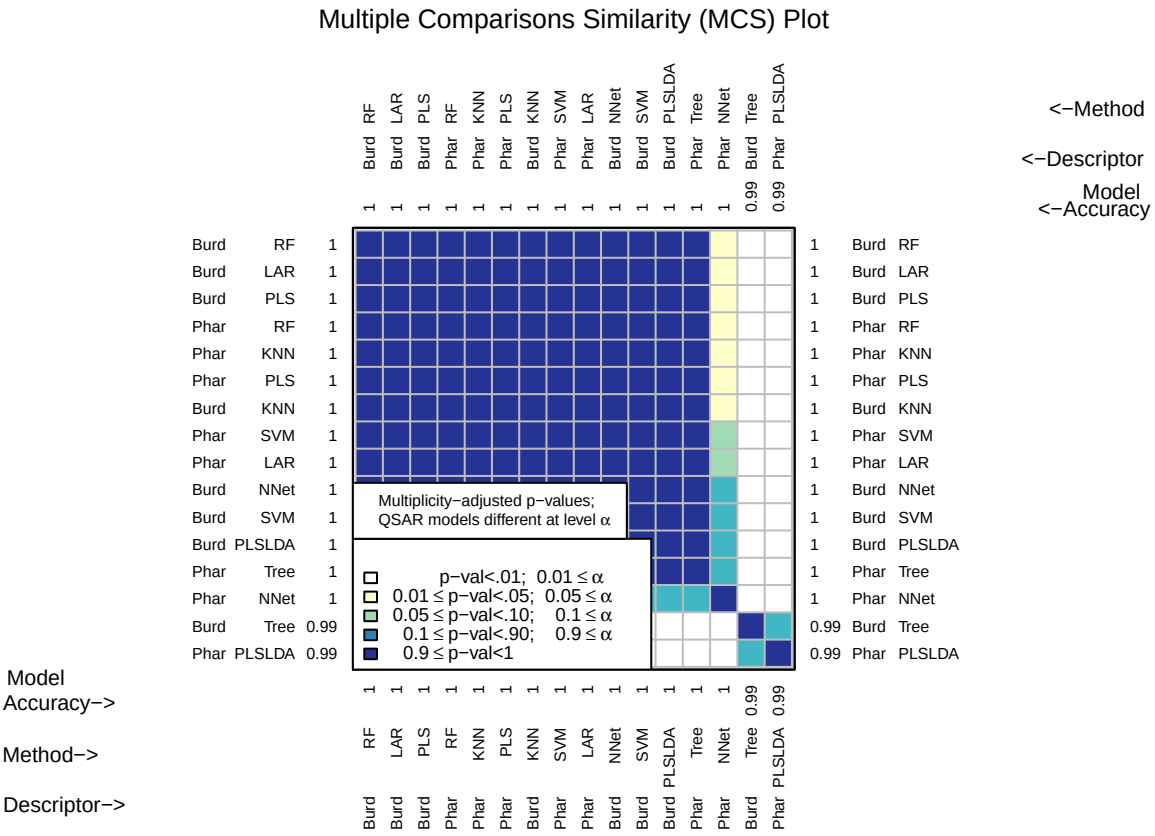
```
CombineSplits(cml, metric = "error rate")

#>    Analysis of Variance on: 'error rate'
#>  Using factors: Split and Descriptor/Method combination
#> Source    DF          SS          MS           F   p-value
#> Model     17   2.358e-04   1.387e-05   3.392e+01    <.0001
#> Error     30   1.227e-05   4.090e-07
#> Total     47   2.481e-04
#>       R-Square   Coef Var   Root MSE       Mean
#>        0.95055    4.14497    0.00064    0.01543
#> Source       DF          SS          MS           F   p-value
#> Split         2   1.98e-07   9.88e-08   2.42e-01    0.7637
#> Desc/Meth    15   2.36e-04   1.57e-05   3.84e+01    <.0001
```



However, this measure may be inappropriate because it equally penalizes to false positives and false negatives. In this particular example, specificity does not do a good job at distinguishing the best performing models, as the set of plausibly best performing models (the group of models that do not show a significant performance measure difference from the best performing model) is quite large:

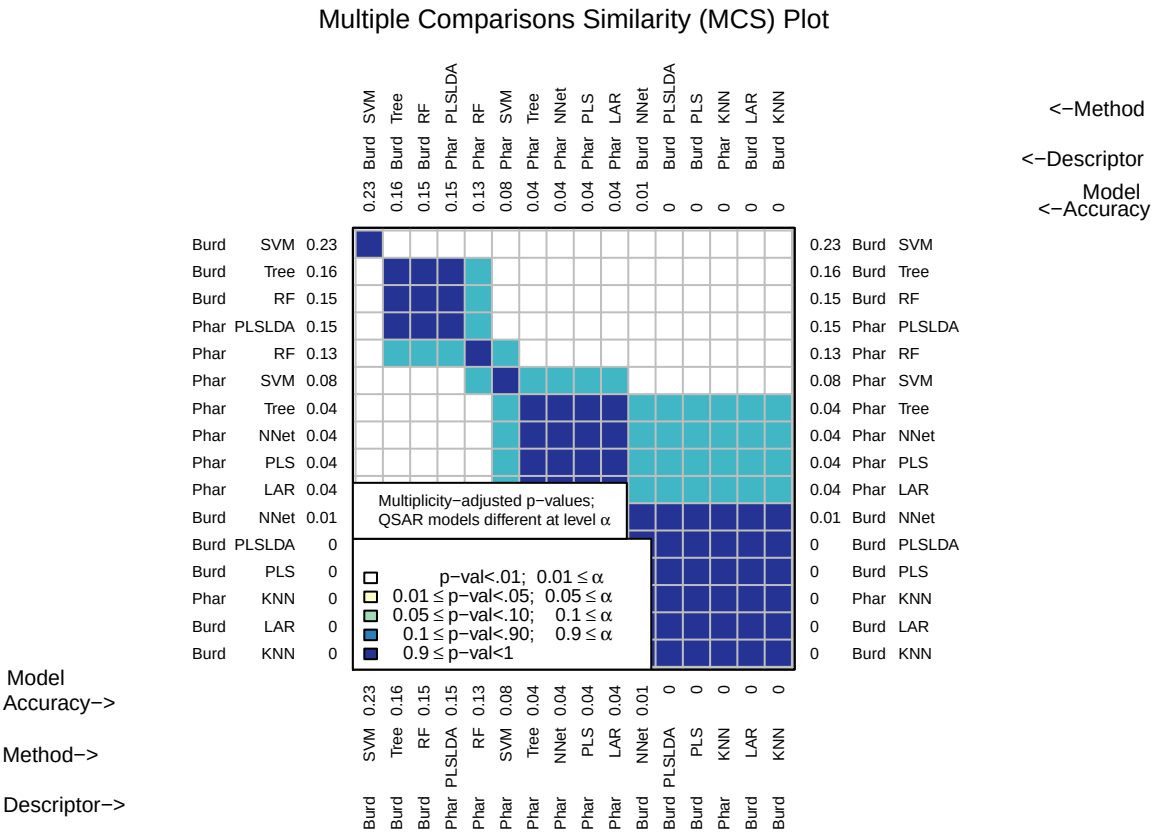
```
CombineSplits(cml, metric = "specificity")
```

```
#>    Analysis of Variance on: 'specificity'
#>  Using factors: Split and Descriptor/Method combination
#> Source     DF          SS          MS           F    p-value
#> Model      17   3.041e-04   1.789e-05   2.530e+01     <.0001
#> Error      30   2.121e-05   7.070e-07
#> Total      47   3.253e-04
#>       R-Square   Coef Var   Root MSE       Mean
#>       0.934808   0.084196   0.000841   0.998646
#> Source       DF          SS          MS           F    p-value
#> Split         2   1.11e-06   5.54e-07   7.84e-01     0.4294
#> Desc/Meth    15   3.03e-04   2.02e-05   2.86e+01     <.0001
```



This is due to the fact that there are many models that have an average specificity that is similar to the best performing model. Sensitivity, however, distinguishes the best performing model much better:

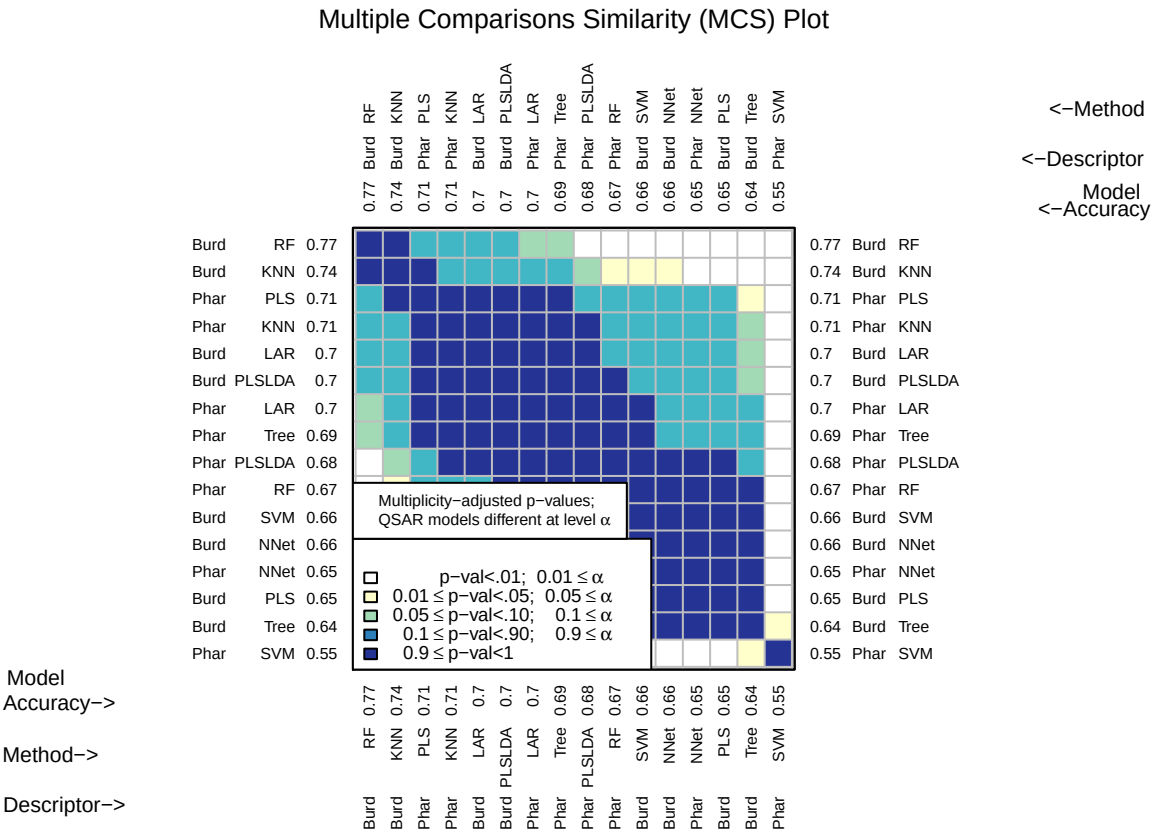
```
CombineSplits(cml, metric = "sensitivity")

#>    Analysis of Variance on: 'sensitivity'
#>  Using factors: Split and Descriptor/Method combination
#> Source    DF          SS          MS           F   p-value
#> Model     17   2.474e-01   1.455e-02   4.895e+01    <.0001
#> Error     30   8.917e-03   2.972e-04
#> Total     47   2.563e-01
#>       R-Square   Coef Var   Root MSE       Mean
#>         0.9652    25.8602     0.0172     0.0667
#> Source       DF          SS          MS           F   p-value
#> Split         2     0.00202     0.00101     3.39252    0.0419
#> Desc/Meth    15     0.24533     0.01636    55.02804    <.0001
```



This example illustrates how using misclassification rate can be misleading if this is the only model performance measure. Missclassification rate suggests several models have the best performance (Burden Numbers-Random Forest and Burden Numbers-Random Forest), but these models actually have low sensitivity. These models identify only a small fraction of the 50 true positives in the dataset. In the context of drug discovery, sensitivity measures the percentage of compounds that were correctly predicted to be active. If the goal of experimental chemists is to correctly identify as many active compounds as possible, models with low sensitivity may be less than ideal. The SVM model with Burden number descriptors clearly is the only model with the highest sensitivity, and may best perform the task at hand (despite its higher missclassification rate).

The area under the receiver operating characteristic curve (ROC) has also been implemented in **chemmodlab**:

```
CombineSplits(cml, metric = "auc")

#>    Analysis of Variance on: 'auc'
#>  Using factors: Split and Descriptor/Method combination
#> Source    DF          SS          MS           F   p-value
#> Model     17    0.110832    0.006520   11.940154    <.0001
#> Error     30    0.016381    0.000546
#> Total     47    0.127213
#>       R-Square   Coef Var   Root MSE       Mean
#>         0.8712     3.4329     0.0234     0.6807
#> Source       DF          SS          MS          F   p-value
#> Split         2    0.00709    0.00355    6.49342     0.005
#> Desc/Meth    15    0.10374    0.00692   12.66638    <.0001
```



Several performance measures have been included for continuous responses. Though root mean squared error (RMSE) is used broadly in statistics, it may not be suitable for continuous chemical assay responses used in cheminformatics. This is because under-predicting and over-predicting biological activity is equally penalized. An appropriate alternative may be initial enhancement. Other options are the coefficient of determination (R^2) and Spearman's ρ.

Results

Summary

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