SOFTWARE TOOL ARTICLE

MSclassifier: median-supplement model-based classification tool for automated knowledge discovery [version 1; peer review: 2 approved]

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Abstract
High-throughput technologies have resulted in an exponential growth of publicly available and accessible datasets for biomedical research. Efficient computational models, algorithms and tools are required to exploit the datasets for knowledge discovery to aid medical decisions. Here, we introduce a new tool, MSclassifier, based on median-supplement approaches to machine learning to enable an automated and effective binary classification for optimal decision making. The MSclassifier package estimates medians of features (attributes) to deduce supplementary data, which is subsequently introduced into the training set for balancing and building superior models for classification. To test our approach, it is used to determine HER2 receptor expression status phenotypes in breast cancer and also predict protein subcellular localization (plasma membrane and nucleus). Using independent sample and cross-validation tests, the performance of MSclassifier is evaluated and compared with well established tools that could perform such tasks. In the HER2 receptor expression status phenotype identification tasks, MSclassifier achieved statistically significant higher classification rates than the best performing existing tool (90.30% versus 89.83%, p=8.62e-3). In the subcellular localization prediction tasks, MSclassifier and one other existing tool achieved equally high performances (93.42% versus 93.19%, p=0.06) although they both outperformed tools based on Naive Bayes classifiers. Overall, the application and evaluation of MSclassifier reveal its potential to be applied to varieties of binary classification problems. The MSclassifier package provides an R-portable and user-friendly application to a broad audience, enabling experienced end-users as well as non-programmers to perform an effective classification in biomedical and other fields of study.
Keywords
Breast cancer, protein subcellular localization, machine learning, software package, HER2 receptor status, classification.

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Introduction

Machine learning tools are required to solve binary classification problems for optimal decision making in medicine and other fields of study. In recent times, they have been used to predict subcellular localization of proteins to assist in the functional annotation of gene products and protein secondary structure\(^1\). As the identification of the subcellular location of any given protein provides insights into its function, this prediction task is highly valuable. This is more so as the specific functions of many proteins remain to be fully characterized. In other contexts, for instance medicine, classifications of patients in breast cancer and other diseases are important for administering therapies. There are five molecular sub-types of breast cancer identified: basal-like, Luminal A, Luminal B, human epidermal growth factor receptor 2- (HER2-) enriched, and normal-like\(^1\). The prognosis and administration of therapies in breast cancer is aided by the determination of molecular subtype phenotypes\(^1\).

However, for various reasons, occasionally immunohistochemistry and other methods for establishing the presence or absence of these receptors do not necessarily cover all available samples. For example, results can be equivocal for some samples. Machine learning techniques can be trained with data from those samples that have been definitively characterized to correctly classify other uncharacterized samples' phenotypes based on gene expression profiles. Machine learning methods rely on availability of large datasets to infer accurate outcomes for appropriate decisions concerning problems. With the advent of DNA microarray and next generation sequencing technologies, huge amounts of data are increasingly becoming available for use by these machine learning methods. These have permitted machine learning methods to be applied to characterize prognostic breast cancer samples for constructing patient-specific networks and disease groupings in precision medicine\(^2\).

Machine learning methods based on Random Forest have been used to identify a gene regulatory program of human breast tumour progression\(^2\). Other methods such as Support Vector Machine and Naive Bayes, have all been applied to studies in breast cancer\(^2\). Other methods applicable to such problems are Logistic Regression, Bayesian Networks, K-nearest neighbours and tree-based methods\(^10\)-\(^12\). In general, binary classification problems, such as breast cancer classification, commonly occur in nature and they rely on these machine learning methods for effective grouping, and the classification of multiple outcomes.

These methods are implemented in software packages/applications. For instance, several of these methods are implemented in the Weka package\(^13\). In R, implementations are provided as fitting functions as well as packages such as randomForest\(^14\), ISLR\(^15\) and e1071\(^16\) among others. Unlike linear regression models, which predict quantitative response variables, these methods infer models to predict qualitative response variables.

Recently, median-supplement approaches were introduced and found to outperform the traditional machine learning methods in binary classification models involving classification of receptor status phenotypes in breast cancer\(^17\). More importantly, these approaches achieve accuracies that compare favourably with other protein/mRNA-based procedures to decipher hormone and HER2-receptor status phenotypes in as much as they outperform traditional machine learning methods\(^17\). This implies that irrespective of the performance of the traditional methods, enhanced approaches provide better results in binary classification problems. However, none of the existing packages (implementations) supports the new median-supplement approaches to the binary classification problems.

Here, we aim to provide a median-supplement based tool, MSclassifier, for automated knowledge discovery from data and illustrate its applicability to both breast cancer and other binary classification problems in broader contexts of study. This provides an effective binary classification tool, preventing biases that may originate from requirements of traditional tools which generally influence the classification decisions. It enhances the capacities of both Naive Bayes and Random Forests to infer models that provide more accurate predictions of classes of observations. This package is implemented in R under free software (GNU General Public Licence).

In performing an effective binary classification, MSclassifier introduces a predetermined number of supplementary instances based on the median of each attribute (feature) of the training sets for binary classification problems involving unequal members of classes. The supplementary instances along with the training instances form a new set from which a Naive Bayes or a Random Forest model is inferred to predict new instances. The provision of additional instances introduced by the new methods increases their prediction accuracies. This is because the effectiveness of the learning methods is improved whenever the training instances are more\(^18\). This has necessitated the design of the software package presented in this report. There are existing tools in R, namely randomForest\(^14\) and e1071\(^16\), which implement both Random Forest and Naive Bayes algo-
Methods
Implementation
The package implements median-supplement approaches to machine learning, robust machine learning techniques that have the advantage of supporting complete compliance efforts by not missing sensitive sub-datasets or allowing certain sub-datasets to escape the classification process when balancing overall datasets. They are applicable to datasets with unequal numbers of instances associated with each class (group).

Median-supplement machine learning algorithms. They involve the following steps:
1. Find the median of each attribute among all the samples (instances).
2. Find the scalar multiplication of the median of each attribute and a corresponding column vector of an m by n matrix of uniformly distributed random numbers between 0 and 1. m is the difference between the numbers of groups of samples, and n is the number of attributes. These form a supplementary set.
3. The supplementary set is added to the expression profiles to form the new balanced, median-supplement data set.
4. Finally, classification models are inferred from the median-supplement data.

There are two kinds of median-supplement approaches, namely, median-supplement Random Forest and median-supplement Naive Bayes methods. Each approach is distinguished by the kind of model constructed from the median-supplement data. For a 'median-supplement Random Forest', a Random Forest classifier is inferred from the median-supplement data to assign classes to instances. To obtain a 'median-supplement Naive Bayes classifier', a Naive Bayes model is developed from the median-supplement data to classify instances. The overview of the underlying principles of median-supplement approaches as implemented in MSclassifier is shown in Figure 1.

Naive Bayes model. This model applies the Bayesian framework to predict classes of new instances. Any classes having the highest posterior probability becomes the class of a new test instance. Let G be a set of attributes. Then, the probability that any instance belongs to any class/category, $C_i$, is given by:
Table 1. Arguments (input parameters) of MSclassifier function.

| Argument | Description |
|----------|-------------|
| X        | A data frame of values of attributes (e.g. gene expression levels) and classes (e.g. receptor status phenotypes in breast cancer). Samples are in rows while attributes are in columns. The last column of X should have the classes for all instances in X (e.g. receptor status phenotypes of samples). This form the training set. |
| Testset  | This is the set of new instances to be classified. The Default is NULL. When set to NULL, the function returns only the model. To classify new instances, specify the data frame of the new instances as the test set. It should have the form (and attributes) of X. |
| Method   | It specifies whether to determine a median-supplement Random Forest or median-supplement Naive Bayes. “MSRandomForest” infers median-supplement Random Forest. “MSNaiveBayes” applies the median-supplement Naive Bayes. The default is median-supplement Random Forest. |
training and test sets are provided with the package. They are used in the illustration of the MSclassifier in the next section.

Illustration (usage) of MSclassifier
In order to illustrate the use of the package, we use HER2 datasets included in the package. These datasets were obtained from an earlier study that explored the use of machine learning techniques to determine hormone and receptor status phenotypes in breast cancer\(^1\). The training data consists of 86 HER2 receptor-negative and 14 HER2 receptor-positive samples while the independent test set consists of 51 HER2 receptor-negative samples and 11 HER2 receptor-positive samples. The illustration shows how to use the MSclassifier after installation.

```
Comprehensive description of function and application can be found in the help file after loading the installed package and getting the full description of the package:
> library(MSclassifier) # load package
> ?MSclassifier

To load package datasets:
> data(her2)
> data(testset)

To view a subset of the package’s her2 training set:
> her2[1:3,1:3]
   NPTXR_23467  DOCK3_1795  LOC400927_400927
  1     266.0075    38.1356    12.7119
  2     461.8575    34.9231     6.5481
  3     199.3335    11.8146     6.9676

To view a subset of the package’s her2 test set:
> testset[1:3,1:3]
   NPTXR_23467  DOCK3_1795  LOC400927_400927
  1     304.5058    21.0756      0.7267
  2     453.4778    10.1620     7.5072
  3     510.8080     3.5776     4.9292

To classify instances/determine her2 status of the test samples using median-supplement Random Forest, the following apply:
> Predictions <- MSclassifier(her2,testset = testset, method = "MSRandomForest")
> head(Predictions)
Sample1  Sample2  Sample3  Sample4  Sample5  Sample6
Negative  Negative Positive  Negative  Negative  Negative
Levels: Negative  Positive

To analyse median-supplement Random Forest for error matrix, here is a sample:
> Model <- MSclassifier(her2, testset = NULL, method = "MSRandomForest")
> predictions <- predict(Model, newdata = testset)
> head(predictions)
  1  2  3  4  5  6
Negative  Negative  Positive  Negative  Negative  Negative
Levels: Negative  Positive

> table(predictions, testset$her2_status)
predictions       Negative  Positive
   Negative    47    10
   Positive     4     1
```
To classify instances/determine her2 status of the test samples using median-supplement Naive Bayes, here is a sample:

```r
> Predictions <- MSclassifier(her2,testset = testset, method = "MSNaiveBayes")
> head(Predictions)
Sample1  Sample2  Sample3  Sample4  Sample5  Sample6
Negative Negative Positive Negative Negative Negative
Levels: Negative Positive
```

To analyse median-supplement Naive Bayes for error (confusion) matrix, the following is an example:

```r
> Model <- MSclassifier(her2, testset = NULL, method = "MSNaiveBayes")
> predictions <- predict(Model, newdata = testset[, -ncol(testset)])
> head(predictions)
[1] Negative Negative Positive Negative Negative Negative
Levels: Negative Positive
> table(predictions, testset$her2_status)
predictions             Negative Positive
Negative   51      8
Positive     0      3
```

**Data sets.** In order to illustrate the performance of the package, we use two real datasets. Particularly, the first data, obtained from previous study\(^\text{17}\) describes gene expression measurements in breast cancer. In this illustration, median-supplement models are inferred with the MSclassifier package to assign classes to new instances of the test set. In the case of the HER2 data, the class of each instance is the expressed receptor status phenotype while attributes are the relevant gene expression profiles. The data consists of 86 HER2 receptor-negative and 14 HER2 receptor-positive samples. These are samples included in the MSclassifier package.

The second (larger) dataset was derived from a study that characterized amino acid sequences of human proteins localized in nine cellular compartments\(^\text{21}\). Code written in LISP was used to determine values of physicochemical properties of proteins known to be primarily localized in the designated subcellular locations were used. Protein properties used are based on the amino acid composition (including hydrophobicity, normalized van der Waals volume, polarity, polarizability, and charge), transitions and distribution as detailed\(^\text{21}\). For instance, “PERCENT-R” is a reference to the percentage of arginine residues in the primary sequence of amino acids of a protein; “HYDROPHOBICITY-PERCENT-GROUP1” is a reference to the percentage of polar amino acids in the primary sequence of amino acids (i.e. group 1 amino acids are polar, group 2 amino acids are neutral, and group 3 amino acids are hydrophobic); “POLARITY-GP1-GP3-TRANSITIONS” is a reference to the frequency of transitions between low polarity residues (L, I, F, W, C, M, V, and Y) and high polarity residues in a given protein’s primary sequence of amino acids (H, Q, R, K, N, E, D). The data comprised of 2635 instances and 126 attributes. Among the instances, 1589 were associated with (localized in) the plasma-membrane and 1046 were associated with the nucleus\(^\text{22}\). In its usage to illustrate the package, instances of the dataset were classified as “nucleus” and “plasma-membrane”.

**Performance measures of packages.** The performance of each method is determined by its classification rate: proportion of correctly classifying instance given by the ratio of correctly classified test instances to the total number of test instances\(^\text{23}\). In general, the classification rates agree with measures of accuracies of such classification methods. Higher classification rate of a method indicates that the package has higher chances of making accurate assignments of samples to their respective classes. Therefore, it is desirable to have higher classification rate. For instance, a higher classification rate for classifying receptor status phenotypes in breast cancer indicates the method has high sensitivity for deciphering the particular receptor status. This is because the sensitivity is also a proportion of correctly classified instances among characterized instances as exemplified in unsupervised learning systems\(^\text{24}\). Furthermore, Mann-Whitney tests are performed to evaluate differences among classification rates of the methods. Both independent and cross-validation testing methods are used to evaluate the packages\(^\text{22}\). While a 10-fold cross-validation is applied to the HER2 data, a 5-fold cross-validation is applied to the subcellular localization of proteins data\(^\text{22}\).
Results and discussion
Performance on independent test sample

In this experiment, HER2 training and test sets made available in the package were used. It was found that the median-supplement Naive Bayes (MNB) implemented in MSclassifier outperformed all the other methods considered in this case (Figure 2). This was to be expected since the MSclassifier implements median-supplement methods, which have been shown to outperform the traditional machine learning methods. Higher performance of this package on this test example is the result of the enhanced median-supplement training set from which MSclassifier infers models. Thus the enhancement makes more instances available to train models.

Performances from cross-validation testing

The classification rates of conventional methods, implemented in existing packages, ranged between 83% and 91%, methods implemented in the MSclassifier had values with minimum of 87% and maximum of 91%. Particularly, it was found that conventional random forest was significantly higher than the Naive Bayes (mean classification rate of 89.83% versus 85.43%, p = 1.48e-11). However, the median-supplement Naive Bayes implemented in MSclassifier achieved the highest classification rates among all the methods. More importantly, it had significantly higher classifications rates than the random forest method (mean is 90.30% versus 89.83%, p = 8.62e-3). These results are consistent with performance of median-supplement methods on HER2 classifications studied earlier.

With regards to the prediction of subcellular localization of proteins, although both MSclassifier and the other packages could attain equally high classification rates (94%) in this test, the minimum classification rate achieved by the median-supplement Naive Bayes was lower compared to the conventional Naive Bayes method (mean of 69% versus 86%, p = 4.55e-14). However, this observation was different in other studies. The difference is attributable to the differences in data and prediction tasks. Nevertheless, these performances are suboptimal when compared to the random forest-based methods which achieved mean classification rates of 93%. Specifically, the performances of both the random forest and the median-supplement random forest were statistically indistinguishable (mean of 93.42% versus 93.19%, p = 0.06). These results are indicative that tree-based random forest methods have better performances on larger datasets. However, the superiority of median-supplement methods over several other machine learning methods when applied to predict hormone and HER2 receptor phenotypes underpinned in the literature. These results demonstrate the potential of MSclassifier to better predict instances of binary classifications problems.

Figure 2. Comparison of MSclassifier and other packages in R. NB is Naive Bayes, RF is Random Forest, MRF is median-supplement Random Forest and MNB median-supplement Naive Bayes. While both MRF and MNB are implemented in MSclassifier, NB is implemented in e1071 and RF is implemented in randomForest packages.
Conclusion
We have presented the MSclassifier package to implement median-supplement approaches for machine learning to support medical decisions. The package was shown to decipher HER2 receptor status phenotypes in breast cancer and also predict subcellular localizations of proteins. MSclassifier compares favourably well with existing packages because it implements enhanced methods which offer effective approach to machine learning. Finally, MSclassifier can be installed and run on most operating systems. The sole requirement is the availability of a recent version of R. MSclassifier, steps for installation and other supplementary information are freely available at https://nweb.gimpa.edu.gh/schools/school-of-technology/software/MSclassifier/. Furthermore, the MSclassifier package and every other supporting data for this work have also been made publicly available at https://doi.org/10.5281/zenodo.394667522.

Software availability
Software available from: https://nweb.gimpa.edu.gh/schools/school-of-technology/software/MSclassifier/
Source code available from: https://github.com/esadabor/MSclassifier.git
Archived source code as at time of publication: https://doi.org/10.5281/zenodo.394667522
License: GPL-3

Data availability
Underlying data
Datasets used in Use Case:
- Gene expression measurements in breast cancer, obtained from previous study17. Dataset available here: http://doi.org/10.5281/zenodo.396451425 (permission to reuse this dataset and to republish on Zenodo has been granted by Oxford University Press).
- Characterized amino acid sequences of human proteins localized in nine cellular compartments, obtained from previous study21. Dataset available here: http://doi.org/10.5281/zenodo.396450326. Protein subcellular localisation dataset available here: https://doi.org/10.5281/zenodo.394667522.

Extended data
Zenodo: Supporting information and data for MSclassifier: Median-Supplement model-based Classification tool for automated knowledge discovery, https://doi.org/10.5281/zenodo.394667522.

This project contains the following extended data:
- Cross-Validation Testing information
- Table S2: Performance of methods on HER2 dataset
- Table S3: Performance of methods on plasma-membrane and nucleus classification dataset

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Alper Uzun
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The authors developed a median-supplement based tool, MSclassifier to automate knowledge discovery from available data sets. They demonstrated that it can be applied to binary classification problems. In this regard they used two datasets to demonstrate their application. The authors implemented the application in R which is freely accessible.

I recommend the manuscript for indexing with minor revision:
- Area Under the Receiver Operator Characteristic (AUROC) is a very useful metric to evaluate models. There are packages available to use AUROC. The manuscript will be benefited by adding this metric into the results.

Is the rationale for developing the new software tool clearly explained?
Yes

Is the description of the software tool technically sound?
Yes

Are sufficient details of the code, methods and analysis (if applicable) provided to allow replication of the software development and its use by others?
Yes

Is sufficient information provided to allow interpretation of the expected output datasets and any results generated using the tool?
Yes

Are the conclusions about the tool and its performance adequately supported by the findings presented in the article?
Yes
**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** I focus on using genomics and bioinformatics to understand the genetic architecture of complex diseases. Our research group is managing large scale data (whole-genome genotyping data, RNA-Seq, targeted sequencing) and developing bioinformatics methods to identify causal variants. We use machine-learning approach to extract disease associated genes from published biomedical literature. We develop bioinformatics tools for both analyzing and visualizing protein protein interaction networks and in addition we develop tools to visualize variants.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 06 January 2021

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Gregory Hart
Department of Therapeutic Radiology, Yale University, New Haven, CT, USA

I would suggest that (and assume it would be easy) you allow for your package to run regular Random Forest and Naive Bayes in addition to the MS versions. While that functionality is already available in other packages it would be nice to have it all in one place.

In addition to the accuracy comparison it would be nice to get a feel for the computational cost of adding MS as well as how the algorithm scales.

Lastly, any reason to only do Random Forest and Naive Bayes? Would there be interest in including other classifiers in the future?

**Is the rationale for developing the new software tool clearly explained?**
Yes

**Is the description of the software tool technically sound?**
Yes

**Are sufficient details of the code, methods and analysis (if applicable) provided to allow replication of the software development and its use by others?**
Yes

**Is sufficient information provided to allow interpretation of the expected output datasets and any results generated using the tool?**
Partly

Are the conclusions about the tool and its performance adequately supported by the findings presented in the article?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My postdoc was focused on machine learning and applying it to cancer diagnosis. The biology/medicine is often over my head by the software/methods are not.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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