WRAPPER AND FILTER METRICS FOR PSO-BASED CLASS BALANCE APPLIED TO PROTEIN SUBCELLULAR LOCALIZATION

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Abstract: Recent advances in proteomic research have generated an unprecedented amount of stored data. Given the size of current databases, manual annotation has become an almost intractable process, paving the way to the use of computational methods. In this context, considering that a single protein can belong to several functional classes, a multi-label classification problem is generated. The most common way to cope with these problems is by training a number of classifiers equal to the number of classes that will allow taking independent decisions on the membership of proteins. Nevertheless, this methodology leads to a high degree of imbalance between classes, magnifying the disparity already present in their size. Current balancing techniques are based on the optimization of criteria leading to a better subset that represent the data. Moreover, most of the sample selection criteria are based on the Wrapper type metrics. However, Wrapper metrics are computationally quite expensive. This work presents a comparative analysis between the Wrapper and Filter metrics as the sample selection criteria in balance techniques. In order to accomplish this task, a subsampling technique based on the Particle Swarm Optimization method to obtain the optimal balance subset is used. The results show that filter metrics notably improved the computational cost obtaining a similar performance when compared with the Wrapper type metrics.

1 INTRODUCTION

One fundamental goal in proteomics and molecular biology is to identify protein functions of various cellular organelles.

The subcellular localization of proteins can provide useful information on how and in what type of environment proteins interact with each other and with other molecules, thus providing important clues to reveal their functionality and understanding the intricate pathways that regulate biological processes at the cellular level (Ehrlich et al., 2002), (Glory and Murphy, 2007), (Chou and Shen, 2010). Although this type of information can be acquired by conducting various biochemical experiment, it is usually very time consuming and practically cumbersome. With the avalanche of protein sequences generated in the post-genomic era, it is highly desirable to develop computational methods that can be used to identify subcellular localization sites of novel proteins (Chou and Shen, 2010). However, since proteins with certain specific locations are more abundant, there exists a high degree of disparity in the number of samples belonging to each class (Al-Shahib et al., 2005) and, since machine-learning classifiers with unbalanced data usually generate larger bias (Meyer, 2007; Sonnenburg et al., 2007), proteins of interest get classified in the redundant category.

There are several ways to address class imbalance problems. One of the most commonly used strategies is the sampling technique, which is composed of subsampling and oversampling. Oversampling reproduces samples of the minority class until they reach the same size as the majority class, either by sample replications (random) or by the generation of synthetic samples (Chawla et al., 2002). However, this strategy induces two major problems: i) over-training (in the case of random-sampling) and ii) noise ad-

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dition in the training set (in the synthetic case), affecting the reliability of protein localization (Chawla et al., 2004), (He and Garcia, 2008). On the other hand, subsampling eliminates samples of the majority class, reaching the same minority class size. However, subsampling might eliminate useful data in the induction model (He and Garcia, 2008). Despite this problem, several studies have shown that subsampling had a better performance when compared with many oversampling techniques (Chawla et al., 2004). To mitigate the loss of useful data, several subsampling techniques using different criteria for the selection of samples based on optimization techniques have been proposed (He and Garcia, 2008).

(Pengyi et al., 2009) shown a subsampling strategy based on particle swarm optimization (PSO), a metaheuristic optimization strategy that simulates the social behavior of a swarm of bird. This method showed a high effectivity and has gained strength as a sampling technique in recent years (Pengyi et al., 2009). Numerous criteria have been proposed to define sample selection based on Wrapper metrics, that is, based on several statistical measurements from the performance of the classifier (Cortes and Mohri, 2004; García and Herrera, 2008). Although these metrics provide good criteria to obtain an appropriate representative subset of the data, they are computationally expensive. Therefore, this paper adresses the class imbalance problem in protein subcellular localization, employing several filter type metrics in order to reduce the computational cost while preserving similar or superior performances compared with Wrapper metrics.

2 METHODOLOGICAL ASPECTS

2.1 Particle Swarm Optimization

The PSO algorithm is a population based optimization tool where the system is initialized with a set of random solutions, seeking for an optimal subset of the population satisfying some performance index over generations. For each potential solution $\mathbf{x}_i$ called a particle, PSO assigns a randomized velocity $\mathbf{v}_i$ so that particles are then ”flown” through the problem space. At each time step, the particles moves depending of the fitness function value q_i, that represents a quality measure calculated by using $\mathbf{x}_i$ as input. Each particle keeps track of its own best position, which is associated with the best fitness it has achieved at that time in a vector $\mathbf{p}_i$. Furthermore, the best obtained positions among all the particles in the population is included in the vector $\mathbf{p}_g$. A new velocity for particle (i) is updated at each time step t by equation (1).

$$\begin{aligned}\mathbf{v}_i(t+1) = w\mathbf{v}_i(t) + c_1\phi_1(\mathbf{p}_i(t) - \mathbf{x}_i(t)) \\ +c_2\phi_2(\mathbf{p}_g(t) - \mathbf{x}_i(t))\end{aligned} \tag{1}$$

where c_1 and c_2 are positive constants, ϕ_1 and ϕ_2 are uniformly distributed random numbers and w is the inertia weight. The term $\mathbf{v}_i$ is limited to the range $\pm V_{max}$. If the velocity violates this limit, it is set at its proper limit. Changing velocity in this way enables the particle i to search around its individual ($\mathbf{p}_i$), and global ($\mathbf{p}_g$) best position. Based on the updated velocities, each particle changes its position according to equation (2).

$$\mathbf{x}_i(t+1) = \mathbf{x}_i(t) + \mathbf{v}_i(t+1) \tag{2}$$

2.2 Filter and Wrapper Fitness Functions

Wrapper methods use learning algorithms directly to inform the search. They calculate the estimated accuracy of the classifier for each sample subset and its accuracy is estimated using hold out validation. Their most noticeable advantage is their capability to interact with the classification task, nonetheless they present a big computational cost (Luengo et al., 2005; Webb, 2002). On the other hand, filter methods use a criterion function that is independent from the classification scheme, allowing for a better computational complexity compared with wrapper approach. In the present work, wrapper approach uses the area under ROC curve (AUC) estimation computed after hold out validation, while filter approach uses several separability criteria based on scatter matrices.

2.2.1 AUC Estimation from a Non-parametric Statistical Test

The AUC is a one-dimensional metric derived from the ROC curve for quantifying the classifier capability for ranking. The normalized Wilcoxon-Mann-Whitney statistic gives the maximum likelihood estimate of the true AUC given positive and negative examples according to equation (3) (Cortes and Mohri, 2004).

$$AUC_{est}(f) = \frac{\sum_{i=1}^{n^+}\sum_{j=1}^{n^-} 1_{f(\mathbf{x}_i^+)>f(\mathbf{x}_j^-)}}{n^+n^-} \tag{3}$$

Where $n+$ and $n-$ are the number of positive and negative samples in the dataset and $1_f(x_i^+)$ and $1_f(\mathbf{x}_i^-)$ are the correct sample classification for each positive and negative classes respectively. Each pair that satisfies $f(\mathbf{x}_i^+) > f(\mathbf{x}_i^-)$ contributes with $\frac{1}{n^+n^-}$ to the overall AUC performance. Maximizing the AUC is therefore equivalent to maximizing the number of pairs satisfying $f(\mathbf{x}_i^+) > f(\mathbf{x}_i^-)$.

2.2.2 Separability Criterion based on Scatter Matrices

Metrics based on separability estimate the overlap between the distributions from which the data are drawn, and favour those sample sets for which this overlap is minimal (i.e., maximizing the separability). A measure of the separation between two data sets, ω_1 and ω_2 can be defined as:

$$J_{as} = \frac{1}{n_1 n_2} \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} d(\mathbf{x}_i, \mathbf{y}_j) \tag{4}$$

where $\mathbf{x}_i \in \omega_1$, $\mathbf{y}_j \in \omega_2$ and $d(\mathbf{x}, \mathbf{y})$ is a distance measure between samples **x** and **y**. The average distance between classes measured in probablistic distances is represented in the following equation:

$$J_{as} = \frac{1}{2} \sum_{i=1}^{C} p(\omega_i) \sum_{j=1}^{C} p(\omega_i) J_{as}(\omega_i, \omega_j) \tag{5}$$

where $p(\omega_i)$ is the prior probability of class ω_i (estimated as p_i=n_i/n). This separability criterion is independent of the final classifier employed and can be computed from the between$-$class (S_b) and within$-$class (S_w) scatter matrices respectively defined in equations 8 and 6.

$$S_w = \sum_{i=1}^{C} \frac{n_i}{n} \widehat{\Sigma}_i \tag{6}$$

$$S_b = \sum_{i=1}^{C} \frac{n_i}{n} (m_i - m)(m_i - m)^T \tag{7}$$

Being $\widehat{\Sigma}_i$ the covariance matrix of the $i-th$ class, m_i the sample mean of the $i-th$ class and m the sample mean of the whole dataset.

This way, J can be expressed as:

i)

$$J_1 = Tr\{S_w + S_b\} = Tr\{\Sigma\} \tag{8}$$

The criterion $J1$ is simply the total variance, which does not depend on class information. It also reduces the scatter grade within the classes. Several other criteria have been proposed to achieve this goal as follows:

ii) The population measure

$$J_2 = Tr\left\{S_w^{-1} S_b\right\} \tag{9}$$

iii) The ratio of the total within-class scatter

$$J_3 = \frac{Tr\{S_b\}}{Tr\{S_w\}} \tag{10}$$

iv) Difference between inter/intra class scatter

$$J_4 = Tr\{S_b - S_w\} \tag{11}$$

3 EXPERIMENTAL SETUP

3.1 Database

The database is constituted by 1016 proteins belonging to Embryophyta taxonomy of the Uniprot database (Jain et al., 2009) with at least one annotation in the Gene Ontology Annotation project (Ashburner et al., 2000). Sequences predicted by computational tools and with no real experimental evidence were discarded. The dataset is composed of eight different classes correspondig to common subcelullar locations. The dataset does not contain protein sequences with a sequence identity superior to 40% in order to avoid bias and overtraining in the training dataset.

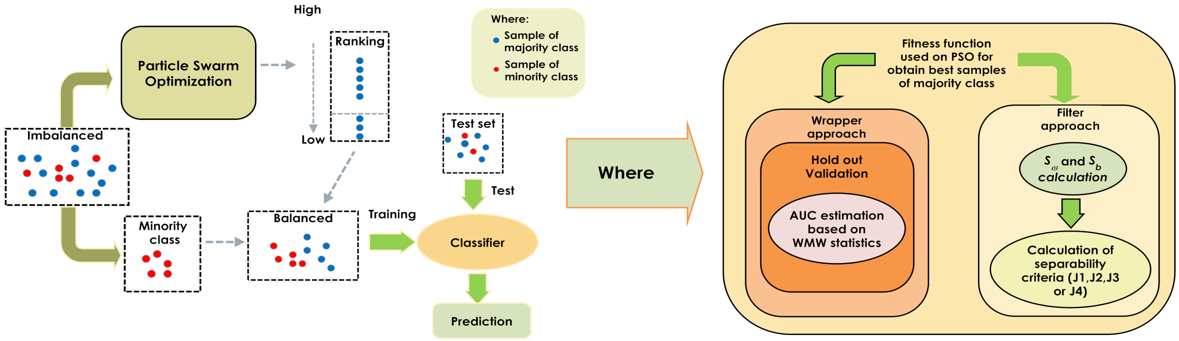
Proteins were characterized according to the schema used in (Jaramillo-Garzón et al., 2010; García-López et al., 2011). It is composed of six physic-chemical characteristics, 20 amino-acid frequencies, 400 dimer frequencies and 12 secondary-structure frequencies from predictions made with Predator 2.1 software. The total set contains 438 attributes.

3.2 Feature Selection

In order to obtain representative characteristics, the feature selection was performed as a pre-processing stage from the relevance and redundancy analysis. Linear correlation measures were used as the selection criteria. The relevant characteristics were quantified by calculating the correlation with the actual labels for all features. The redundant features were identified through the analysis of the feature correlation matrix of dimension nxn. To reduce computational cost, a fast filter-selection algorithm proposed in (Yu and Liu, 2004) was used.

3.3 Class Imbalance and Classification Schemes

To balance data in learning models for protein location, a subsampling algorithm based PSO was used as


High
Low
Ranking
Particle Swarm Optimization
Imbalanced
Minority class
Balanced
Training
Test set
Test
Classifier
Prediction
Where:
Sample of majority class
Sample of minority class
Where
Fitness function used on PSO for obtain best samples of majority class
Wrapper approach
Hold out Validation
AUC estimation based on WMW statistics
Filter approach
S_ω and S_b calculation
Calculation of separability criteria (J1,J2,J3 or J4)

As we can see, in the image above outlines the strategy for balancing the two classes from the particle swarm optimization. At the bottom shows the two approaches used as criteria for samples selection, these are the Wrapper type metric based on the AUC estimation from a Hold-out validation and the Filter type metrics based on separability criteria between the classes.

Figure 1: Methodological scheme.

the representative methodology. Given that the subsampling system used on this study needs a sample selection criterion as the fitness function, several metrics to determine sample selectivities are used. In this work, Wrapper and Filter type metrics were used such as: AUC from the Wilcoxon-Mann-Whitney non-parametric statistical test ((3) Wrapper type) and metrics based on class separability from scatter matrices ((8),(9), (10) ,(11) Filter type). The methodological block diagram is shown in Figure 1, where the Wrapper and Filter as sample selection criteria are illustrated. The ensemble method known as Random Forest was chosen as the classification scheme with 1000 iterations, it was chosen because of its low computational cost despite being an ensemble method and good performance in prediction task. To evaluate the performance of the protein location prediction, a cross-validation with 10 folds was used. The results were measured with sensitivity,specificity and geometric mean measurements, defined as:

i) Sensitivity

$$Sensitivity = \frac{TP}{TP+FN} \tag{12}$$

ii) Specificity

$$Specificity = \frac{TN}{TN+FP} \tag{13}$$

iv) Geometric mean

$$Geometricmean = \sqrt{Sensitivity * Specificity} \tag{14}$$

Table 1 shows the different classes used on this study with its imbalance ratio and the number of samples for each class.

Table 1: Class imbalance table.

Class	Minority class instances	Imbalance ratio
Nucleoplasm	55	1:17
Cytoplasm	266	1:2.85
Endosome	22	1:45.18
Vacuole	274	1:2.71
Peroxisome	82	1:11.39
Endo ret	201	1:4.054
Golgi	92	1:10.43
Ribosome	115	1:7.83

4 RESULTS AND DISCUSSION

Figure 2 shows the performances of the balancing algorithm using different metrics. Notably, the better located proteins were found in the Ribosomal and Cytoplasmic regions. This indicate that these proteins are highly sensitive to both the separability and the estimation accuracy metrics used as selection criteria. As shown in Figure 2 and Figure 3, the proteins with the lowest level of prediction were located in the Endosomal region. In addition, this region shows a big difference in the geometric means between all the metrics used as criterion functions. This difference suggests that such behavior may be due to the fact that the Endosome class contains very few proteins, thus generating much more variability between class probability distributions. If we consider that the minority class size represents a insignificant fraction of the total training dataset size, the sampling error will be noticeable bigger. In this case, having so few samples, its probability distribution is more spread out or dispersed than majority class, yielding incertain changes in the final decision making. However, that effect was not reflected in the trainig subset built from the J1 metric, where this exhibits the highest geometric mean for that region. Notably, it even outranges in large margin the Wrapper metric results.

Figure 4 shows the results of efficiency of the PSO-based subsampling, using each of the metrics as a separation criterion, to see which was the computational cost of the metric compared to the metric Filter Wrapper, taking this last as a baseline to compare results. As we can see , the criteria based on the

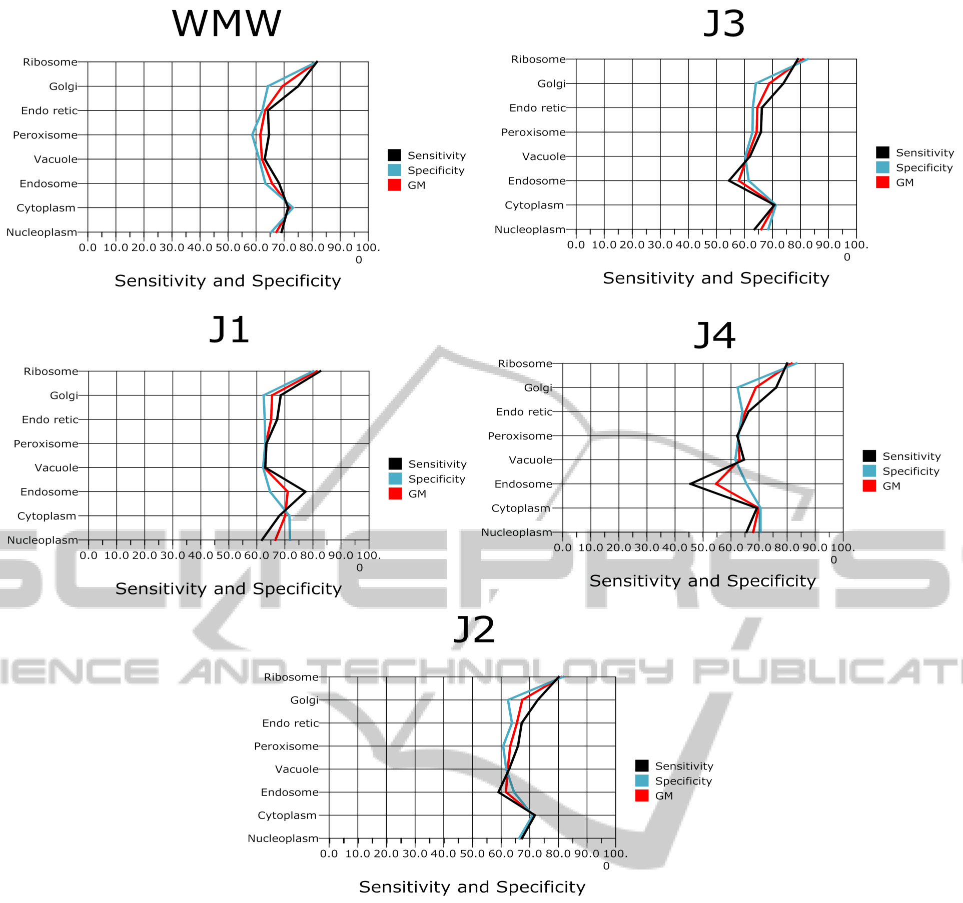


Figure 2: Performance for the evaluated metrics.

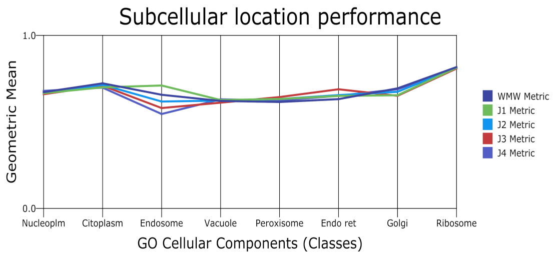


Figure 3: Geometric mean comparisons between each class.

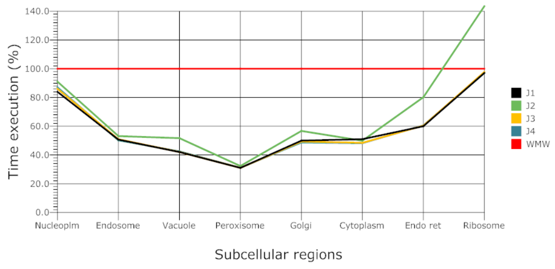


Figure 4: Efficiency.

separability metrics (Filter) executed the protein locations faster than the Wrapper criterion (WMW). The J2 metric showed the lowest reduction time compared to other separability criteria. Furthermore, the J2 metric increased the computational time in the Ribosome and Nucleoplasm protein location. One possible explanation is the fact that both the calculation of the inverse matrix and the matrix multiplication consume more time to be computed. Nevertheless, the subsampling with the Filter metrics shown a similar time reduction.

5 CONCLUSIONS

In this paper, a comparative analysis between wrapper and filter type metrics as a sample selection criteria for balance and further protein prediction associated to some subcellular region using methods based on pattern recognition techniques was proposed. The purpose was studying the influence of these metrics over class imbalance present in subcellular location, taking into account both performance and compute time as evaluation judgments. In general, filter metrics offer a similar, even superior performance than Wrapper metrics. Also, Filter type metrics allow very drastic reduction costs. Here, a great alternative for the evaluation of the criteria for sample selection is suggested. This alternative reduces the computational time required to predict protein location without decreasing accuracy even obtaining better performances than with Wrapper metrics. Nevertheless, it is necessary to develop a methodology that includes class information to get a better understanding of the influence of this feature on the interaction performances balance using filter metrics.

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