Sequence analysis

Correcting mistakes in predicting distributions

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Abstract

Motivation: Many applications monitor predictions of a whole range of features for biological datasets, e.g. the fraction of secreted human proteins in the human proteome. Results and error estimates are typically derived from publications.

Results: Here, we present a simple, alternative approximation that uses performance estimates of methods to error-correct the predicted distributions. This approximation uses the confusion matrix (TP true positives, TN true negatives, FP false positives and FN false negatives) describing the performance of the prediction tool for correction. As proof-of-principle, the correction was applied to a two-class (membrane/not) and to a seven-class (localization) prediction.

Availability and implementation: Datasets and a simple JavaScript tool available freely for all users at http://www.rostlab.org/services/distributions.
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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

Proteome-wide distributions of biological characteristics are relevant for many experimental and computational tools. Two examples pertinent to assess experiments and resources are: what fraction of the proteins are enzymes? What fraction of sequence variants strongly affects function? Often neither experimental annotations nor computational predictions infer the true distribution.

Here, we introduced a simplified approximation to compensate bias. To implement this approximation, users only need the confusion matrix describing the performance of a method along with predictions for entire proteomes or more generally datasets.

2 Materials and methods

2.1 Error correction approximation

First, look up the confusion matrix, i.e. the matrix (or table) describing the evaluation of a method. For two class-predictions these are typically the true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN). The matrix M with elements $M_{p,o}$ gives the number of proteins predicted in class $p$ and observed in class $o$. Correct predictions are diagonal $o = p$. M has the dimension $n$ (number of classes), e.g. $n = 2$ for distinguishing secreted from non-secreted proteins. From this matrix follows a new $n \times n$ matrix $M'$ representing the confusion ratio for each class with:

$$M'_{p,o} = \frac{M_{p,o}}{\sum_{i=1}^{n} M_{p,i}}$$

Each value $M'_{p,o}$ in this new matrix represents the ratio of events predicted in class $p$ and observed as $o$ over all events predicted in class $p$. From this matrix predictions for an entire proteome/dataset $P = (p_1, p_2, \ldots, p_n)$ are corrected to $P_c = (c_1, c_2, \ldots, c_n)$ by:

$$c_x = \sum_{i=1}^{n} M'_{x,i} \cdot p_i$$

Each value $c_x$ represents the number of events predicted in class $x$ multiplied by the ratio of events correctly predicted as $x$ (real $x$) added to the number of events predicted in every other class multiplied by the confusion rate of this other class to $x$.

2.2 Datasets and prediction methods

Two datasets with experimentally determined localization were used. (i) The set with all 5563 human protein annotations from Swiss-Prot (Pundir et al., 2017) was used to build the confusion matrices for the methods. (ii) All high-confidence annotations were
extracted from The Human Protein Atlas (Thul et al., 2017) (HPA ‘Validated’ and ‘Supportive’) to evaluate the correction proposed [Equation (2)]. To avoid overlap, only proteins without Swiss-Prot annotations were added. This gave 2000 proteins. Three tools: Hum-mPloc3.0 (Zhou et al., 2017), LocTree2 (Goldberg et al., 2012) and MultiLoc2 (Blum et al., 2009) were run to evaluate the error correction (Supplementary Table S1 for class conversion).

2.3 Distance between distributions
The error correction [Equation (2)] was used to compare 7-class distributions with and without error correction. The Euclidean distance (square root mean distance for all classes) served as proxy for the difference between the two.

3 Results and discussion
The approximation for the bias correction in experimental and computational data was applied to two problems: one was a hypothetical two-class prediction of the fraction of transmembrane proteins; the other illustrated a 7-class classification of protein localization. The correction was based on performance estimated using all experimental annotations for human in Swiss-Prot (Pundir et al., 2017).

3.1 Mistakes may dominate for the non-optimized class
Many methods optimize the prediction of membrane helices. Those typically focus on membrane proteins. Assume such a method misses less than 1% of all proteins with membrane helices. Assume the same method incorrectly finds membrane regions in 10% of the non-membrane proteins. Organism H might have 20 000 (20k) proteins, with 5k transmembrane. The prediction method would make 1.5k mistakes in the 15k non-membrane (10% error) and 30 in the membrane proteins. Thus, instead of finding 25% as membrane, methods would suggest ~32% (3000−30 + 1500−450/20000). The error corrected version would find the correct number 25%. The extreme imbalance in performance between the class optimized (membrane) and the other (non-membrane) is not unusual for prediction methods (Chen et al., 2002; Reeb et al., 2015).

3.2 Distributions approximated better after correction
The error correction was benchmarked on a multi-class problem using 2000 new proteins with experimental 7-class annotations from HPA (Thul et al., 2017). The problem (predict 7-class distribution) was particularly interesting because the correct distribution (HPA) differed substantially from data used for method development, i.e. all methods optimized a different distribution. On top, none of today’s experimental distributions might capture the entire proteome or genome, all patients in a region) is neither limited to two classes (Fig. 1), nor to proteins, genes, or any other omics. Instead, it is applicable to all datasets that estimate distributions for any aspect. The correction only requires that the confusion matrix reflecting the performance of a method (computational or experimental) correctly reflects unseen data. Nevertheless, our example also showed that methods might use different distributions and still improve substantially through applying the approximation.

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