Methods

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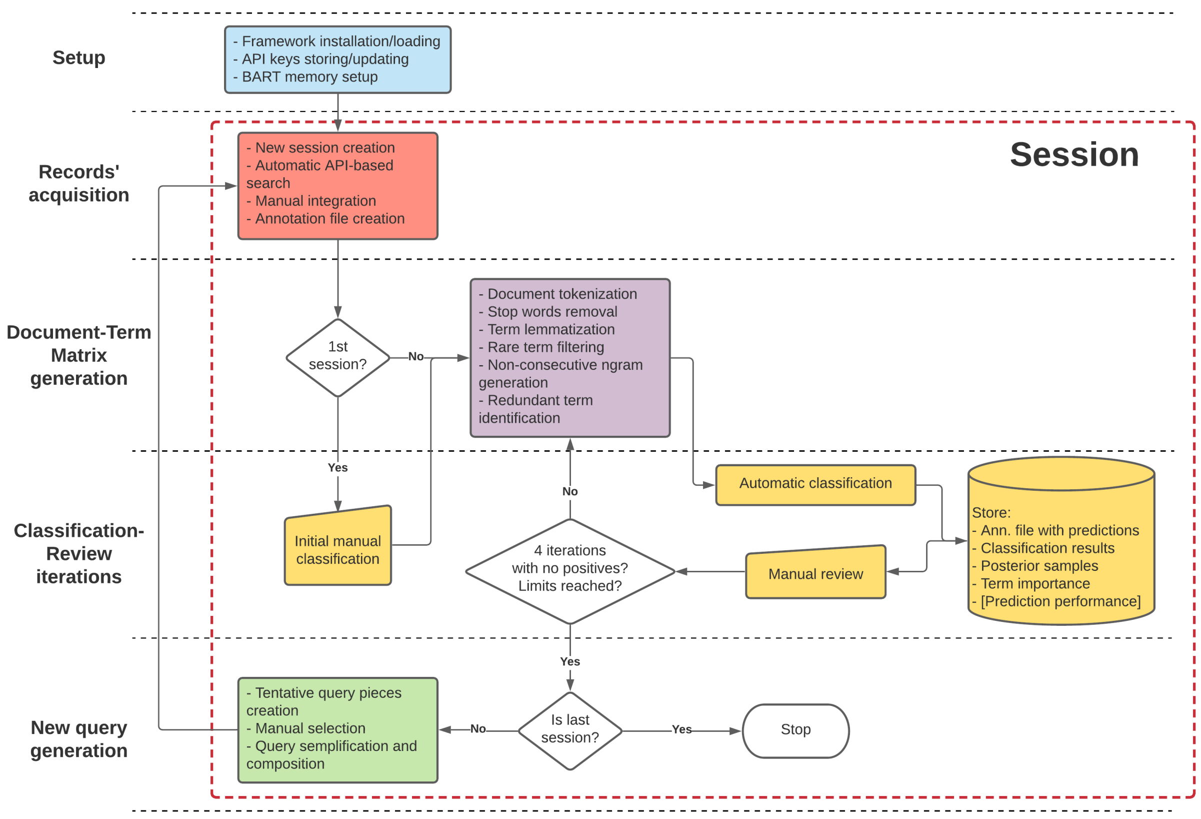
General description

We built an R (R Core Team, 2020) based framework with the goal of simplifying two aspects of systematic reviews: record acquisition and classification. The framework is composed of several components which act together while being independent enough to be in principle be substituted by alternative implementations, given that the structure of the intermediate data outputs is respected. See Supplemental Material S1 for an in-depth description of the framework and how to use it.
The tasks carried out by the framework are grouped into "sessions," that is, a set of actions that starts from using a search query to obtain a set of scientific publications (records), which will be eventually labelled as relevant ("positive" in the rest of the text) or not ("negative") for the topic of interest (Fig. 1). From this labelled set, the framework allows to generate a new query and perform a new session.
The researcher should use the framework with a specific query from which she expects a high relevant/non-relevant record ratio.
Follows a description of the framework's components.

Record's acquisition and initial labelling

We built a set of tools to let users automatically search and download records data from three major scientific databases ("sources"): MEDLINE (https://pubmed.ncbi.nlm.nih.gov/), Web Of Science (WOS, https://apps.webofknowledge.com/) and the Institute of Electrical and Electronics Engineers (IEEE, https://ieeexplore.ieee.org/Xplore/home.jsp). The user needs to input a search query and a date range. The query may contain boolean operators AND, OR, NOT and nested parentheses.
For WOS, an Application Programming Interface (API) key is necessary to use the automatic search tools; for IEEE, if an API key is not available, a slower, web scraping-based solution will be employed; for MEDLINE, an API key is required only for high-frequency requests to the NCBI server (Sayers, 2010), or if a large number of records is expected since our tool splits big API requests in multiple smaller ones.
It is also possible to download and import records in the framework manually. This is particularly useful to acquire records from the SCOPUS (https://www.scopus.com/search/form.uri?display=basic#basic) and EMBASE databases (https://www.embase.com/#advancedSearch/default), for which a comprehensive API interface was not easy to build. A short guide on how to set up the framework for each supported database is available in Supplemental Material S3.
Once the records are downloaded and acquired, the framework merges them into a single database, resolving duplicates and different formatting between sources, ordering the records by simple query term frequency ("simple ordering"), putting the most likely relevant records on top. The output is an "Annotation file."

A first initial set of manually labelled records is needed to start the automatic classification. We suggest manually label the first 250 records (see "hyperparameter optimization" later).



Setup
- Framework installation/loading
- API keys storing/updating
- BART memory setup
Session
Records' acquisition
- New session creation
- Automatic API-based search
- Manual integration
- Annotation file creation
Document-Term Matrix generation
1st session?
No
Yes
- Document tokenization
- Stop words removal
- Term lemmatization
- Rare term filtering
- Non-consecutive ngram generation
- Redundant term identification
Classification-Review iterations
Initial manual classification
Automatic classification
Store:
- Ann. file with predictions
- Classification results
- Posterior samples
- Term importance
- [Prediction performance]
Manual review
4 iterations with no positives? Limits reached?
No
Yes
New query generation
- Tentative query pieces creation
- Manual selection
- Query semplification and composition
Is last session?
No
Yes
Stop

Figure 1.Framework's visual depiction.

Document-Term matrix generation

The annotation file produced in the previous step has a number of fields characterizing a scientific publication. The framework models the relevance of a record based on the following fields: title, abstract, authors, keywords, MESH terms (Lipscomb, 2000). A series of Natural Language Processing (NLP) techniques (*should I put a general reference?*)) are employed to transform the textual information in these fields into features for machine learning. The processing of free text fields includes tokenization (i.e., extracting the terms), common stopwords (i.e. sentence components bringing no meaning) removal, part-of-speech filtering (only nouns, adjectives, verbs and untagged terms are retained), and lemmatization of the terms (i.e. reduction to their base grammar form). Processing for authors, keywords and MESH terms identify logical units (e.g., author's full names, composite keywords) without breaking them into single terms, and no stopwords removal or lemmatization are applied.

To reduce noise and save computation time, terms that appeared in less than 5% of the labelled documents (positive and negatives) are removed from negative records. All terms in the positive set are kept to increase sensitivity at the cost of specificity.

Some terms tend to co-appear in records (non-consecutive ngrams, nc-ngrams), often carrying a particular meaning when copresent. To detect nc-ngrams, we generated a network representation posing edges between terms with a cosine similarity in terms of records copresence > 0.5. We extracted the maximal cliques in the network (Eppstein et al., 2010) representing highly correlated groups of terms; These generated terms are added to the data set. To avoid overfitting, we kept nc-ngrams of a maximum of ten terms.

A similarity network is built again using a similarity threshold of 0.9 and finding the cliques again. In this case, the cliques represent terms that always appear together and therefore can be considered synonyms. These terms are merged in the data set to increase computation efficiency and reduce overfitting.

The final output is a matrix, also called a Document-Term Matrix (DTM), with N_d rows representing the records D, N_t terms column for the t_{field} terms (divided by record field) and $0, 1$ values whether $t_{field} \in D$. We also enriched the DTM with features storing the number of terms in each field to help the model scale term importance based on the document length.

Label prediction

We used a Bayesian Additive Regression Trees (BART) machine learning model (Chipman et al., 2010) (in the implementation of Kapelner & Bleich, 2013) to predict the probability of a record of being relevant, given the information coded into the enriched DTM. BART models have several advantages: as other boosted trees techniques (Hastie et al., 2009), they can model complex non-linearities, perform variable selection, manage missing data while sporting high performance in predictive power. However, the Bayesian framework they are built on provides further benefits: less sensitivity on hyperparameter choices, natural regularization, and, most of all, predictive distributions as output in place of point-wise predictions.

We set up the BART model to use 2000 iterations (after 250 burn-in iterations) and 50 trees; we used a k value of 2 to regularized extreme prediction and let the model use missing fields in the DTM as features (Kapelner & Bleich, 2015). Since the goal is to find all positive matches (i.e., focus on sensitivity), positive records are oversampled ten times.

The output is a posterior predictive distribution (PPD) of each record's probability of a positive match. An ensemble of ten models was fitted to improve prediction stability by averaging the predictions between models.

To choose how to label a record, we exploit the uncertainty typical of Bayesian estimates to decide a record label and whether it requires manual evaluation. To describe the process formally, we define

$$\pi_i = \frac{1}{M} \sum_m Pr(L_i = \text{pos} | DTM, model_m)$$

as the PPD of a record D_i being assigned a positive label (L_i), averaging the PPDs of the ensemble of $M = 10$ models, and

$$\pi_{i,l} = \{\pi_i : Pr(\pi_i) = 1\%\}\pi_{i,u} = \{\pi_i : Pr(\pi_i) = 99\%\}$$

as respectively the lower and upper boundaries of the 98% quantile interval of π_i (98% predictive interval, 98% PrI).
Then we identify the "uncertainty zone"

$$U_\pi = [\max_{D_i \in L_n} \pi_{i,u}, \min_{D_i \in L_p} \pi_{i,l}]$$

that is, a range of π values between the smallest $\pi_{i,l}$ in the set of already labelled positive records L_p and the largest $pi_{i,u}$ related to the negative ones L_n, noting that the two limits can appear in any order.
Consequently, a record D_i will be labelled as positive if

$$\pi_{i,l} > \max_{\pi \in U_\pi} \pi$$

that is, its lower 98% PrI boundary should be higher than every value in the uncertainty zone. In other words, for a record to be labelled positive, its PPD should be within the range of the mixture of PPD of the previously labelled positive records and not cross the distributions of the negative records.
Conversely, a record is labelled as negative if

$$\pi_{i,u} > \min_{\pi \in U_\pi} \pi$$

All other records are labelled as uncertain and will require manual labelling. Also, positive labelled records are to be reviewed to avoid false positives. Furthermore, if a predicted label differs from the existing one, a manual check will be required; this could identify uncertainty in the labelling criteria of the same researcher or between different researchers.

The automatic classification task and the manual review step form an iterative loop (CR iterations). The whole algorithm falls in the pattern defined as active machine learning (Settles, 2009), with the machine querying the user to address and progressively resolve uncertainty in the classification.
The CR iterations continue until no new positive matches are found in four consecutive iterations. The framework supports alternative stopping conditions like limits on the fraction or number of total records reviewed and on the total number of positive matches found.

New search query generation

We created an algorithm that helps create a new search query that could detect further relevant publications missed during the first search, possibly at a reasonable cost in specificity (i.e., a higher number of negative results).
The algorithm encompasses a number of steps:

- We fit a partition tree (Therneau & Atkinson, 2019) between the DTM and 800 samples from the PPD; if a term is present multiple times in the DTM (e.g. both title and abstract), they are counted just one, and field term count features are removed. This step generates a list of rules composed by AND/NOT "conditions" made of terms/authors/keywords/MESH, which together identify a group of records.
- For each rule, we add a set of negative conditions (NOT statements in the rule), removing non-relevant records in a group: a condition removing the largest number of non-relevant records is found, and then iteratively, more are added with the same logic, until no conditions are found that would not also remove positive records.

- The extended set of rules is sorted by the difference between the number of positive and negative records they identify in descending order. Given this ordered list, the cumulative number of unique positive records is computed and used to group the rules: each rule in the same group of rules adds the same number of positive records to the preceding group but are ordered according to the number of negative records they identify.
- These groups of rules are outputted, and the researcher is asked to review them, selecting one or more (useful if they convey radically different meaning) rules from each group, or edit them (in case too specific positive or negative conditions were included). By default, the framework suggests keeping the first rule of each group since it would identify the lower number of non-relevant records for the same number of positive one (.e., higher specificity). It is possible to exclude a group of rules altogether, especially the last ones with very low positive/negative records ratios.
- The selected rules are joined together by OR statements, defining a subset of records with a sensibly higher proportion of positive records than the original one.
- Given this data set, the next step removes redundant rules (i.e., rules whose positive records are already included in more specific ones) and conditions (i.e., conditions that once removed do not decrease the total number of positive or do not increase the negative records).
- Finally, the rules are re-elaborated in a format usable on the major scientific databases.

It is important to note that this process is entirely data-driven. The algorithm is only aware of the "world" defined by the data set, itself generated by a specific search query focused on a particular topic. Therefore, the new query may not be specific once applied to an unbounded search domain, returning an unmanageable amount of unrelated results. We suggest extending the query by adding domain-specific terms linked by an AND statement, separating the original query and the new addendum in two distinct logical blocks by enclosing them in parentheses. See the Results for the specific query used in the second session. *not sure whether to put this part here or in the discussion*

Hyperparameter search

The machine learning model behind the algorithm has a number of hyperparameters in addition to the BART specific ones: the number of ensemble models, the source of randomness between models (just derived from MCMC sampling, the default, or whether to bootstrap the data first), the oversampling of positive records, the PrI quantiles, the number of initial manually labelled records. These parameters have a relevant effect on the algorithm performance.
We set up a grid search to evaluate the parameters on a subset made of the first 1200 records from the first session; these records were fully labelled as relevant or not. We run the framework for each combination of parameter values, automatizing the manual review part using the already collected labels. The framework ran until four CR iterations with no positive records were returned, or the whole dataset was labelled.
For each combination, a performance score was computed as the product of *Efficiency* (number of records that required review over the total) and *Sensitivity* (number of positive records found over the total of positives). We then identified homogeneous "performance clusters" of parameter values using a decision tree on the score. For the final analysis, we chose the best cluster of parameter value combinations and, inside the cluster, the best combination in order of Sensitivity and Efficiency.

Performance evaluation

It is hard to estimate the generalized performance of such a model since the data is not a random sample (the records are presumably the whole population of articles from the searched databases for those search criteria), and since the order of records matters (it drives the choice of the initial labelling set). Therefore we postulated that usual random train/test methods to estimate the out-of-sample machine learning performance (Kohavi & others, 1995) would not be representative in this situation. Also, common time-series based predictive performance methodologies would reveal inadequate (Tashman, 2000) since the expected proportion of positive matches is not constant throughout the data set and is expected to fall fast as the

first matches are found.
Our solution was to use Bayesian logistic regression to model the label of the manually reviewed records on the lower bound of the [98% PrI] produced by our algorithm. For the model we used weakly regularizing, robust priors for the intercept (Student T with $\nu = 3, \mu = 0, \sigma = 2.5$) and the linear coefficient (Student T with $\nu = 3, \mu = 0, \sigma = 1.5$). The goal of the model is to estimate the PPD of the missed number of positive matches in the whole data set. Given that this model is conditional only on the BART predictions and not on the DTM, it is characterized by more uncertainty, providing a plausible worst-case scenario. The quality of the model was evaluated through Bayesian R^2 (Gelman et al., 2019) of which we reported the posterior median and 90% Credible Interval [90% CrI].
The predictive distribution of the number of missed positive records allows to estimate the expected long-run *Sensitivity* and the *Work saved over random* (WSoR) of the algorithm. The WSoR is based on a negative hypergeometric model to estimate the number of records to manually label to find the same number of positives if records were evaluated in random order (Chae, 1993); the WSoR is then one minus the ratio of the reviewed records over this number. For the number of predicted positive records, the sensitivity and WSoR, we reported the truncated 90% PrI [trunc. 90% PrI], which is the uncertainty interval bounded at the number of observed total positive records: since each positive match is manually verified, the probability of a number of total positive records lower than observed is zero.

Chae, K.-C. (1993). Presenting the negative hypergeometric distribution to the introductory statistics courses. *International Journal of Mathematical Education in Science and Technology*, *24*(4), 523–526.

Chipman, H. A., George, E. I., McCulloch, R. E., & others. (2010). BART: Bayesian additive regression trees. *The Annals of Applied Statistics*, *4*(1), 266–298.

Eppstein, D., Löffler, M., & Strash, D. (2010). Listing all maximal cliques in sparse graphs in near-optimal time. *International Symposium on Algorithms and Computation*, 403–414.

Gelman, A., Goodrich, B., Gabry, J., & Vehtari, A. (2019). R-squared for bayesian regression models. *The American Statistician*.

Hastie, T., Tibshirani, R., & Friedman, J. (2009). Boosting and additive trees. In *The elements of statistical learning* (pp. 337–387). Springer.

Kapelner, A., & Bleich, J. (2013). bartMachine: Machine learning with bayesian additive regression trees. *arXiv Preprint arXiv:1312.2171*.

Kapelner, A., & Bleich, J. (2015). Prediction with missing data via bayesian additive regression trees. *Canadian Journal of Statistics*, *43*(2), 224–239.

Kohavi, R., & others. (1995). A study of cross-validation and bootstrap for accuracy estimation and model selection. *Ijcai*, *14*, 1137–1145.

Lipscomb, C. E. (2000). Medical subject headings (MeSH). *Bulletin of the Medical Library Association*, *88*(3), 265.

R Core Team. (2020). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. https://www.R-project.org/

Sayers, E. (2010). A general introduction to the e-utilities. *Entrez Programming Utilities Help [Internet]. Bethesda (MD): National Center for Biotechnology Information (US)*.

Settles, B. (2009). *Active learning literature survey*.

Tashman, L. J. (2000). Out-of-sample tests of forecasting accuracy: An analysis and review. *International Journal of Forecasting*, *16*(4), 437–450.

Therneau, T., & Atkinson, B. (2019). *Rpart: Recursive partitioning and regression trees*. https://CRAN.R-project.org/package=rpart