Methodological considerations

*The statistical methods suggested for the paper are not trivial. I will therefore try to describe my thoughts about it. This is based on my initial proposal and with some additional modifications based on a literature review after Szilard’s suggestions.*

# Interpretable model

An interpretable model would be ideal. This would favor a model with as few predictors as possible (Ockham’s razor), combined in a straightforward manner. A more advanced black-box method might yield better predictions [1], but might be hard to motivate in clinical practice.

A multivariable logistic regression model might seem easily interpretable, but is not [2]. Interdependencies among covariates yields non-trivial relations between predictors and outcome (not to be confused by a linear model [3]). Difficulties increase further for possibly dependent predictors (usually allowed in predictive modelling).

There might be no such thing as a “semi-interpretable method”. Moreover, if there is, it might be even worse than a black box method, since it might further invite to misleading interpretations. Nevertheless, it seems like some methods are described as such in the applied literature. Least absolute shrinkage and selection operator (Lasso) has been used at least twice recently to increase “transparency” for prediction of 30-day mortality after total hip and knee arthroplasties [4,5]. Also, a hierarchical Tree-Lasso logistic regression has been explicitly presented as an “interpretable predictive model” in the field of pediatrics [6].

# Lasso regression

We must note of course that logistic Lasso regression has the same flaws as ordinary logistic regression considering interpretability (above). The difference lies in the use of a regularizing penalty term when estimating the regression coefficients. An -norm, multiplied by an arbitrary constant λ (usually found by some cross-validated optimization), is used to force some coefficients to zero, keeping only a subset of the initial predictors.

This is most relevant for settings with a vast number of candidate predictors. To find a minimal subset of predictors is however one of the explicit goals of the project, wherefore this type of variable selection might still be relevant.

# Ensemble Lasso

Variable selection by Lasso is known to include potential predictors that are false positives (that should not be included in the final model). The method is also associated with some bias. A robust alternative is ensembles of multiple Lassos performed to different resamples of the original data set. The Bolasso method suggested in 2008 combines bootstrap replicates and Lasso to a consistent estimator [7]. Consistency in variable selection was also proven for “stability selection” more broadly in 2010 [8]. Then in 2015, some additional improvements were made to the method, suggesting the “bootstrap ranking procedure”, applying Lasso to bootstrap samples using variable importance for variable ranking and variable selection [9].

# Class imbalance

We have a highly imbalanced data set with very few deaths compared to survivors. This makes ordinary methods such as logistic regression (and therefore Lasso and its ensemble version) problematic.

There are some strategies to this problem:

1. **Ignore** and proceed. This is easily done and not necessarily as bad as it sounds. No other method is perfect and enough deaths might exist even if survivors dominates.
2. **Cost-sensitive learning,** assuming there is a known cost imbalance difference between misclassification of either deaths as survivors and survivors as deaths. Those costs are rarely known however, and will therefore not be considered further.
3. **Data preprocessing by re-sampling** to bypass the imbalance.

## Re-sampling approaches

Re-sampling is made by up sampling (of deaths), down sampling (of survivors), a combination of the two, or some more advanced sampling technique [10].

Up sampling does have its merits but computational requirements would in our case be infeasible due to the combination of bootstrap resampling. A review of different methods have shown that down sampling is in fact preferred due to simplicity, low risk of over-fitting and superior result when evaluating predictive power on an independent test data set [11].

Down sampling with ensemble Lasso (stability selection) has been used to discover adverse drug reactions by sampling four times as many cases than controls [12].

A modified down sampling procedure with pre-clustered data and balanced sampling from each cluster has also been used to predict credit scores [13]. The method slightly outperformed random forest and some other traditional methods if including well-designed prediction features as independent variables. The result was however inferior without elaborate variable transformations and binning. Also, a more advanced Bayesian approach with Markov-Chain Monte Carlo algorithms including stratified and importance-weighted sub-sampling was very recently suggested [14] (article not yet peer-reviewed). Those methods, and others, might be theoretically appealing, and perhaps superior to simple down sampling. They do seem a little esoteric however and are not commonly applied.

# Biased probability estimates

Logistic regression, as implemented by maximum likelihood (ML), is asymptotically unbiased under regularity conditions. A finite-sample bias however exist. This can introduce bias in estimation of very rare events. A method for bias-correction was therefore suggested in 1993 [15][[1]](#footnote-1), and the method has been developed further [16,17][[2]](#footnote-2).

In addition, re-sampling changes the underlying distribution of the data. Thus, changing the scale of estimated probabilities. This might go unnoticed if models are chosen simply based on predictive performance. A high AUC value indicates that, for one survivor and one dead chosen randomly, the dead had a higher predicted probability to die. This relation is maintained through re-sampling since the rank order of estimated probabilities goes unchanged. The estimated class probabilities on the other hand does change. General technics might reduce the bias but the approximate Bayesian estimator [18,19][[3]](#footnote-3) might give a better balance between bias and variance. It adjusts the model coefficients and therefore the probabilities. Hence, it reduces the root mean square error (RMSE) of logistic regression models with rare events.

Another recently developed method specifically target calibration of down sampled data due to unbalanced logistic regression [20]. The estimated event probability after down sampling () is used to estimate the overall probability by:

where α is the proportion of positive to negative outcomes in the original data set.

The method was proposed for ordinary logistic regression, but could hopefully be applied also to the down sampled bootstrap ranking procedure with logistic Lasso regression.

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1. logistf R package: <https://cemsiis.meduniwien.ac.at/en/kb/science-research/software/statistical-software/fllogistf/> [↑](#footnote-ref-1)
2. brglm2 R package: <https://github.com/ikosmidis/brglm2> [↑](#footnote-ref-2)
3. Zelig R package: http://docs.zeligproject.org/articles/zelig\_relogit.html [↑](#footnote-ref-3)