Beating the International Prognostic Index for high-risk DLBCL patients

Master thesis progress report

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March 12, 2024

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Set the arena

DLBCL: a heterogeneous cancer with a homogeneous therapy

In practice, there is only one treatment regimen: immunochemotherapy with R-CHOP. It cures two thirds of the patients.

Cure rates among relapsed and refractory patients are low. Hence, we should not send them to R-CHOP therapy in the first place, but into alternative treatments including clinical trials.

We define high-risk patients as those with a progression-free survival (PFS) < 2 years.

The goal of this thesis (and the MMML-Predict project) is ...

... to develop a cost-efficent ($<$ 1500 euros) classifier filtering out high-risk DLBCL patients before an R-CHOP treatment begins or at least at an early stage of it.

Candidate input features for the new classifier are

- clinical data (like the IPI, see next slide),
- transcriptomic (RNA-seq, signatures like LAMIS, ABC vs. GCB),
- proteomic signatures,
- somatic genetic factors (translocations like MYC),

all of which are measured at diagnosis, as well dynamic features like

- the tumor burden according to a liquid biopsy after 2 and 4 cycles of R-CHOP.

To beat: the International Prognostic Index (IPI) for non-Hodgkin's lymphoma

The IPI [1] is a simple risk score ranging from 0 to 5 depending on how many of the following clinical questions for a patient one can answer with "yes":

- Age > 60?
- Ann Arbor stage III or IV: is the cancer advanced?
- Serum LDH (lactacte dehydrogenase) level: higher than normal?
- Performance status: is the patient no longer ambulatory?
- Number of extranodal sites (like bone marrow, liver, lung) involved: more than one?

The lower the IPI, the better the patient's outlook: higher progression-free survival (PFS) and overall survival (OS).

The IPI is a 30-year old dinosaur

Yet, it's still state of the art in clinical practice when it comes to assessing a DLBCL patient's risk because it's simple, cheap and robust (after all, it's based on a rigorous statistical analysis and Cox regression).

Still, just six values the IPI can attain mean it's very rough. In particular, it fails to identify a clinically relevant high-risk group:

- The cohort with IPI $= 5$ is too small to get attention from clincians.
- The cohort with IPI ≥ 4 lacks precision[1] in identifying high-risk patients: 16% of patients have an IPI ≥ 4, but only 40% of them are high-risk. This is too low to persuade a clinician to change the treatment plan.

[1] Proportion of true positives among all positives.

What does ”beating the IPI” mean?

We need data to demonstrate the new classifier’s superiority. MMML-Predict aims to enroll 300 DLBCL patients (200 training, 100 test cohort). For my thesis, I need to use already existent data.

Beating the IPI means, on the test cohort the new classifier needs to

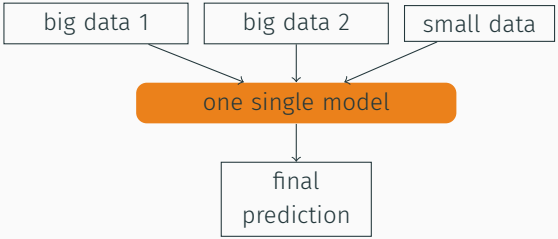
- be more precise in identifying high-risk patients than the IPI: the 95% confidence interval (CI) of the precision according to Clopper-Pearson must not include 35%[2],
- yield two cohorts with significantly differing survival (PFS): logrank-test p-value < 0.05.

Calculations with the size of the test cohort ($n = 100$) suggest that a precision $\geq 50\%$ with a prevalence[3] $\geq 15\%$ is enough.

[2] This is the precision of IPI ≥ 4 on pooled data from DSNHNL trials (2721 samples).
[3] The rate of positive predictions.

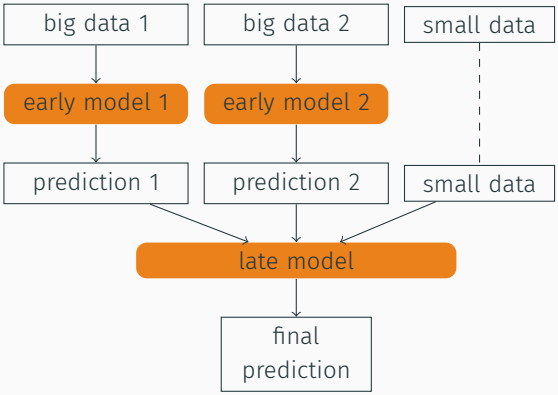
Meet the players

Early versus late integration



- Provide all data as input features to a single well-known model.
- Upside: easy to implement, one algorithm fits and picks the model including a cross validation.
- Downside: data on vastly different scales may confuse the model and its minimizer.

Early versus late integration



- Early models deal with high-throughput data and its curses: curse of high dimensionality, measurement errors.
- Upside: modularizes the model selection process, allows for very sophisticated late models.
- Downside: implementing the model selection process becomes more complicated, how to deal with cross validation in the early models?

The key player for early-stage models: zeroSum

We feed high-troughput data into

- Cox proportional-hazards models and
- logistic models,

with LASSO regularization and the zero-sum constraint. Both aim to estimate the response y_i of sample i by a predictor $x_i \in \mathbb{R}^p$ via

$$y_i = f(\beta_0 + x_i^T \beta) + \varepsilon_i \tag{1}$$

for a link function $f : \mathbb{R} \to \mathbb{R}$, a vector of coefficients (β_0, β), and a residual ε_i.

The zero-sum constraint, $\sum_{j=1}^{p} \beta_j = 0$, enforces scale-invariance, i.e., the model output for $\alpha \cdot x_i$ $(\alpha > 0)$ *after taking the log* is the same as for x_i.

Wrap it all into a loss function

Training such a model comes down to minimizing a loss function of the form

$$\mathcal{L}_{X,y,\lambda,u,v,w}(\beta_0, \beta) = -\sum_{i=1}^{n} w_i \ell_{X,y,\beta}(\tilde{y}_i, \beta_0 + x_i^T \beta) + \lambda \sum_{j=1}^{p} v_j |\beta_j| \quad \text{subject to } \sum_{j=1}^{p} u_j \beta_j = 0 \qquad (2)$$

for hyperparameters

- $\lambda > 0$, the LASSO penalty factor (tuned in a cross-validation),
- $u \in \mathbb{R}^p_{\geq 0}$, the zero-sum weights (often $u = \mathbf{1}$),
- $v \in \mathbb{R}^p_{\geq 0}$, the LASSO penalty weights (often $v = \mathbf{1}$), and
- $w \in \mathbb{R}^n_{\geq 0}$, the sample weights (often $w = \frac{1}{n}\mathbf{1}$).

$\ell_{X,y,\beta} : \mathbb{R}^2 \to \mathbb{R}$ is some kind of model-dependent log likelihood. $\tilde{y}_i$ is closely related to y_i (if not the same), its nature again depends on the model.

More on ℓ and y_i

In the Cox model,

- y_i is the relative hazard of sample i: the higher it is, the earlier we expect sample i to face the event compared to the other samples.
- $\tilde{y}_i$ is the time to event.
- $\ell_{X,y,\beta}$ tries to enforce the correct ordering: $\beta_0 + x_i^T\beta$ should be monotonic in $\tilde{y}_i$.

In the logistic model,

- we need to threshold the time to event to get a binary response: $\tilde{y}_i = y_i = 1$ if the event happens before a certain time T, 0 otherwise. One can view T as yet another hyperparameter.
- $\ell_{X,y,\beta}$ forces $\beta_0 + \beta x_i^T$ to be high if $\tilde{y}_i = 1$ and low else.

What this means for right-censoring

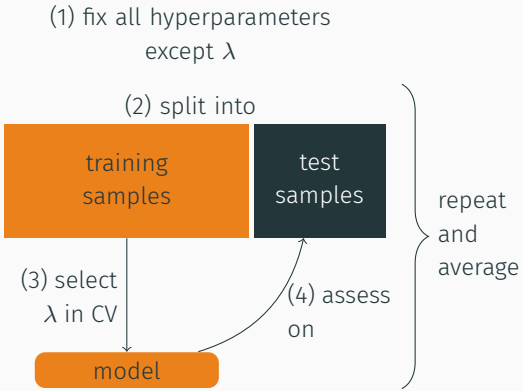
In reality, the data contains patients that dropped out of the study before the event could occur (right-censoring).

The Cox model, more precisely $\ell_{X,y,\beta}$, can take this information into account.

For the logistic model, however, we cannot use patients censored before T.

Train the players and select the best

Train-test paradigm



Hyperparameters excluding λ may be

- the model type,
- zero-sum weights, regularization weights, sample weights,
- the threshold T for the logistic model[4].

We assess the models

- with a scalar metric (like the ROC-AUC) to get a pre-selection,
- in scatter plots (like prevalence versus precision) to threshold the scores output by the pre-selected models.

[4] Similarly for the Cox model, we can right-censor samples with time to event $> T$ at T.

Software

zeroSum R package [4] for fitting and cross-validating the logistic and Cox models. It extends the glmnet package by the zero-sum constraint.

When integrating a model selected in a cross validation into another model I want to continue the cross validation of the early model. zeroSum does not report enough details, so I added this functionality in a fork zeroSumLI [5].

Training and assessing a bunch of models on several data sets means a lot of administrative, repetitive work. I automized and outsourced this part into an R package patroklos [2].

Watch the game: the results

The data

I trained models predicting progression-free survival < 2 years on data including bulk RNA-seq taken from Schmitz et al. [6].

- It has $n = 229$ patients with survival information, $p = 25\,066$ genes.
- 78 (34%) of these are high risk.
- 135 (59%) are low risk.
- 16 (7%) we cannot assign.
- All IPI features are available in pheno data.
- The IPI does a pretty good job on it, see Table 1.

IPI $\geq$	prevalence	precision
5	0.01	1.00
4	0.13	0.65
3	0.35	0.55
2	0.59	0.48
1	0.85	0.41
0	1.00	0.37

Table 1: Classifying PFS < 2 years on [6].

The line-up: the models tried out

hyperparamter	choices
model family	Cox, logistic regression.
input data	Gene expression only; gene expression with early integrated IPI: as one continuous variable (”with ipi cont”) or five binary variables (”with disc ipi feat”).
zero-sum weights	$u = 0$; $u_i = 1$ for gene-expression features, else $u_i = 0$ (”zerosum”).
LASSO weights	Standardization, i.e., v_i is the standard deviation of feature i (”std”); $v_i = 1$ for gene-expression features, else 0.
sample weights	$w = \mathbf{1}/n$.
T	$1, 1.25, 1.5, \ldots, 2.5$; additionally ∞ for Cox.

Table 2: Terms in quotation marks are used in model names on the following slides.

Pre-selection via ROC-AUC

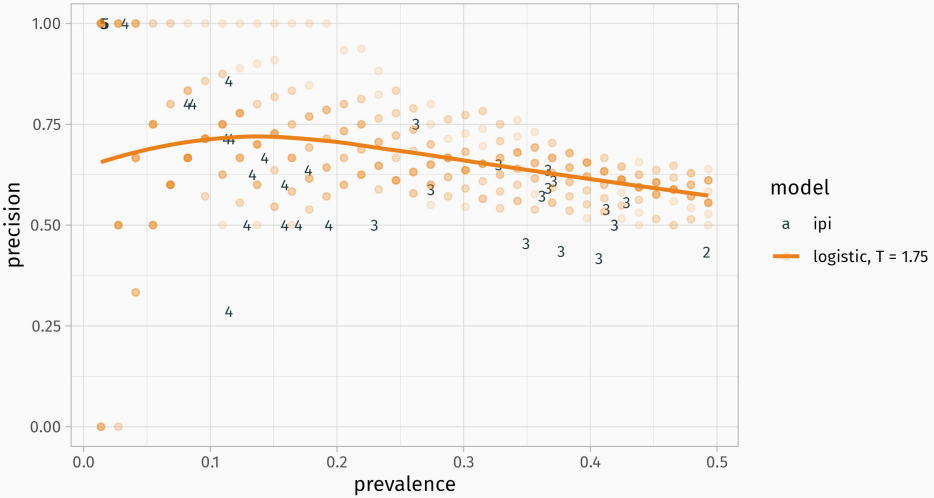
rank	model	T	AUC
1	logistic	1.75	0.770
2	logistic zerosum	1.75	0.769
3	cox	1.75	0.762
4	cox zerosum	1.75	0.761
5	cox	2	0.755
6	logistic zerosum	1.5	0.755
7	cox zerosum	1.5	0.752
8	cox	1.5	0.750
9	cox	Inf	0.749
10	cox zerosum	Inf	0.748

Table 3: Split into train and test cohort, train a model on train cohort, calculate ROC-AUC on test cohort. Repeat this 15 times and average.

What does this mean for choosing the hyperparameters?

- Logistic versus Cox regression not that important.
- With zero-sum constraint usually a bit worse than without.
- Choose $T = 1.75$.
- Early integration and standardization disappoint.

Is this enough to meet our initially stated goals?



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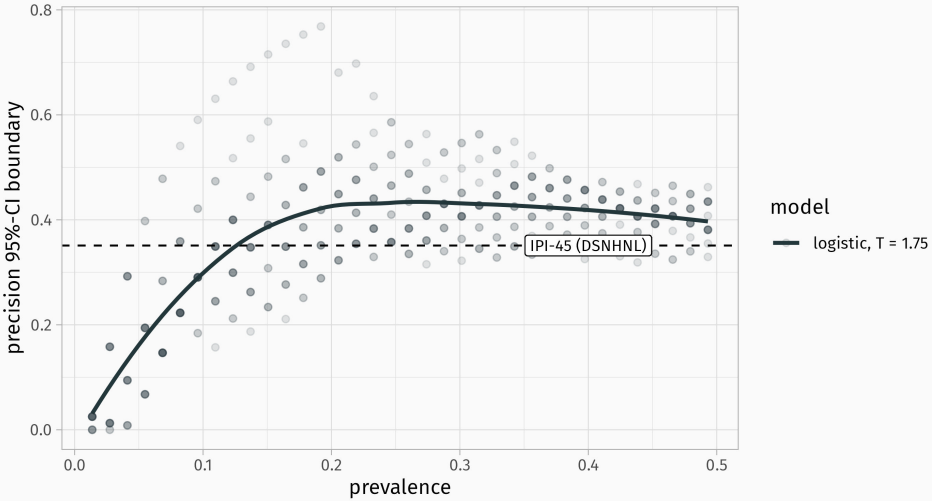

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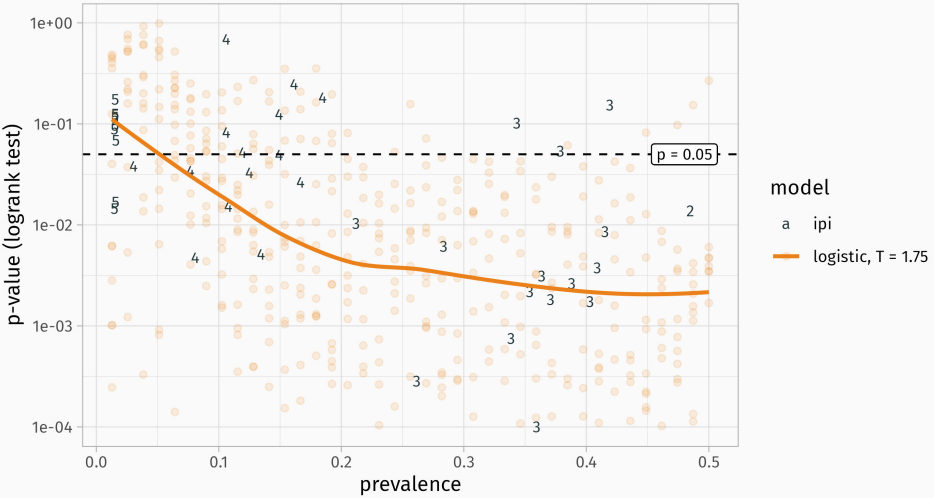

What comes next?

On the data front, I want to

- do the afore-mentioned on a bigger ($n = 624 \gg 229$) data set by Reddy et al. [3].
- Downside: only overall, no progression-free survival included (fine for this thesis, less helpful for MMML-Predict).

On the methods front, I want to

- try to get early integration with zeroSum working,
- use sample weights $w \neq \frac{1}{n}\mathbf{1}$ to give less weight to patients with a PFS close to 2 years in the loss,
- implement late integration: with, e.g., linear regression, random forest as second-stage models,
- integrate more features.

Thank you for your attention!

Questions?

References

[1] **“A Predictive Model for Aggressive Non-Hodgkin’s Lymphoma”.** In: *New England Journal of Medicine* 329.14 (1993). PMID: 8141877, pp. 987–994. DOI: 10.1056/NEJM199309303291402.

[2] Lukas Gessl. ***patroklos: An R package pipelining omics-based cancer survival analysis.*** R package version 0.4.0. 2024. URL: https://lgessl.github.io/patroklos/.

[3] Anupama Reddy et al. **“Genetic and Functional Drivers of Diffuse Large B Cell Lymphoma”.** In: *Cell* 171.2 (2017), 481–494.e15. DOI: 10.1016/j.cell.2017.09.027.

[4] Thorsten Rehberg. ***zeroSum.*** URL: https://github.com/rehbergT/zeroSum.

[5] Thorsten Rehberg and Lukas Geßl. ***zeroSumLI.*** URL: https://github.com/lgessl/zeroSumLI.

[6] Roland Schmitz et al. **“Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma”.** In: *New England Journal of Medicine* 378.15 (2018), pp. 1396–1407. DOI: 10.1056/NEJMoa1801445.