Collinearity in prognostic models for dysphagia

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Background

Normal Tissue Complication Probability (NTCP) models predict the risk of radiation induced complications and can be used to optimize dosage plans of radiation-based therapies to minimize the risk of such complications. Dosage delivered to organs at risk (OARs) surrounding the targeted tumor is often highly collinear ($r^2 > 0.8$), inducing high variance on coefficient estimates. Consequently, many NTCP models are developed using only a subset of relevant OAR, especially for complex complications, like dysphagia, involving many relevant OAR. Excluding OAR can be problematic when using NTCP models for dosage optimization as it steers dosage towards excluded OAR.

Aim

To compare different methods to address collinearity without degradation of model performance.

Methods

We compared five methods that constrain the coefficient search space (reducing coefficient variance) for standard logistic regression: Lasso, Ridge, principal component regression, dropout regularization (random dropout of predictors during iterative model fitting), and non-negativity constraints for OAR dosage coefficients. Each method is empirically evaluated, using a 16-predictor logistic regression NTCP model for dysphagia grade ≥2 (predictors are: primary tumor location, and mean dose for 11 OARs).

	10-Fold Cross Validation					External Validation			
Method	**%$\beta^{OAR<0}$**	**AUROC**	**C^{ITL}**	**C^{SLOPE}**	**Brier**	**AUROC**	**C^{ITL}**	**C^{SLOPE}**	**Brier**
Log.Reg.	0.40 ±0.04	0.75 ±0.05	-0.16 ±0.34	0.90 ±0.61	0.16 ±0.01	0.76 ±0.04	-0.26 ±0.29	0.70 ±0.16	0.17 ±0.01
PCR	0.15 ±0.04	0.77 ±0.08	0.16 ±0.54	1.31 ±0.84	0.15 ±0.02	0.78 ±0.02	0.02 ±0.26	0.98 ±0.29	0.16 ±0.01
Lasso	0.16 ±0.05	0.76 ±0.11	1.18 ±2.89	2.26 ±3.06	0.16 ±0.02	0.76 ±0.03	0.38 ±0.62	1.16 ±0.38	0.16 ±0.01
Ridge	0.18 ±0.04	0.78 ±0.04	0.27 ±0.40	1.32 ±0.43	0.15 ±0.01	0.77 ±0.02	0.28 ±0.30	1.23 ±0.25	0.16 ±0.00
Dropout	0.23 ±0.05	0.77 ±0.07	0.43 ±0.67	1.50 ±0.81	0.15 ±0.01	0.75 ±0.02	0.14 ±0.47	1.10 ±0.37	0.16 ±0.01
β+	0.00 ±0.00	0.76 ±0.08	-0.03 ±0.45	0.99 ±0.50	0.15 ±0.02	0.79 ±0.02	0.27 ±0.35	1.18 ±0.28	0.15 ±0.01

Table 1: Comparison of methods for a within-hospital 10-fold-cross-validation (n=489) and an external validation (n^{dev}=489, n^{test}=143). Reported statistics (and standard deviations) are: the percentage of negative OAR coefficients (%$\beta^{OAR<0}$), area under the receiver-operating-characteristic curve (AUROC), calibration in-the-large (C^{ITL}), calibration slope (C^{SLOPE}), and Brier score.

Results & Conclusions

Table 1 shows similar AUROC and Brier across methods, and similar calibration (in-the-large and slope) at cross-validation. PCA and non-negativity constraints stand out in terms of calibration at external validation. All methods reduce but still contain one or more negative coefficients for OAR dosage variables except when using non-negativity constraints (β+). If accepted for presentation, we expect to show results of combining PCA and non-negativity constraints as well, as we concluded these methods to be most beneficial for this use case based on these preliminary results.

Keywords

Collinearity, NTCP, radiotherapy, prediction, dysphagia