Automated feature selection of predictors in electronic medical records data

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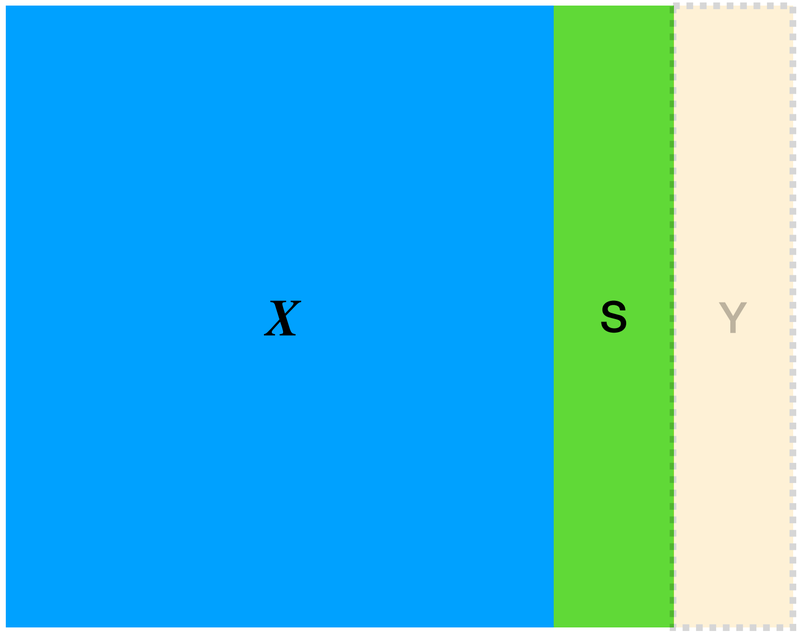
Agenda

- (Quick) Introduction
- Proposed Methods
- Simulation Study
- Data Analysis
- Discussion

Introduction

EHR Data



- X: wide range of candidate features
- Interested in true disease status Y, but…
  - Chart review is labor-intensive
- S: easily extracted from EHR data and closely related to y

Can we accurately extract features that are predictive of Y using only S?

Methods

Notation Set-up

- N *i.i.d.* random vectors $\mathcal{F} = \{(Y_i, \boldsymbol{X}_i^T, \boldsymbol{S}_i^T)^T, i = 1,..,N\}$
- only $\mathcal{D} = \{\boldsymbol{W}_i = (\boldsymbol{X}_i^T, \boldsymbol{S}_i^T)^T, i = 1,...,N\}$ is observed
- Assumptions
  - $P(Y = 1 \mid \boldsymbol{X}) = g(\alpha_0 + \boldsymbol{X}^T\boldsymbol{\beta}_0) = g(\overrightarrow{\boldsymbol{X}}^T\boldsymbol{\theta}_0)$; Y follows a GLM
    $\overrightarrow{\boldsymbol{X}} = (1, \boldsymbol{X}^T)^T, \boldsymbol{\theta}_0 = (\alpha_0, \boldsymbol{\beta}_0^T)^T$
  - $\boldsymbol{S} \perp \boldsymbol{X} \mid Y$ $\boldsymbol{S}$ depends on $\boldsymbol{X}$ only through Y
  - $\boldsymbol{X}$ is elliptical symmetric

Methods

Unsupervised feature selection procedure

- Step I :
  - Estimate $\pi_S = P(Y = 1 \mid \boldsymbol{S})$
- Step II:
  - Penalized regression $\hat{\pi}_S$ against $\boldsymbol{X}_i$
  - Candidate features are in $\widehat{\mathscr{A}} = \{j : \hat{\beta}_j \neq 0\}$

Methods

Step I: Clustering

$S \sim \tau f_{\boldsymbol{\Theta}_1} + (1-\tau) f_{\boldsymbol{\Theta}_0}$ *working* parametric mixture model

- $\tau := P(Y = 1)$
- $S \mid Y \sim f_{\boldsymbol{\Theta}_y}$; $f_{\boldsymbol{\Theta}_y}$ is specified up to unknown parameters $\boldsymbol{\Theta}_y$; e.g. $S \mid Y = 1 \sim N(\boldsymbol{\mu}_1, \Sigma_1)$
- unknown $\boldsymbol{\Theta}_\cdot = (\boldsymbol{\Theta}_1^T, \boldsymbol{\Theta}_0^T, \tau)^T$

$\widehat{\boldsymbol{\Theta}_\cdot}^{MLE} = argmin_{\boldsymbol{\Theta}_\cdot}\{-N^{-1}\sum_{i=1}^{N} l(\boldsymbol{\Theta}_\cdot \mid S_i)\}$ can be found using EM alogirthm

$$\hat{\pi}_S = \frac{P(Y=1,S)}{P(S)} = \frac{\hat{\tau} f_{\hat{\boldsymbol{\Theta}}_1}}{\hat{\tau} f_{\hat{\boldsymbol{\Theta}}_1} + (1-\hat{\tau}) f_{\hat{\boldsymbol{\Theta}}_0}}$$

Methods

Step II: Regularized Estimation

$$\hat{\boldsymbol{\theta}} = (\hat{\alpha}, \hat{\boldsymbol{\beta}}^T)^T = argmin_{\boldsymbol{\theta}} \Bigg\{ N^{-1} \sum_{i=i}^{N} \underbrace{l(\boldsymbol{\theta}^T \overrightarrow{\boldsymbol{X}}_i \,|\, \hat{\pi}_{S_i})}_{\text{negative likelihood}} + \underbrace{\lambda_N \sum_{j=1}^{p} \frac{|\beta_j|}{|\tilde{\beta}_j|}}_{\text{adaptive lasso penalty}} \Bigg\}$$

let $\tilde{\boldsymbol{\theta}}$ be the MLE of the average negative likelihood.

$$\approx argmin_{\boldsymbol{\theta}} \Bigg\{ (\boldsymbol{\theta} - \tilde{\boldsymbol{\theta}})^T \Sigma_{\boldsymbol{X}}^{-1} (\boldsymbol{\theta} - \tilde{\boldsymbol{\theta}}) + \lambda_N \sum_{j=1}^{p} \frac{|\beta_j|}{|\tilde{\beta}_j|} \Bigg\}$$

Methods

Summary

- $E(\bar{\pi}_S \mid \boldsymbol{X}) \approx g(\boldsymbol{\theta}_0^T \overrightarrow{\boldsymbol{X}}) = E(Y \mid \boldsymbol{X})$ provided that $E(\bar{\pi}_S \mid Y = y) \approx y$
- Fitting $\hat{\pi}_S$ (the "error-corrupted" version of Y) can be viewed as mis-specification of link function (Neuhaus, 1999)
- Even mixture model fails to hold, if $\boldsymbol{X}$ follows elliptical symmetric distribution, then
  - $E(\hat{\boldsymbol{\beta}}) = c\boldsymbol{\beta}_0$ provided that $cov(\bar{\pi}_S, \boldsymbol{\theta}_0^T \overrightarrow{\boldsymbol{X}}) \neq 0$ (Li and Duan, 1989)
  - $P(\widehat{\mathscr{A}} = \mathscr{A}) \rightarrow 1$ as $N \rightarrow \infty$ (Appendix)

Neuhaus, John M. "Bias and Efficiency Loss Due to Misclassified Responses in Binary Regression." *Biometrika* 86, no. 4 (1999): 843–55.
Li, Ker-Chau, and Naihua Duan. "Regression Analysis Under Link Violation." *The Annals of Statistics* 17, no. 3 (September 1989): 1009–52. https://doi.org/10.1214/aos/1176347254.

Methods

Variable selection via resampling

- $\boldsymbol{X}_{\widehat{\mathscr{A}}}$ does not perform as well as $\boldsymbol{X}_{\mathscr{A}}$ due to uncertainty in $\widehat{\mathscr{A}}$
- Let $\hat{\boldsymbol{\theta}}^{(m)}$ be the minimizer solved in m^{th} **subsample** of size N_b
  - $\hat{\rho}_{0j} := P(\hat{\beta}_j = 0) = \mathbb{P}_m(I\{\hat{\beta}_j^{(m)} = 0\})$
  - Variable selected if $\hat{\rho}_{0j} < 0.5$

Simulations

Methods compared

- Suppose training data $n = 100$, validation set $N = 5000$, two surrogate marker $\boldsymbol{S}$
- AUC is used to compare prediction performance
- Supervised approach:
    - L_{100}: $Y \sim \boldsymbol{X} + \boldsymbol{S}$ using ALASSO
    - L_{100}^{2step}: $Y \sim \boldsymbol{X}_{\mathscr{A}} + \boldsymbol{S}$; $\boldsymbol{X}_{\mathscr{A}}$ selected using $Y \sim \boldsymbol{X}$
- Proposed unsupervised approach:
    - AutoClust: $Y \sim \boldsymbol{X}_{\mathscr{A}} + \boldsymbol{S}$; $\boldsymbol{X}_{\mathscr{A}}$ selected using $\hat{\pi}_{\boldsymbol{S}} \sim X$
    - AutoClust$_R$: $Y \sim \boldsymbol{X}_{\mathscr{A}} + \boldsymbol{S}$; $\boldsymbol{X}_{\mathscr{A}}$ selected using $\hat{\pi}_{\boldsymbol{S}} \sim X$ with resampling

Simulations

Methods compared

- Other unsupervised approach:
  - PenReg$_{S_1+S_2}$: $Y \sim \boldsymbol{X}_{\mathscr{A}} + \boldsymbol{S}$; $\boldsymbol{X}_{\mathscr{A}}$ selected using $S_1 + S_2 \sim \boldsymbol{X}$
  - PenReg$_{\boldsymbol{S}}$: $Y \sim \boldsymbol{X}_{\mathscr{A}} + \boldsymbol{S}$; $\boldsymbol{X}_{\mathscr{A}}$ selected using $\boldsymbol{S} \sim \boldsymbol{X}$
  - RankCor$_{S_1+S_2}$: $Y \sim \boldsymbol{X}_{\mathscr{A}} + \boldsymbol{S}$; $\boldsymbol{X}_{\mathscr{A}}$ selected based on rank correlation [1]
  - Extreme: $Y \sim \boldsymbol{X}_{\mathscr{A}} + \boldsymbol{S}$; $\boldsymbol{X}_{\mathscr{A}}$ selected based on extreme sampling [2]

1. Yu, Sheng, Katherine P Liao, Stanley Y Shaw, Vivian S Gainer, Susanne E Churchill, Peter Szolovits, Shawn N Murphy, Isaac S. Kohane, and Tianxi Cai. “Toward High-Throughput Phenotyping: Unbiased Automated Feature Extraction and Selection from Knowledge Sources.” *Journal of the American Medical Informatics Association* 22, no. 5 (September 1, 2015): 993–1000. https://doi.org/10.1093/jamia/ocv034.
2. Yu, Sheng, Abhishek Chakrabortty, Katherine P Liao, Tianrun Cai, Ashwin N Ananthakrishnan, Vivian S Gainer, Susanne E Churchill, et al. “Surrogate-Assisted Feature Extraction for High-Throughput Phenotyping.” *Journal of the American Medical Informatics Association: JAMIA* 24, no. e1 (April 2017): e143–49. https://doi.org/10.1093/jamia/ocw135.

Simulations

Setting 1: Correct model specifications

Generate data:

- $Y \sim Bin(N = 5000, p = 0.3)$
- $\boldsymbol{X}_i \sim MVN(y_i \Sigma^{\boldsymbol{X}} \boldsymbol{\beta}_0, \Sigma^{\boldsymbol{X}})$ $logit(P(Y = 1 \mid \boldsymbol{X})) = (\alpha_0 + \boldsymbol{\beta}_0^T)\boldsymbol{X}$
- $\boldsymbol{S}_i^0 \sim MVN(0, \Sigma^{\boldsymbol{S}}) + \boldsymbol{\mu}^{\boldsymbol{S}} + y_i \Delta_0^{\boldsymbol{S}}$ $\boldsymbol{S} \perp \boldsymbol{X} \mid Y$
- $\boldsymbol{S} = log\{\lfloor \exp(\boldsymbol{S}^0) \rceil + 1\}$ Count Data; log-transformation to stabilize model fitting and standardize unit variance

Parameter values:

- Strong signals: $\boldsymbol{\beta}_0 = [1.2, -1.2, 0.5, -0.3, 0.3, 0.1, 0.1, \mathbf{0}^T_{(p-7)\times 1}]^T$, $\Delta_0^{\boldsymbol{S}} = [0.75, 0.3]^T$

TABLE 1 Percent of times each feature was selected over 500 replications as well as the average AUC attained for final algorithm training with 100 or 200 labeled examples (AUC_{100}, AUC_{200}) when the covariate distribution is elliptically symmetric for the strong signal based on (i) supervised training with all features and 100 or 200 labeled samples (L_{100}, L_{200}) or with features selected via the two-step approach (L_{100}^{2step}, L_{200}^{2step}) (ii) the automated feature selection method with and without resampling (AutoClust, $AutoClust_R$), (iii) a penalized regression with $S_1 + S_2$ or **S** as the outcome ($PenReg_{S_1+S_2}$, $PenReg_{\mathbf{S}}$), (iii) the rank correlation method based on $S_1 + S_2$ ($RCor_{S_1+S_2}$) (iv) the extreme sampling method (Extreme) and (iv) the method of Agarwal et al. (2016) based on $S_1 + S_2 \geq 1$ as the silver standard label ($Agarwal_{S_1+S_2\geq 1}$).

(a) $p = 50$

Method	1.2	−1.2	0.5	−0.3	0.3	0.1	0.1	0	AUC_{100}	AUC_{200}
L_{100}	85	46	3	6	14	11	9	3	79.9	
L_{100}^{2step}	88	59	4	5	19	13	9	4	81.1	
L_{200}	100	99	26	12	46	32	28	10		84.5
L_{200}^{2step}	100	99	32	12	47	33	27	11		84.3
AutoClust	100	100	91	43	66	28	29	12	84.2	86.3
$AutoClust_R$	100	100	74	15	42	12	10	2	85.3	86.6
$PenReg_{S_1+S_2}$	100	100	100	96	97	65	66	45	81.9	85.4
$PenReg_{\mathbf{S}}$	100	100	99	65	96	79	72	34	82.4	85.6
$RankCor_{S_1+S_2}$	36	0	0	0	0	0	0	0	79.7	80.2
Extreme	100	95	1	0	6	4	1	0	85.3	86.2
$Agarwal_{S_1+S_2\geq 1}$	100	100	99	66	85	38	38	14	83.9	86.2

(b) $p = 100$

Method	1.2	−1.2	0.5	−0.3	0.3	0.1	0.1	0	AUC_{100}	AUC_{200}
L_{100}	58	13	2	0	4	4	3	0	76.5	
L_{100}^{2step}	47	8	1	0	2	4	2	0	79.6	
L_{200}	98	84	6	3	25	20	13	3		82.5
L_{200}^{2step}	100	92	8	3	31	23	15	3		83.9
AutoClust	100	100	90	39	65	31	24	11	83.5	85.8
$AutoClust_R$	100	100	68	12	34	11	6	2	85.2	86.5
$PenReg_{S_1+S_2}$	100	100	100	96	99	67	62	46	79.6	84.4
$PenReg_{\mathbf{S}}$	100	100	97	42	95	78	61	20	82.1	85.4
$RankCor_{S_1+S_2}$	36	0	0	0	0	0	0	0	79.6	80.2
Extreme	98	58	0	0	3	0	0	0	84.1	84.8
$Agarwal_{S_1+S_2\geq 1}$	100	100	98	59	81	35	32	11	83.4	85.9

Simulations

Setting 2: Distribution of X not elliptical symmetric

Generate data:

- $Y \sim Bin(N = 5000, p = 0.3)$
- $\boldsymbol{X}_i \sim MVN(y_i \Sigma^{\boldsymbol{X}} \boldsymbol{\beta}_0, \Sigma^{\boldsymbol{X}}) \Rightarrow \log(\lfloor \exp(\boldsymbol{X}) \rceil + 1)$
- $\boldsymbol{S}_i^0 \sim MVN(0, \Sigma^{\boldsymbol{S}}) + \boldsymbol{\mu}^{\boldsymbol{S}} + y_i \Delta_0^{\boldsymbol{S}}$
- $\boldsymbol{S} = log\{\lfloor \exp(\boldsymbol{S}^0) \rceil + 1\}$

Simulations

Setting 3: $S \not\perp\!\!\!\perp X \mid Y$

Generate data:

- $Y \sim Bin(N = 5000, p = 0.3)$
- $\boldsymbol{X}_i \sim MVN(y_i \Sigma^{\boldsymbol{X}} \boldsymbol{\beta}_0, \Sigma^{\boldsymbol{X}})$
- $\boldsymbol{S}_i^0 \sim MVN(0, \Sigma^{\boldsymbol{S}}) + \boldsymbol{\mu}^{\boldsymbol{S}} + y_i \Delta_0^{\boldsymbol{S}} + [X_1, X_3]$
- $\boldsymbol{S} = log\{\lfloor \exp(\boldsymbol{S}^0) \rceil + 1\}$

TABLE 2 Model Sizes and AUCs for final algorithm training with (a) $p = 100$ or (b) $p = 200$ labeled samples (AUC_{100}, AUC_{200}) for the strong signal when $\mathbf{X}$ is not elliptically symmetric based on (i) supervised training with all features and 100 or 200 labeled samples (L_{100}, L_{200}) or with features selected via the two-step approach (L_{100}^{2step}, L_{200}^{2step}) (ii) the automated feature selection method with and without resampling (AutoClust, $AutoClust_R$), (iii) a penalized regression with $S_1 + S_2$ or $\mathbf{S}$ as the outcome ($PenReg_{S_1+S_2}$, $PenReg_{\mathbf{S}}$), (iii) the rank correlation method based on $S_1 + S_2$ ($RCor_{S_1+S_2}$) (iv) the extreme sampling method (Extreme) and (iv) the method of Agarwal et al. (2016) based on $S_1 + S_2 \geq 1$ as the silver standard label ($Agarwal_{S_1+S_2\geq 1}$).

(a) $p = 50$

Method	Model Size	AUC_{100}	AUC_{200}
L_{100}	1	77.8	
L_{100}^{2step}	1.1	79.8	
L_{200}	4.7		82.8
L_{200}^{2step}	5.4		83.4
AutoClust	10.1	82.8	85
$AutoClust_R$	4.3	84	85.4
$PenReg_{S_1+S_2}$	26	80.3	84.3
$PenReg_{\mathbf{S}}$	19.6	81.3	84.6
$RankCor_{S_1+S_2}$	0.3	79.3	79.9
Extreme	1.3	82.5	83.3
$Agarwal_{S_1+S_2\geq 1}$	11	82.6	85

(b) $p = 100$

Method	Model Size	AUC_{100}	AUC_{200}
L_{100}	0.5	75.6	
L_{100}^{2step}	0.2	78.7	
L_{200}	1.9		80
L_{200}^{2step}	2.4		82.6
AutoClust	14.9	82	84.7
$AutoClust_R$	4.6	83.9	85.3
$PenReg_{S_1+S_2}$	50.3	77.8	82.6
$PenReg_{\mathbf{S}}$	22	80.9	84.3
$RankCor_{S_1+S_2}$	0.3	79.3	79.8
Extreme	0.8	81	81.6
$Agarwal_{S_1+S_2\geq 1}$	15.1	82	84.8

TABLE 3 Model Sizes and AUCs for final algorithm training with 100 or 200 labeled samples (AUC_{100}, AUC_{200}) for the strong signal when $\mathbf{S} \not\perp\!\!\!\perp \mathbf{X} \mid Y$ based on (i) supervised training with all features and 100 or 200 labeled samples (L_{100}, L_{200}) or with features selected via the two-step approach (L_{100}^{2step}, L_{200}^{2step}) (ii) the automated feature selection method with and without resampling (AutoClust, $AutoClust_R$), (iii) a penalized regression with $S_1 + S_2$ or $\mathbf{S}$ as the outcome ($PenReg_{S_1+S_2}$, $PenReg_{\mathbf{S}}$), (iii) the rank correlation method based on $S_1 + S_2$ ($RCor_{S_1+S_2}$) (iv) the extreme sampling method (Extreme) and (iv) the method of Agarwal et al. (2016) based on $S_1 + S_2 \geq 1$ as the silver standard label ($Agarwal_{S_1+S_2\geq 1}$).

(a) $p = 50$

Method	Model Size	AUC_{100}	AUC_{200}
L_{100}	3.3	81.2	
L_{100}^{2step}	3.6	81.6	
L_{200}	6.8		85.8
L_{200}^{2step}	7.9		84.5
AutoClust	5.7	85.3	86.5
$AutoClust_R$	4	85.6	86.6
$PenReg_{S_1+S_2}$	30.6	83	86.1
$PenReg_{\mathbf{S}}$	19	83.9	86.1
$RankCor_{S_1+S_2}$	2.6	83.6	84.5
Extreme	2.3	82.1	83
$Agarwal_{S_1+S_2\geq 1}$	9.1	84.9	86.4

(b) $p = 100$

Method	Model Size	AUC_{100}	AUC_{200}
L_{100}	1.1	76.9	
L_{100}^{2step}	0.8	81.2	
L_{200}	5.1		84.3
L_{200}^{2step}	5.7		84.1
AutoClust	7.4	85.1	86.4
$AutoClust_R$	4.2	85.6	86.6
$PenReg_{S_1+S_2}$	53.1	80.6	85.2
$PenReg_{\mathbf{S}}$	21.2	83.8	86
$RankCor_{S_1+S_2}$	2.6	83.6	84.4
Extreme	2	81.3	82.1
$Agarwal_{S_1+S_2\geq 1}$	12.6	84.6	86.1

Data Analysis

Rheumatoid arthritis

- $46{,}111$ potential RA subjects
- 435 subjects are labeled via chart review
- S_1 : number of RA icd-9 codes; S_2 : counts of NLP mentions of RA
- $\boldsymbol{X}$: $p = 77$ NLP features
- Randomly sample $N = 5000$ unlabelled data for feature selection
- $n = 100{,}200$ training data; $435 - n$ validation set.

TABLE 4 (a) Number of features included in the algorithm training as well as coefficient estimates and AUC of the resulting algorithms trained with (b) $n = 100$ and (c) $n = 200$ labels when fitting the full model (L) as well as when only including features selected based on the AutoClust, AutoClust$_R$, RankCor$_{S_1+S_2}$, Extreme, and Agarwal$_{S_1+S_2\geq 1}$ methods for the EMR-based study of RA.

	(a) Number of features selected				
	AutoClust	AutoClust$_R$	RankCor$_{S_1+S_2}$	Extreme	Agarwal$_{S_1+S_2\geq 1}$
	33.00	26.80	69.20	23.80	45.10
(b) Coefficient and AUC estimates with $n = 100$ labels					
	L_{100}	AutoClust	AutoClust$_R$	RankCor$_{S_1+S_2}$	Extreme	Agarwal
RA$_{ICD}$	0.35	0.66	0.7	0.4	0.73	0.58
RA$_{NLP}$	0.27	0.68	0.74	0.32	0.85	0.49
Methotraxate$_{NLP}$	0.08	0.14	0.14	0.09	0.13	0.11
AM Stiffness$_{NLP}$	0.04	0.12	0.13	0.05	0.15	
Echography$_{NLP}$					−0.21	
AUC	91.1	92.7	92.8	91.2	93.4	91.7
(c) Coefficient and AUC estimates with $n = 200$ labels						
	L_{200}	AutoClust	AutoClust$_R$	RankCor$_{S_1+S_2}$	Extreme	Agarwal
RA$_{ICD}$	0.7	0.85	0.87	0.72	0.87	0.79
RA$_{NLP}$	0.72	1.26	1.35	0.79	1.52	1.07
Methotraxate$_{NLP}$	0.13	0.15	0.15	0.14	0.14	0.15
MRI$_{NLP}$	−0.05			−0.09		
AM Stiffness$_{NLP}$	0.1	0.28	0.29	0.12	0.29	0.17
Physiotherapy$_{NLP}$	−0.07					−0.15
Echography$_{NLP}$	−0.08				−0.53	−0.26
Note Count$_{NLP}$		−0.37	−0.41		−0.36	
Antinuclear Antibodies$_{NLP}$		−0.11	−0.13			
Redness$_{NLP}$			−0.16	−0.06		
Intravenous Infusion$_{NLP}$					−0.15	
AUC	92.8	94.3	94.5	92.9	94.8	94.2

Discussion

- AutoClust Vs AutoClust$_R$
  - AUC is similar
  - AutoClust$_R$ tends to select smaller number of variables
- Combine label and unlabeled data
  - $$\sum_{i=1}^{N} l(\boldsymbol{\theta}^T \overrightarrow{\boldsymbol{X}}_i \mid \hat{\pi}_S) + \sum_{j=N+1}^{N+n} l(\boldsymbol{\theta}^T \overrightarrow{\boldsymbol{X}}_i \mid Y_i)$$