NONPARAMETRIC ADJUSTMENT FOR MEASUREMENT ERROR IN TIME TO EVENT DATA: APPLICATION TO RISK PREDICTION MODELS

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Setting

Risk prediction model has first been developed based on **error-free time to event data**, and subsequently implemented in practical setting where **time to event data can be error-prone**.

Motivation I

Mendelian risk prediction models in genetic counseling:

- Calculating the probability that an individual carries a cancer causing inherited mutation based on his/her **family history**.
- Predicting the absolute risk of developing the disease over time given his/her mutation-carrier status and **family history**.

These models are in wide clinical use and web-based patient-oriented tools: breast cancer, ovarian cancer, Lynch syndrome, pancreatic cancer, melanoma etc.

These models were developed based on error-free data.

Studies about accuracy of self-reported family history show that sensitivity and specificity for reported disease status vary by degree of relative and cancer type.

65% of truly affected are reported affected

2% of truly unaffected are reported as affected

Breast cancer:

Disease status, sensitivity 65% - 95%; specificity 98% - 99%.

Age of diagnosis was misreported for 3.1% of relatives, average of 4.5 years between the true and misreported ages (Mai et al 2011; Ziogas and Anton-Culver, 2003).

Ovarian cancer:

Age of diagnosis was misreported for 4.2% of relatives, average of 4.2 years between the true and misreported ages (Ziogas and Anton-Culver, 2003).

Misreporting of family history, especially in disease status, leads to distortions in predictions (Katki, 2006).

Q: Is it possible to develop prediction models based on error-prone data?

A: Not in the context of Mendelian risk prediction models which relies on penetrance estimates from the literature, based on error-free data.

disease probability given carrier status

Motivation II

Survival prediction models:

Time to progression – length of time until the disease gets worse or spread

In some disease settings, such as cancer, TTP is one of the predictors for survival.

Assume a model has been developed based on **error-free TTP**.

In practice, **TTP is error-prone**:

- Tumor assessment is done using imaging, which varies by observers.
- Scans are taken at regularly intervals.

The current setting vs the common settings

The usual measurement error setting:

- ✓ Error-prone covariate observed in the main study.
- ✓ The goal is estimating the relationship between the outcome and the true covariate.

Current setting:

- ✓ The relationship between the outcome and the true covariate is known.
- ✓ The goal is to use this model for risk estimation based on an error-prone covariate.

Naïvely using the error-prone covariate will lead to biased results.

The data:

Y - outcome

T^o - the true failure time

C - the true right-censoring time

Error-free predictor: $H = (T, \delta)$ (for simplicity, one relative)

where $T = \min(T^o, C)$ $\delta = I(T^o \leq C)$

Example: $Y = 0$ or 1 and T^o the mother's age at onset.

Error-free predictor: $H = (T, \delta)$

Error-prone predictor: $H^* = (T^*, \delta^*)$

Example: the counselee doesn't know that his/her relative had the disease, or the correct age at onset.

Assumption: We have a validation study with

$$H = (T, \delta) \quad \text{and} \quad H^* = (T^*, \delta^*)$$

but no need for the outcome Y.

The risk prediction model: $\Pr(Y \mid H)$

Our goal is estimating $\Pr(Y \mid H^*)$

Our goal is estimating $\Pr\left(Y \mid H^*\right)$

Main idea:

$$\mathrm{P}\left(Y \mid H^*\right) = \int_H \mathrm{P}\left(Y, H \mid H^*\right) dH$$

$$= \int_H \mathrm{P}\left(Y \mid H, H^*\right) \mathrm{P}\left(H \mid H^*\right) dH$$

$$= \int_H \mathrm{P}\left(Y \mid H\right) \mathrm{P}\left(H \mid H^*\right) dH$$

Assumptions:

surrogacy assumption

- H^* contains no information on predicting Y beyond H.
- The measurement error model $\mathrm{P}\left(H \mid H^*\right)$ is transportable.

A non parametric estimator of $\Pr\left(H \mid H^*\right)$

The distribution is left unspecified

Assume, for simplicity, one family member → $H=\left(T,\delta\right) \qquad H^*=\left(T^*,\delta^*\right)$

Main idea:

$$\mathrm{P}\left(T,\delta \mid T^*,\delta^*\right)$$

$$=\lambda\left(T \mid T^*,\delta^*\right)^{\delta} S\left(T \mid T^*,\delta^*\right) h\left(T \mid T^*,\delta^*\right)^{1-\delta} G\left(T \mid T^*,\delta^*\right)$$

Conditional hazard and survival of true failure time

Conditional hazard and survival of true censoring time

Assumptions:

Conditional independence of event and censoring times given H^*.

$$\mathrm{P}\left(T,\delta \mid T^*,\delta^*\right)$$

$$= \lambda\left(T \mid T^*,\delta^*\right)^{\delta} S\left(T \mid T^*,\delta^*\right) h\left(T \mid T^*,\delta^*\right)^{1-\delta} G\left(T \mid T^*,\delta^*\right)$$

These hazards and survival functions can be estimated non-parametrically by using the validation data – a large study population that does not involve the counselee.

Validation data

$$T_i = \min\left(T_i^o, C_i\right) \quad \delta_i = I\left(T_i^o \le C_i\right) \quad i = 1,\ldots,n$$

dependent individuals

$$H_i = \left(T_i,\delta_i\right) \quad H_i^* = \left(T_i^*,\delta_i^*\right)$$

Use kernel smoothed Kaplan-Meier estimator (Beran, 1981).

Kernel smoothed Kaplan-Meier estimator (Beran, 1981):

Nadaraya-Watson weight

$$W_i\left(t;b_{nl},l\right)=I\left(\delta_i^*=l\right)K\left(\frac{t-T_i^*}{b_{nl}}\right) \qquad i=1,\ldots,n \quad l=0,1$$

Bandwidth sequences

Known kernel function

$$\hat{S}\left(t\,|\,t^*,l\right)=\prod_{T_i\le t,\delta_i=1,\delta_i^*=l}\left(1-\frac{W_i\left(t^*;b_{nl},l\right)}{\sum_{j=1,\delta_j^*=l}^{n}W_j\left(t^*;b_{nl},l\right)I\left(T_j\ge T_i\right)}\right)$$

and we get $\hat{S}\left(t\,|\,t^*,0\right)$, $\hat{S}\left(t\,|\,t^*,1\right)$ for $t,t^*\in(0,\tau]$.

For estimating the survival function of the censoring time, apply the above while treating the censoring times as events and the event times as censoring.

Summary

provided

$$\hat{\mathrm{P}}\left(Y \mid H^*\right) = \int_H \mathrm{P}\left(Y \mid H\right) \hat{\mathrm{P}}\left(H \mid H^*\right) dH$$

$$H = \left(H_1, \ldots, H_R\right)$$

$$H^* = \left(H_1^*, \ldots, H_R^*\right)$$

$$\mathrm{P}\left(H \mid H^*\right) = \prod_{j=1}^{R} \mathrm{P}\left(H_j \mid H_j^*\right)$$

$$\hat{\mathrm{P}}\left(H \mid H^*\right) = \prod_{j=1}^{R} \hat{\mathrm{P}}\left(H_j \mid H_j^*\right)$$

$$\hat{\mathrm{P}}\left(H_j \mid H_j^*\right) = \hat{\mathrm{P}}\left(T_j, \delta_j \mid T_j^*, \delta_j^*\right)$$

$$= \hat{\lambda}\left(T_j \mid T_j^*, \delta_j^*\right)^{\delta_j} \hat{S}\left(T_j \mid T_j^*, \delta_j^*\right) \hat{h}\left(T_j \mid T_j^*, \delta_j^*\right)^{1-\delta_j} \hat{G}\left(T_j \mid T_j^*, \delta_j^*\right)$$

provided

$$\hat{\mathrm{P}}\left(Y \mid H^{*}\right)=\int_{H} \mathrm{P}\left(Y \mid H\right)\hat{\mathrm{P}}\left(H \mid H^{*}\right)dH$$

In case integrating over all possible values of H is computational challenging, a Monte-Carlo estimator can be used, by sampling

$$H^{(1)},\ldots,H^{(B)}$$

From $\hat{\mathrm{P}}\left(H \mid H^{*}\right)$ and the final proposed estimator is given by

$$\hat{\mathrm{P}}\left(Y \mid H^{*}\right)=\frac{1}{B}\sum_{b=1}^{B}\hat{\mathrm{P}}\left(Y \mid H^{(b)}\right)$$

Application: Mendelian Risk Prediction Model

A counselee provides information on R relatives:

$$H_i^* = \left(T_i^*, \delta_i^*\right) \text{ instead of } H_i = \left(T_i, \delta_i\right) \qquad i = 1, \ldots, R$$

Let

$$\gamma_i = \left(\gamma_{i1}, \ldots, \gamma_{iM}\right), \quad \gamma_{im} = 0 \text{ or } 1$$

$\gamma_{im} = 1$ indicates carrying the genetic variant that confer disease risk

Aims:

- Estimating $\mathrm{P}\left(\gamma_0 \mid H_0, H_1^*, \ldots, H_R^*\right)$
- Estimating $\mathrm{P}\left(T_0^o > t \mid H_0, H_1^*, \ldots, H_R^*\right)$

Carrier probability $\mathrm{P}(Y \mid H) = \mathrm{P}(\gamma_0 \mid H_0, H_1, \ldots, H_R)$

Write

$$\mathrm{P}(\gamma_0 \mid H_0, H_1, \ldots, H_R) = \frac{\mathrm{P}(\gamma_0) \sum_{\gamma_1, \ldots, \gamma_R} \prod_{i=0}^{R} \mathrm{P}(H_i \mid \gamma_i) \mathrm{P}(\gamma_1, \ldots, \gamma_R \mid \gamma_0)}{\sum_{\gamma_0} \mathrm{P}(\gamma_0) \sum_{\gamma_1, \ldots, \gamma_R} \prod_{i=0}^{R} \mathrm{P}(H_i \mid \gamma_i) \mathrm{P}(\gamma_1, \ldots, \gamma_R \mid \gamma_0)}$$

conditional independence of family members' phenotype given their genotypes.

BRCAPRO estimate it via meta-analysis, and family history information is verified using medical records

and in practice $\mathrm{P}(Y \mid H^*) = \mathrm{P}(\gamma_0 \mid H_0, H_1^*, \ldots, H_R^*)$

is naively being used. We propose

$$\hat{\mathrm{P}}(\gamma_0 \mid H^*) = \int_H \mathrm{P}(\gamma_0 \mid H) \hat{\mathrm{P}}(H \mid H^*) dH$$

Survival probability $\mathrm{P}\left(Y \mid H\right) = \mathrm{P}\left(T_0^o > t \mid H_0, H_1, \ldots, H_R, \gamma_0\right)$

Write

$$\mathrm{P}\left(T_0^o > t \mid H_0, H_1, \ldots, H_R, \gamma_0\right)$$

$$= \frac{\mathrm{P}\left(T_0^o > t \mid \gamma_0\right) \sum_{\gamma_1,\ldots,\gamma_R} \prod_{i=1}^{R} \mathrm{P}\left(H_i \mid \gamma_i\right) \mathrm{P}\left(\gamma_1, \ldots, \gamma_R \mid \gamma_0\right)}{\sum_{\gamma_1,\ldots,\gamma_R} \prod_{i=0}^{R} \mathrm{P}\left(H_i \mid \gamma_i\right) \mathrm{P}\left(\gamma_1, \ldots, \gamma_R \mid \gamma_0\right)}$$

and in practice $\mathrm{P}\left(Y \mid H^*\right) = \mathrm{P}\left(\gamma_0 \mid H_0, H_1^*, \ldots, H_R^*\right)$

is naively being used. We propose

$$\hat{\mathrm{P}}\left(T_0^o > t \mid H^*\right) = \int_H \mathrm{P}\left(T_0^o > t \mid H\right) \hat{\mathrm{P}}\left(H \mid H^*\right) dH$$

Simulation Study

- Setting: $\mathrm{P}\left(Y \mid H\right) = \mathrm{P}\left(\gamma_0 \mid H_0, H_1, \ldots, H_R\right)$ with single gene BRCA1
- Two datasets were generated, one to model the measurement error distribution, and the other represents the counselees.
- The BRCA1 carrier probability 0.006098.
- The penetrance function $\mathrm{P}\left(H \mid \gamma\right)$ from BRCAPRO version 2.08.
- Normal censoring, mean 55, SD 10.
- **Measurement error in disease status**: sen=0.954, spec=0.974; sen=0.649 and spec=0.990.
- **Measurement error in age**:

$$T^* = T + \varepsilon \quad \varepsilon \sim N\left(0, \sigma^2\right) \quad \sigma = 1,3,5$$

$$T^* = TU \quad U \sim Exp\left(1\right)$$

50,000 counselees

100,000 families, each with 5 members (mother, father, 3 daughters)

Results

Table 1: Mendelian Risk Prediction Simulation Results. MSEP and O/E improve using the adjusted proposed method, ROC-AUC either improves or remains the same depending on the setting.

Counselee	Sens/Spec	Error in Age	$\sqrt{MSEP^{\dagger}} * 1000$			O/E			ROC-AUC		
			Error-Free	Error-Prone	Adjusted	Error-Free	Error-Prone	Adjusted	Error-Free	Error-Prone	Adjusted
Mother	0.954, 0.974	a: $N(0,5^2)$	0.0000	19.1351	16.7405	0.9773	0.8190	0.9712	0.8160	0.8090	0.8086
		a: $N(0,3^2)$	0.0000	18.1006	15.9490	0.9773	0.8280	0.9746	0.8160	0.8098	0.8078
		a: $N(0,1^2)$	0.0000	17.5526	15.6430	0.9773	0.8327	0.9746	0.8160	0.8102	0.8115
		m: $exp(1)$	0.0000	43.2855	21.3037	0.9833	0.6063	0.9484	0.8145	0.7185	0.8020
	0.649, 0.990	a: $N(0,5^2)$	0.0000	21.3122	20.8859	0.9773	1.0466	0.9783	0.8160	0.7814	0.7803
		a: $N(0,3^2)$	0.0000	20.7947	20.5099	0.9773	1.0556	0.9792	0.8160	0.7821	0.7815
		a: $N(0,1^2)$	0.0000	20.5213	20.1459	0.9773	1.0604	0.9737	0.8160	0.7826	0.7818
		m: $exp(1)$	0.0000	36.0314	23.8184	0.9817	0.8026	0.9565	0.8155	0.7140	0.7752
Daughter	0.954, 0.974	a: $N(0,5^2)$	0.0000	18.8437	16.5614	0.9719	0.8166	0.9680	0.8171	0.8070	0.8082
		a: $N(0,3^2)$	0.0000	17.7033	15.6918	0.9719	0.8256	0.9659	0.8171	0.8083	0.8086
		a: $N(0,1^2)$	0.0000	17.1421	15.1775	0.9719	0.8301	0.9680	0.8171	0.8093	0.8083
		m: $exp(1)$	0.0000	43.4717	21.0365	0.9785	0.6028	0.9445	0.8162	0.7146	0.7976
	0.649, 0.990	a: $N(0,5^2)$	0.0000	20.1613	20.0763	0.9719	1.0573	0.9872	0.8171	0.7895	0.7862
		a: $N(0,3^2)$	0.0000	19.6759	19.5498	0.9719	1.0661	0.9834	0.8171	0.7913	0.7904
		a: $N(0,1^2)$	0.0000	19.4507	19.1871	0.9719	1.0708	0.9803	0.8171	0.7928	0.7911
		m: $exp(1)$	0.0000	35.2381	23.0851	0.9760	0.8087	0.9535	0.8165	0.7229	0.7745

† MSEP: difference between (adjusted) error-prone and error-free predictions.

a: indicates a classical additive model; $T^* = T + \varepsilon$ where $\varepsilon \sim N(0, \sigma^2)$, m: indicates a multiplicative measurement error model, $T^* = TU$, $U \sim exp(\lambda)$.

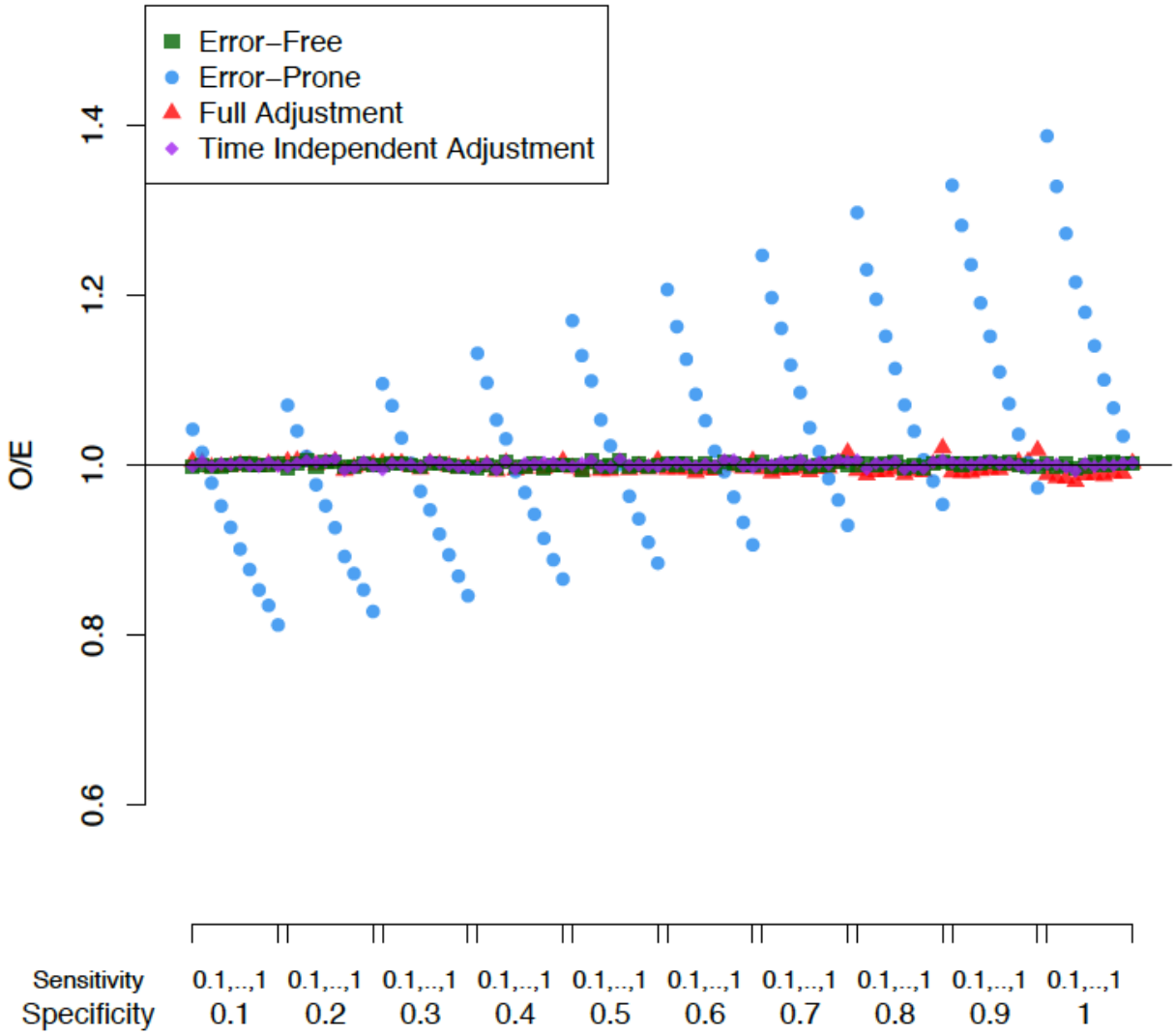
$$\text{O/E} = \sum_i I\left(\gamma_{0i} = 1\right) / \sum_i \hat{P}_i$$

$$\text{MSEP} = n^{-1} \sum_i \left\{ \hat{P}_i - \hat{\text{P}}_i\left(\gamma_0 \mid H\right) \right\}^2$$

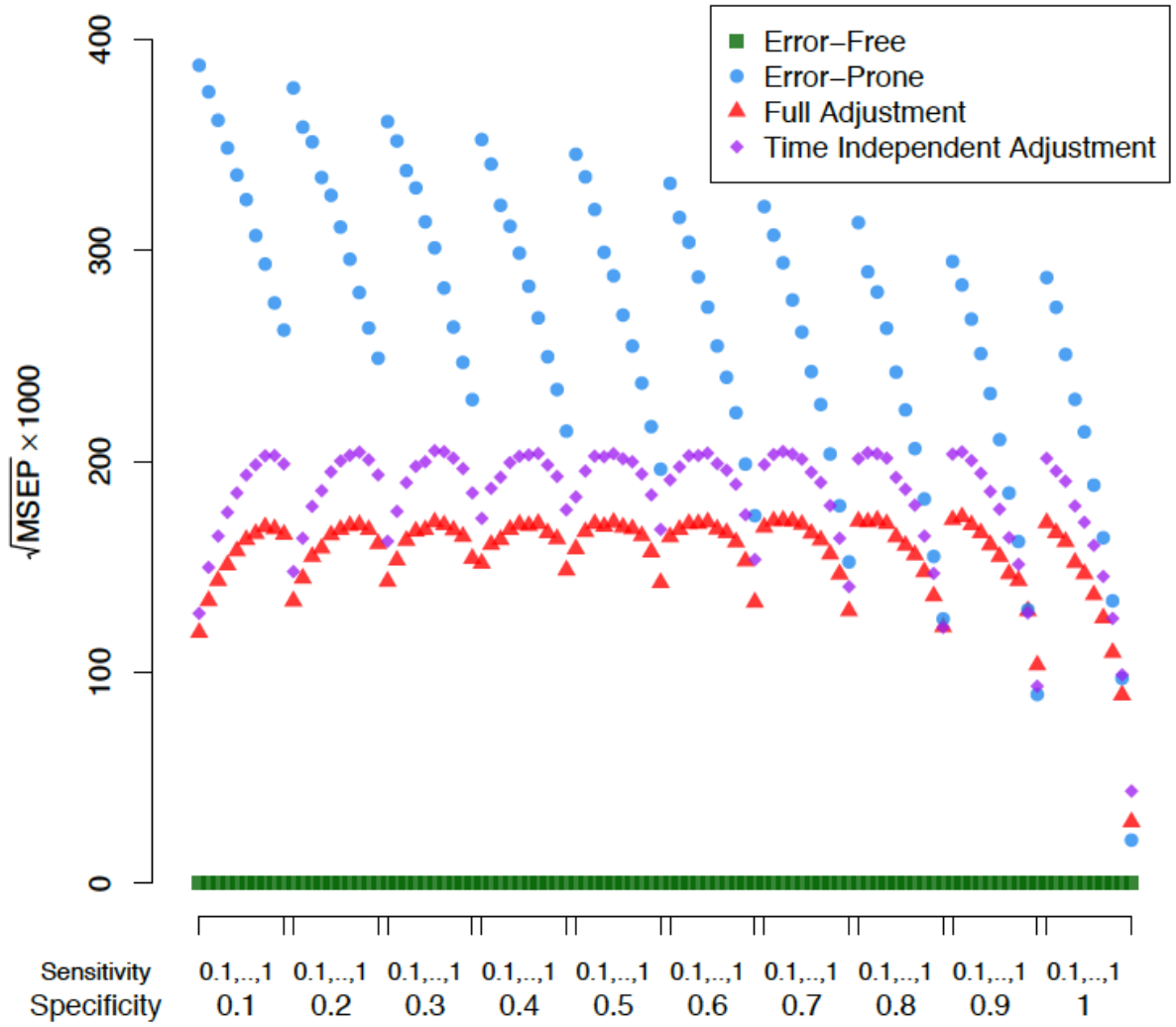
Summary of simulation results

- We are able to eliminate almost all the bias induced by ME in histories (O/E).
- We are able to improve accuracy (MSEP).
- **We are able to improve discrimination (ROC-AUC) only to some degree.**

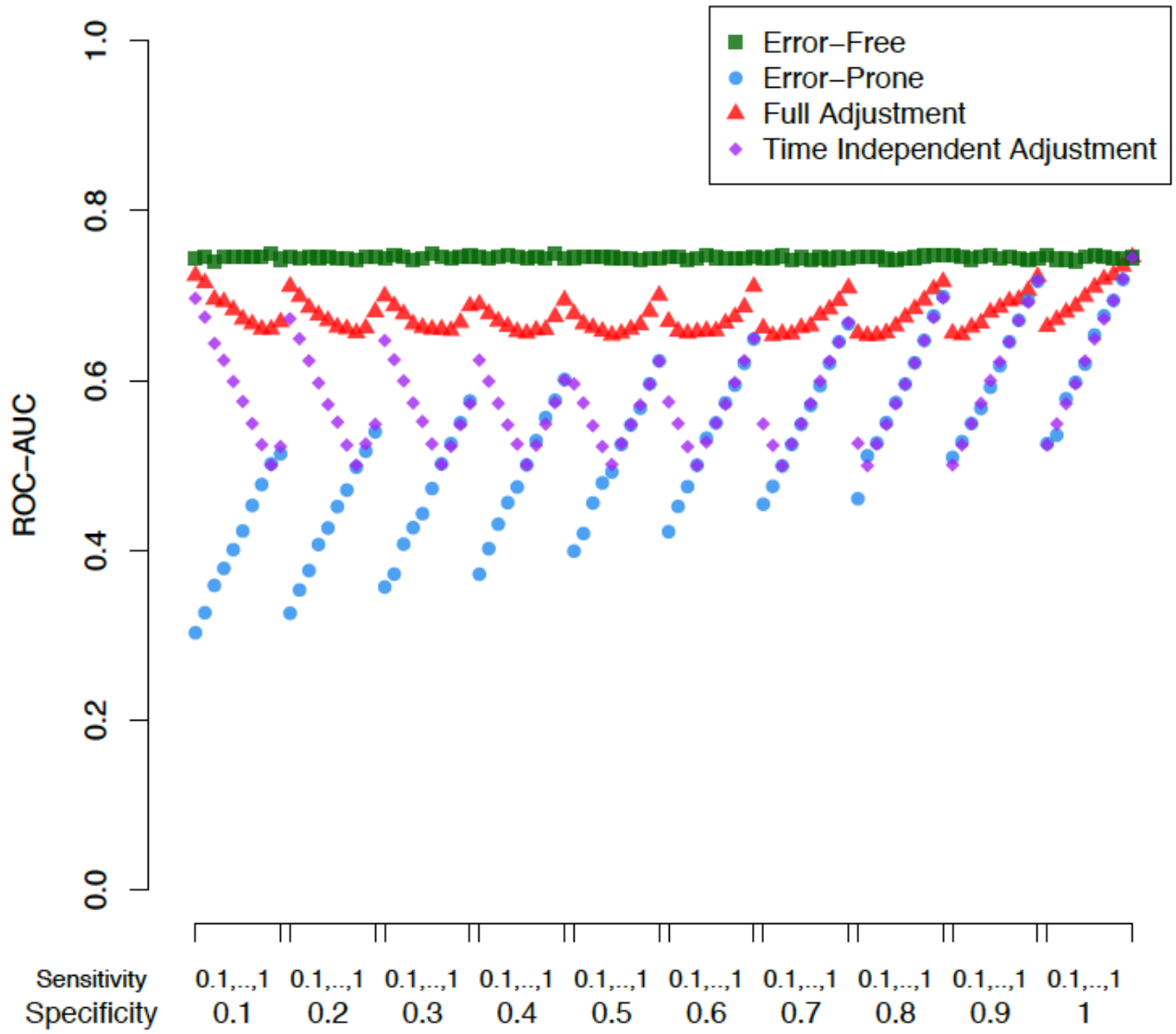
Survival prediction - summary of simulation results (multip.)



Survival prediction - summary of simulation results (multip.)



Survival prediction - summary of simulation results (multip.)



Concluding remarks

- ✓A non-parametric adjustment is provided, for measurement error in time to event predictor.
- ✓Ignoring the measurement error, provides miscalibrated models.
- ✓The proposed adjustment improves calibration and total accuracy.
- ✓The proposed method can be easily incorporated in BayesMendel R package for direct clinical use.

Model discrimination only partially improved.

END

Example – misreporting breast cancer

Counselees:

- Data from the Cancer Genetics Network (CGN) Model Evaluation Study, with known carrier status.
- 2038 families, 34310 relatives.
- 9.2% of the relatives have breast cancer.
- Only error-prone self-reported family history is available.

Validation data:

- Data from U of California at Irvine (UCI).
- 719 cancer affected counselees (breast, ovarian or colon cancer).
- 1521 female relatives, 19.3% with breast cancer.
- Error-prone and error-free family history are available.

Example – misreporting breast cancer

Log of O/E and 95% confidence intervals for being a BRCA carrier for counselees in CGN dataset, stratified by risk decile:

- **Transportability?**
- **Small sample?**

Very small improvement in Brier score and ROC-AUC.