

Dynamic predictions from Joint Models using Super Learning

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1 Background & Motivation

Setting: Follow-up studies

- ▷ multiple longitudinal outcomes
 - * biomarkers
 - * patient parameters
 - * patient reported outcome scores

- ▷ one or multiple endpoints
 - * relapse of disease
 - * requirement for intervention
 - * death

1 Background & Motivation (cont'd)

Obtain accurate predictions for the (cumulative) risk of an event to guide decision making

Using the available longitudinal information

1 Background & Motivation (cont'd)

University of Michigan Prostatectomy Data

- ▷ 3634 PCa patients followed-up in 1996–2013
 - * aged 40 to 84 years with clinically localized cT1 to cT3 disease
 - * received radical prostatectomy

1 Background & Aim (cont'd)

University of Michigan Prostatectomy Data

Patients remain at risk of metastasis

▷ Follow-up

- * PSA levels at frequent intervals
- * when PSA increases, physicians consider Salvage Therapy (ST)
- * ST androgen deprivation therapy, radiation therapy, chemotherapy, and combinations

1 Background & Motivation (cont'd)

University of Michigan Prostatectomy Data

**Use the longitudinal PSA & baseline covariates to predict
the risk of metastasis**

1 Background & Motivation (cont'd)

- Two main frameworks to obtain such predictions
 - ▷ *Landmarking*
 - * a series of Cox models at different landmark times
 - * biomarker last value as a baseline covariate or a mixed model
 - * Breslow estimator of survival probabilities
 - ▷ *Joint Models*
 - * complete specification of the joint distribution of the outcomes
 - * direct derivation of conditional risk probabilities

1 Background & Motivation (cont'd)

Landmarking

▷ *Advantages*

- * easier to use, available in standard software
- * can generalize to multiple biomarkers without (much) extra computational cost

▷ *Disadvantages*

- * predictions not consistent
- * not plausible LOCF for biomarkers
- * does not account for measurement error and endogeneity
- * not valid causal interpretation

1 Background & Motivation (cont'd)

Joint Models

▷ *Advantages*

- * consistent predictions
- * accounts for measurement error and endogeneity
- * biomarkers follow a trajectory
- * valid causal interpretation

▷ *Disadvantages*

- * computationally intensive
- * *sensitive to modeling assumptions*

1 Background & Motivation (cont'd)

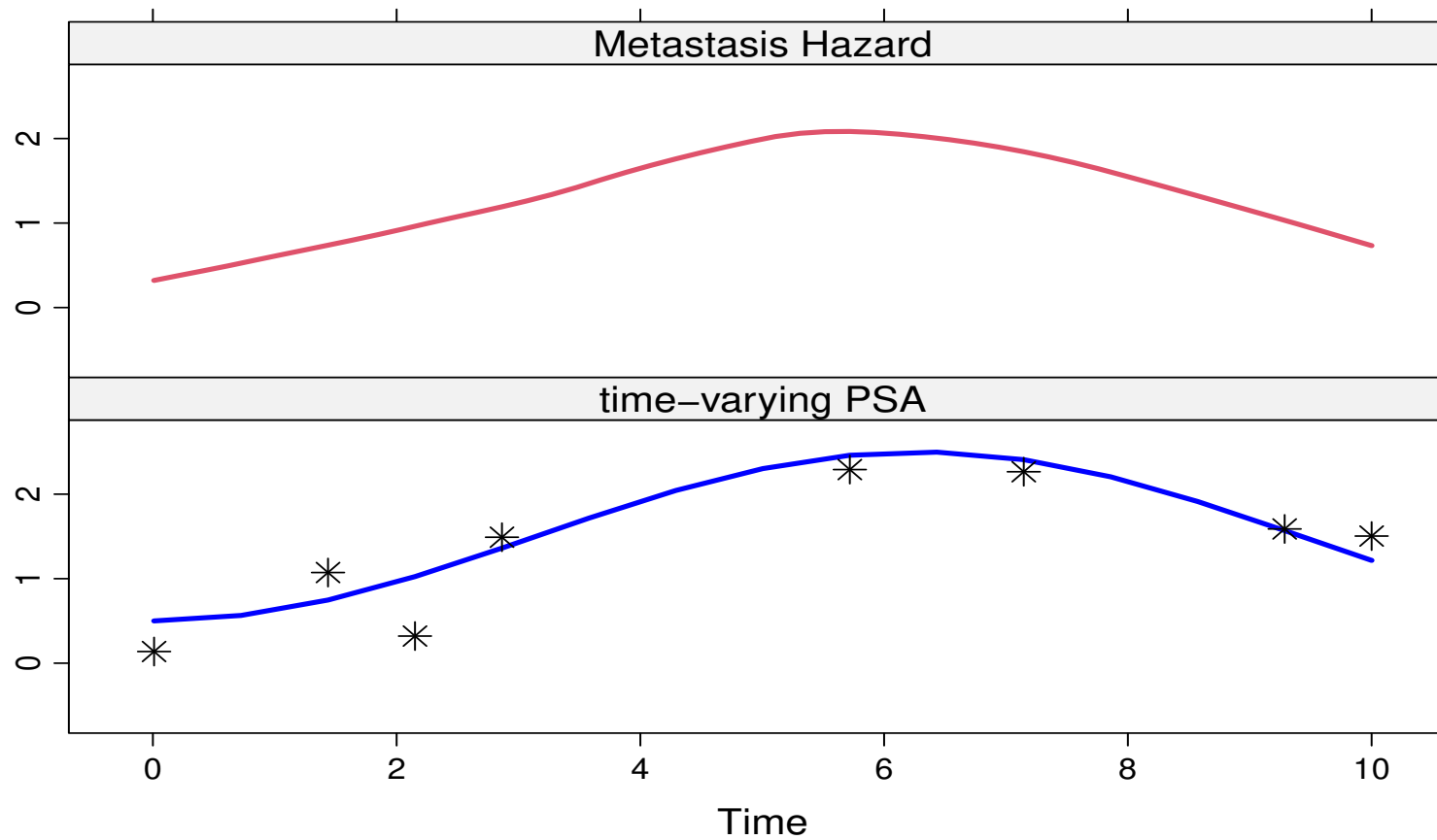
- *Sensitive to modeling assumptions*
 - ▷ *Longitudinal profiles shape*
 - * non-linear subject-specific trajectories
 - ▷ *Functional form*
 - * how to link the hazard of the event with the longitudinal outcome

2 Joint Models

Joint Models Framework - Basic Idea

- ▷ Use a model to describe the subject-specific longitudinal trajectories
- ▷ Use these trajectories in a hazard model for the event
- ▷ Random effects explain the association

2 Joint Models (cont'd)



2 Joint Models (cont'd)

Some notation

- ▷ T_i^* : True event time for patient i
- ▷ T_i : Observed event time for patient i
- ▷ δ_i : Event indicator, i.e., equals 1 for true events
- ▷ y_i : Longitudinal covariate

2 Joint Models (cont'd)

More formally

$$\left\{ \begin{array}{l} h_i(t \mid \mathcal{H}_i(t, \mathbf{b}_i)) = h_0(t) \exp\{\boldsymbol{\gamma}^\top \mathbf{w}_i + f(\alpha, \mathcal{H}_i(t, \mathbf{b}_i))\}, \\ \mathcal{H}_i(t, \mathbf{b}_i) = \{\eta_i(s, \mathbf{b}_i); 0 \leq s \leq t\} \\ \\ y_i(t) = \eta_i(t, \mathbf{b}_i) + \varepsilon_i(t) \\ = \mathbf{x}_i^\top(t) \boldsymbol{\beta} + \mathbf{z}_i^\top(t) \mathbf{b}_i + \varepsilon_i(t), \quad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2), \\ \\ \mathbf{b}_i \sim \mathcal{N}(\mathbf{0}, \mathbf{D}) \end{array} \right.$$

2 Joint Models (cont'd)

- We follow a Bayesian estimation paradigm treating θ and $\{b_i, i = 1, \dots, n\}$ are regarded as parameters
- Inference is based on the full posterior distribution

$$p(\theta, b \mid T, \delta, y) = \frac{\prod_i p(T_i, \delta_i \mid b_i; \theta) p(y_i \mid b_i; \theta) p(b_i; \theta) p(\theta)}{\prod_i p(T_i, \delta_i, y_i)}$$

$$\propto \prod_{i=1}^n \left\{ p(T_i, \delta_i \mid b_i; \theta) p(y_i \mid b_i; \theta) p(b_i; \theta) \right\} p(\theta)$$

2 Joint Models (cont'd)

- Dynamic predictions from joint models

$$\pi_i(u \mid t) = \Pr\{T_i^* \geq u \mid T_i^* > t, \mathcal{Y}_i(t), \mathcal{D}_n\}, \quad u > t$$

where

- ▷ $\mathcal{Y}_i(t) = \{y_i(s), 0 \leq s \leq t\}$ available measurements up to t
- ▷ \mathcal{D}_n denotes the sample on which the joint model was fitted

2 Joint Models (cont'd)

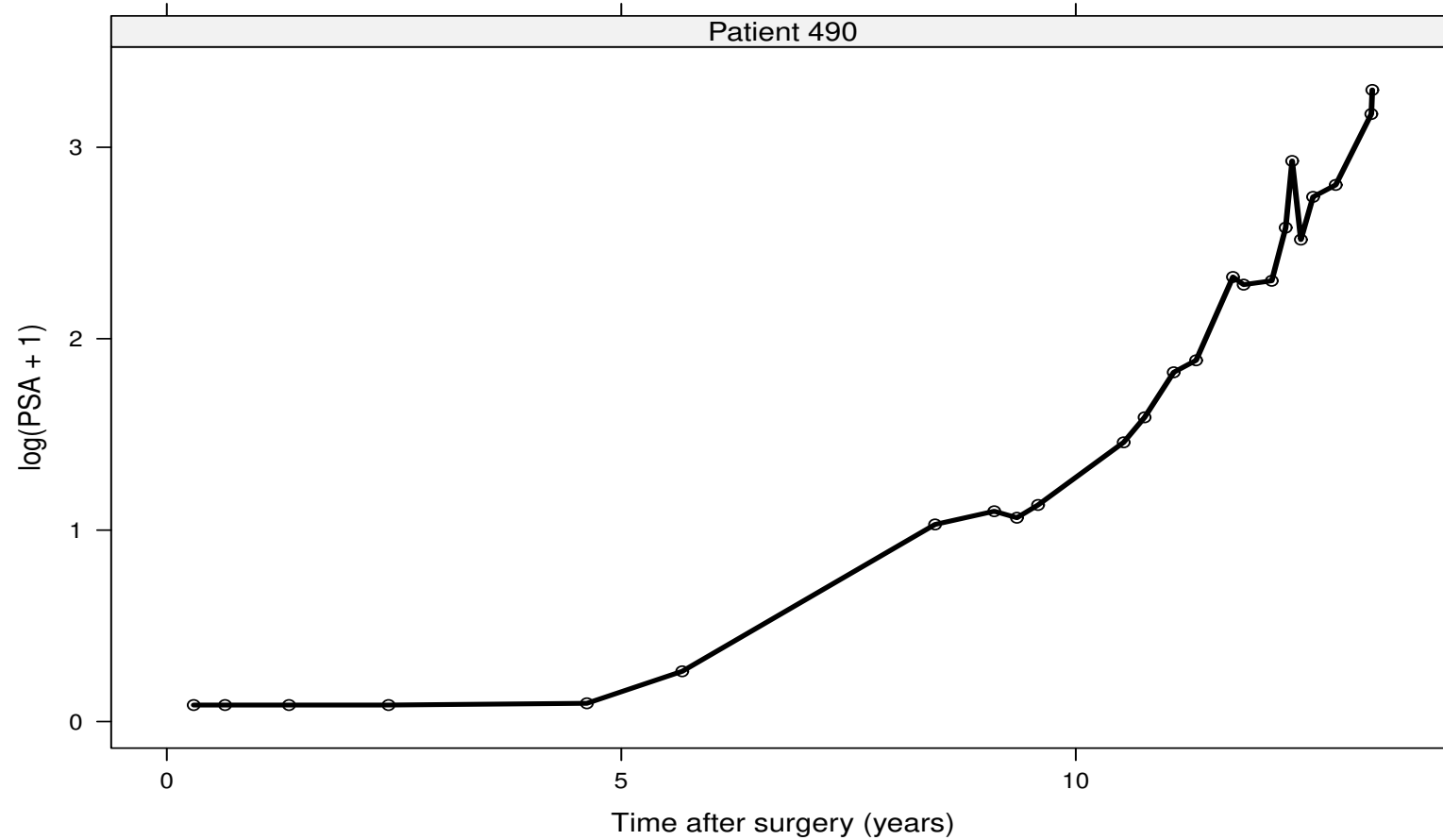
- Under the Bayesian formulation $\pi_i(u | t)$ is written as

$$\Pr\{T_i^* \geq u \mid T_i^* > t, \mathcal{Y}_i(t), \mathcal{D}_n\} = \int \Pr\{T_i^* \geq u \mid T_i^* > t, \mathcal{Y}_i(t); \theta\} p(\theta \mid \mathcal{D}_n) d\theta$$

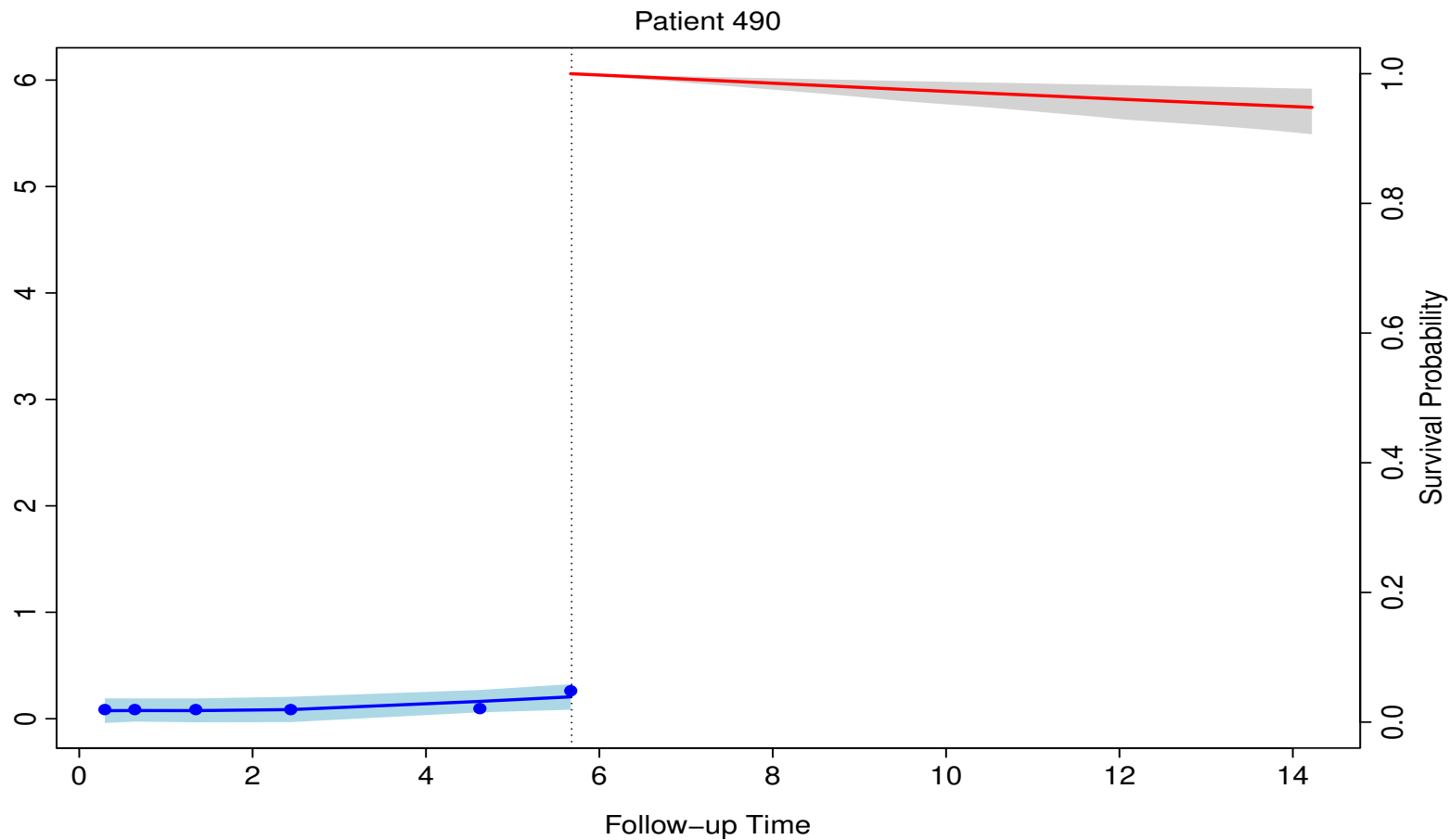
- With the first term taking the form

$$\begin{aligned} \Pr\{T_i^* \geq u \mid T_i^* > t, \mathcal{Y}_i(t); \theta\} &= \\ &= \int \frac{S_i\{u \mid \mathcal{H}_i(u, b_i, \theta); \theta\}}{S_i\{t \mid \mathcal{H}_i(t, b_i, \theta); \theta\}} p(b_i \mid T_i^* > t, \mathcal{Y}_i(t); \theta) db_i \end{aligned}$$

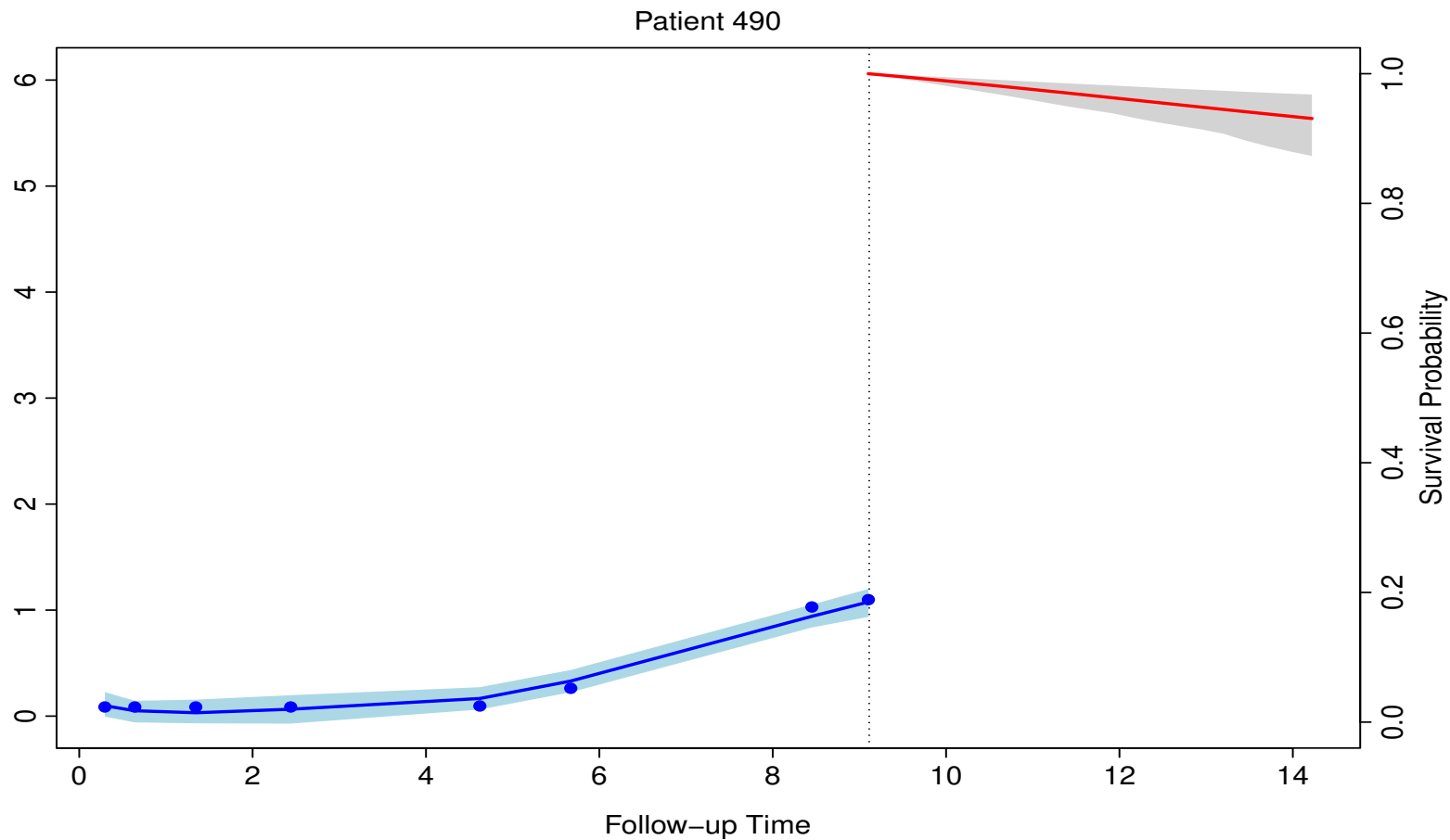
2 Joint Models (cont'd)



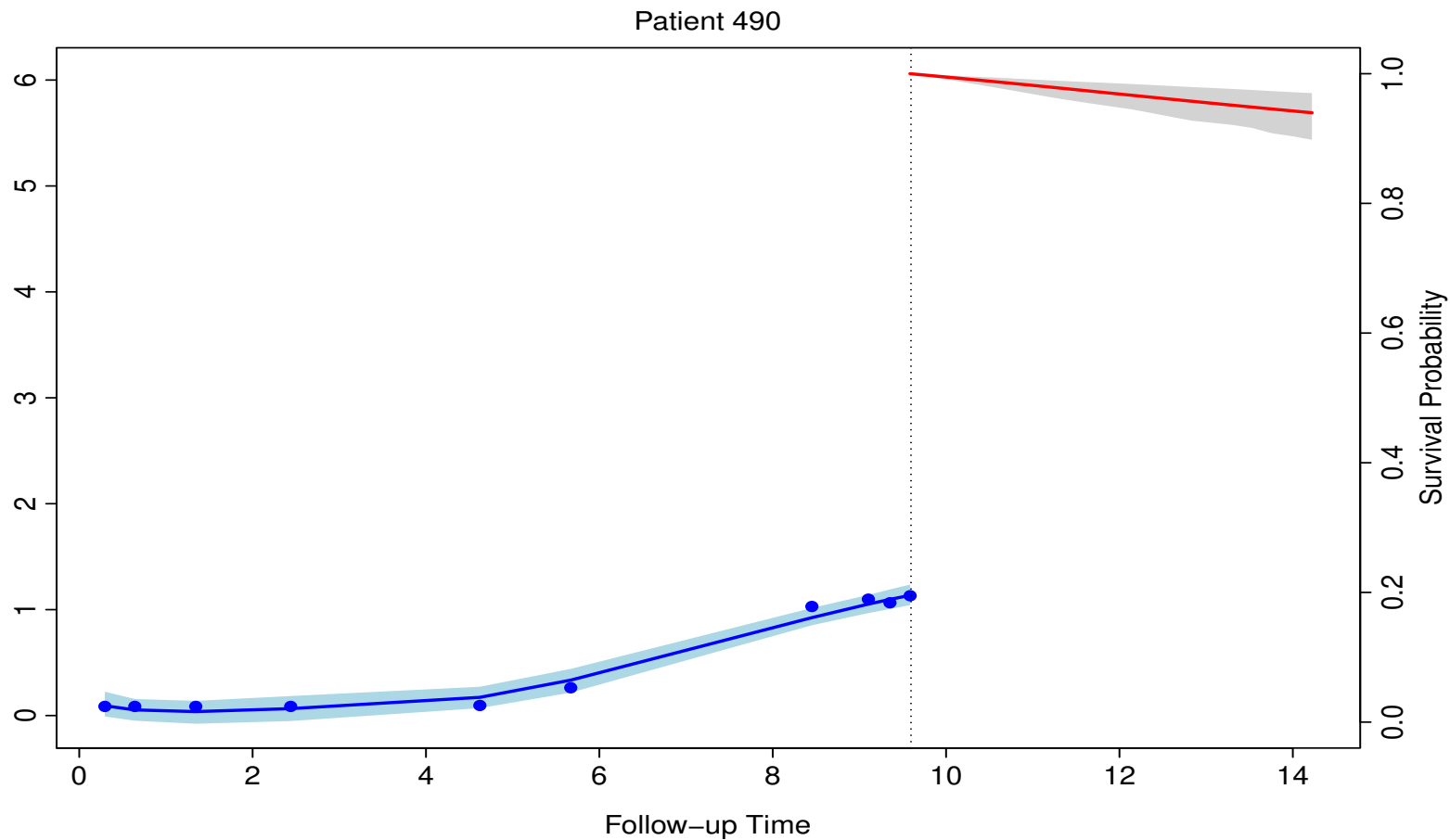
2 Joint Models (cont'd)



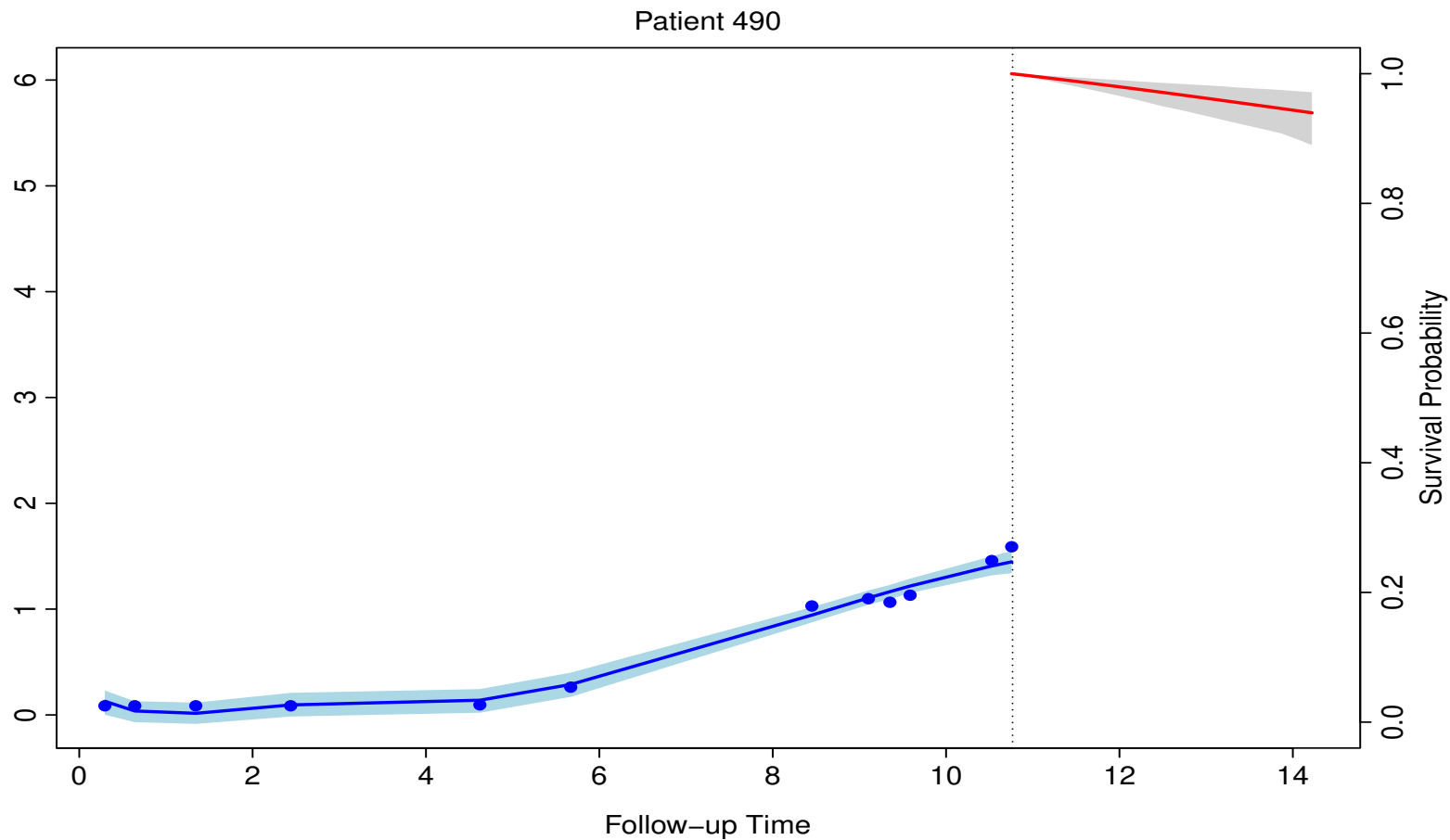
2 Joint Models (cont'd)



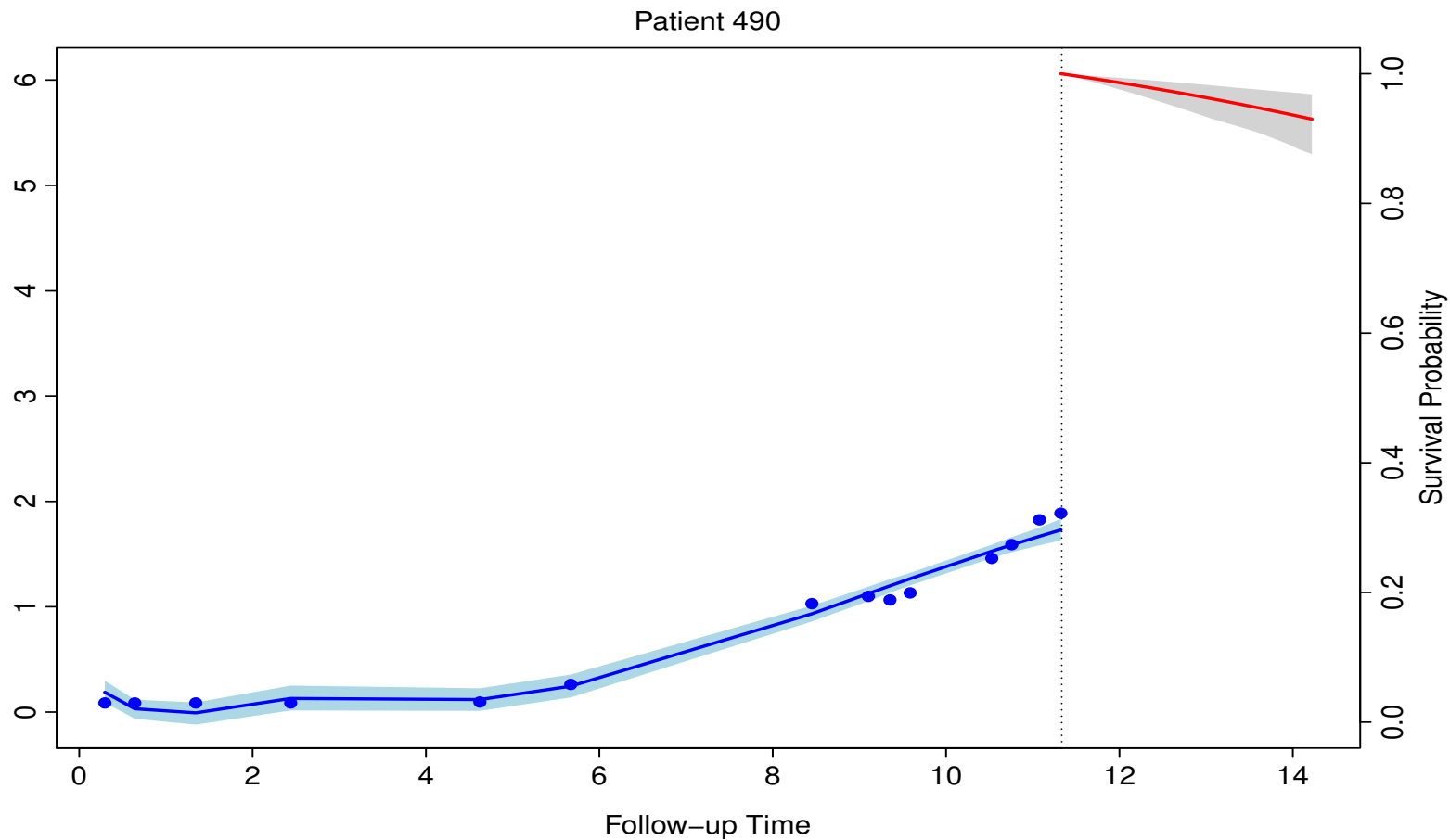
2 Joint Models (cont'd)



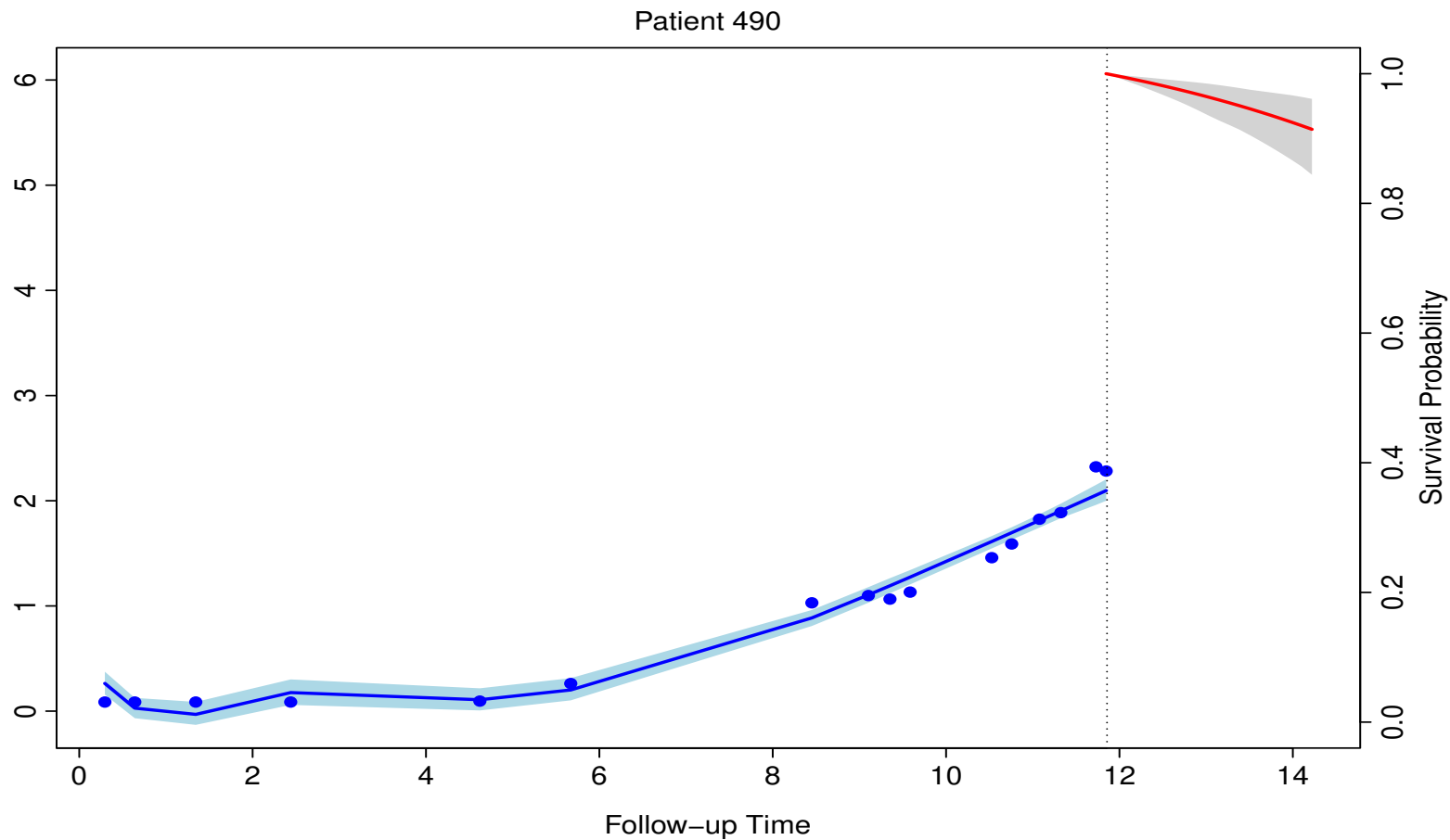
2 Joint Models (cont'd)



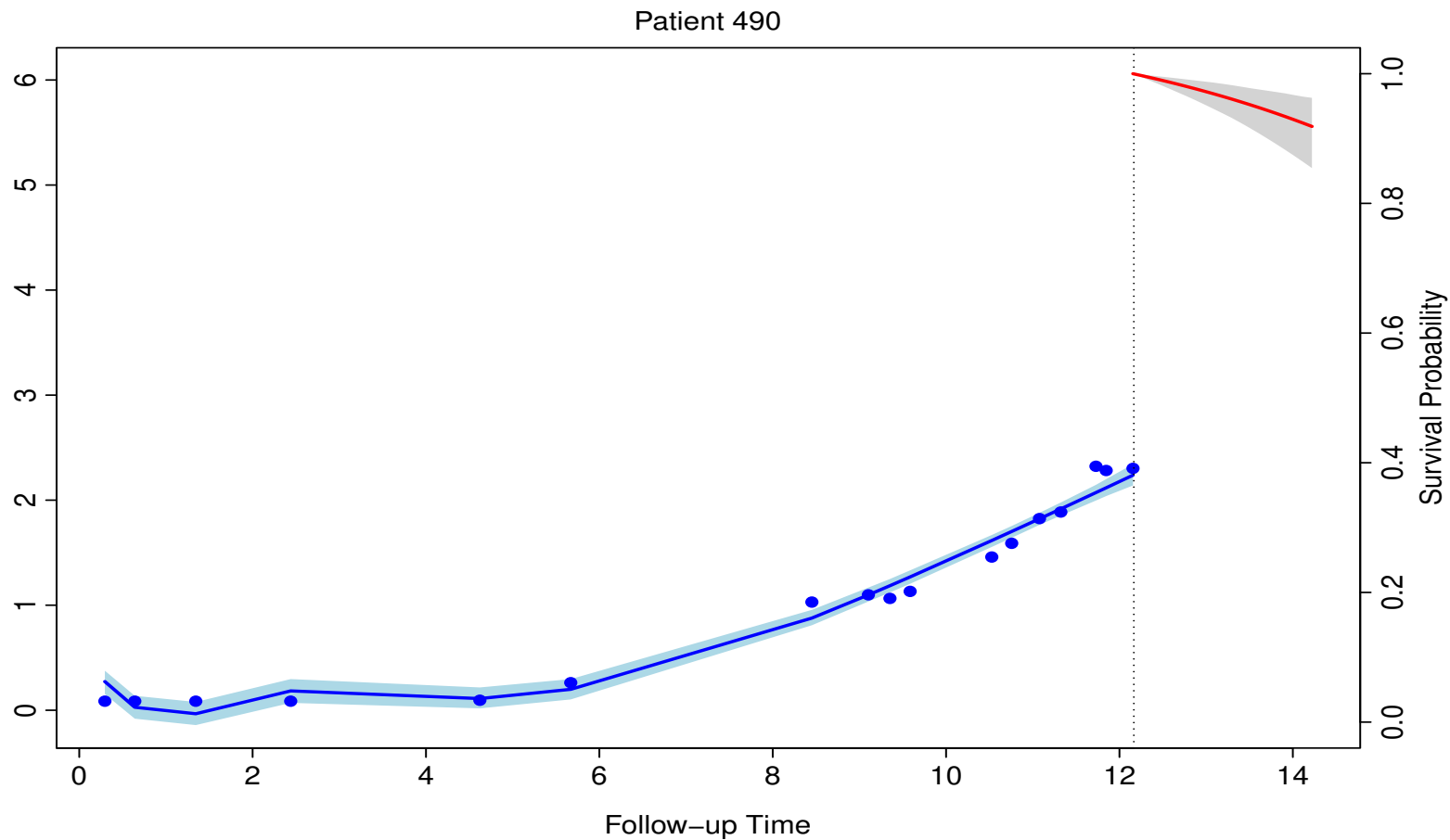
2 Joint Models (cont'd)



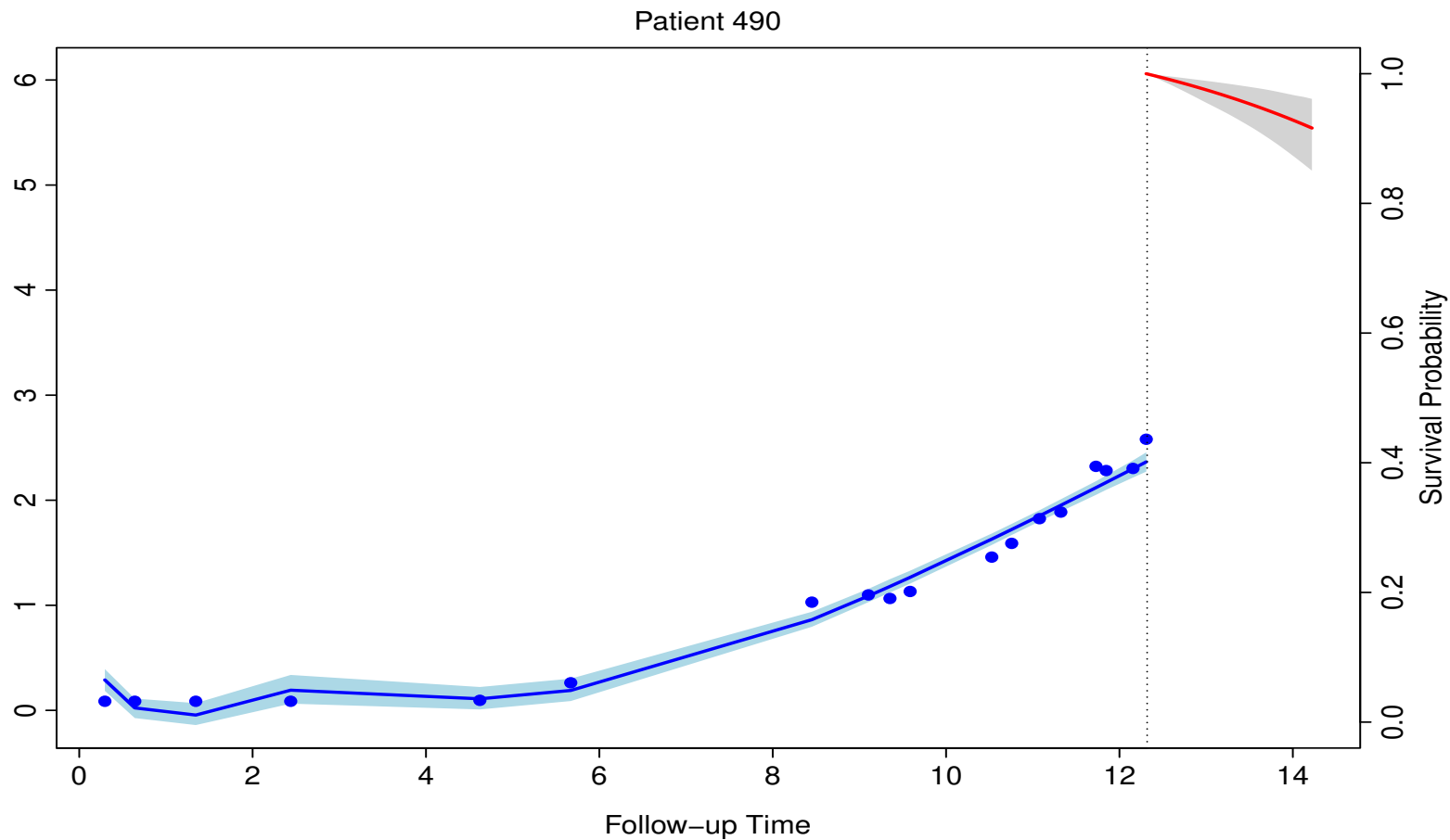
2 Joint Models (cont'd)



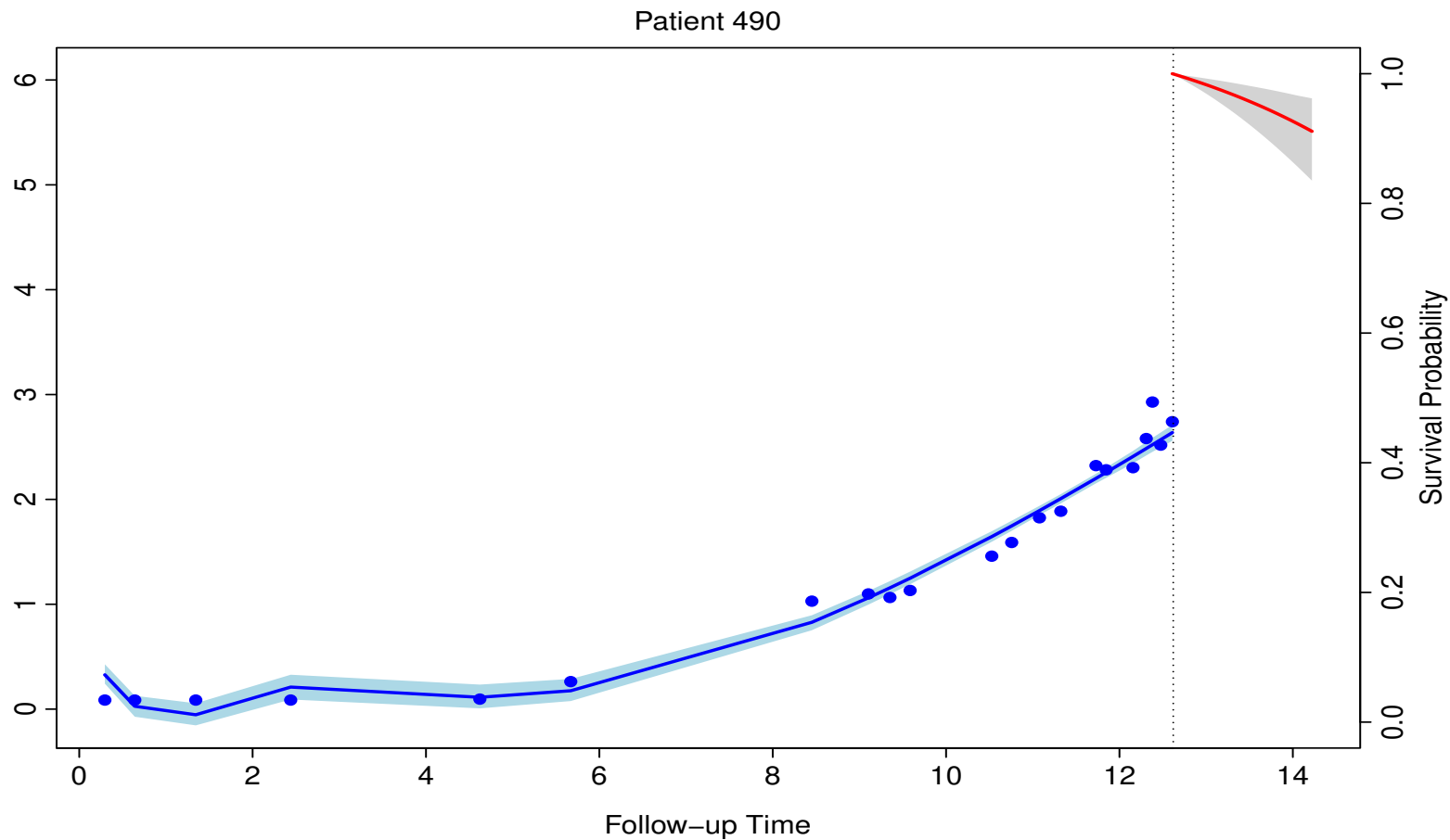
2 Joint Models (cont'd)



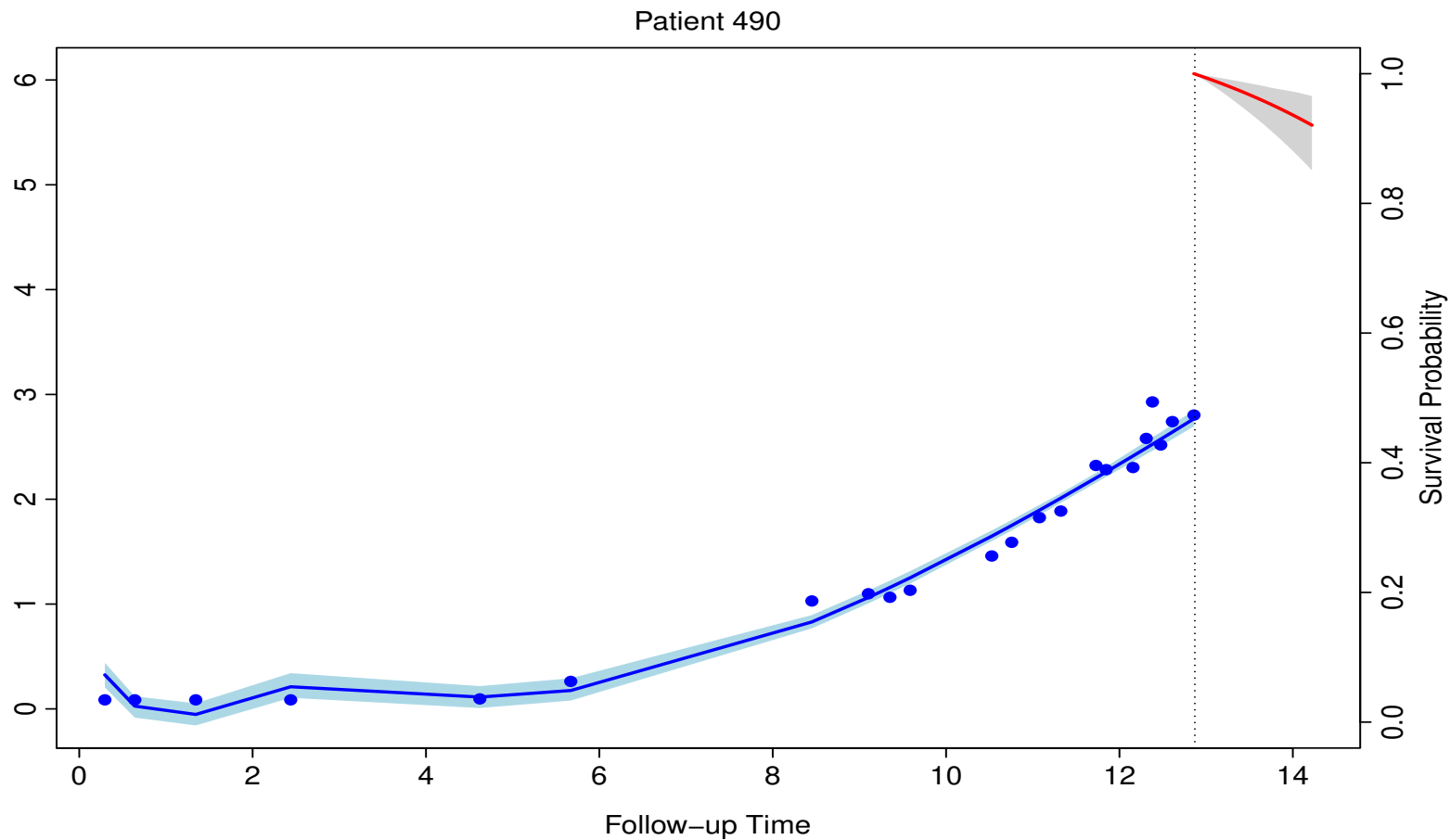
2 Joint Models (cont'd)



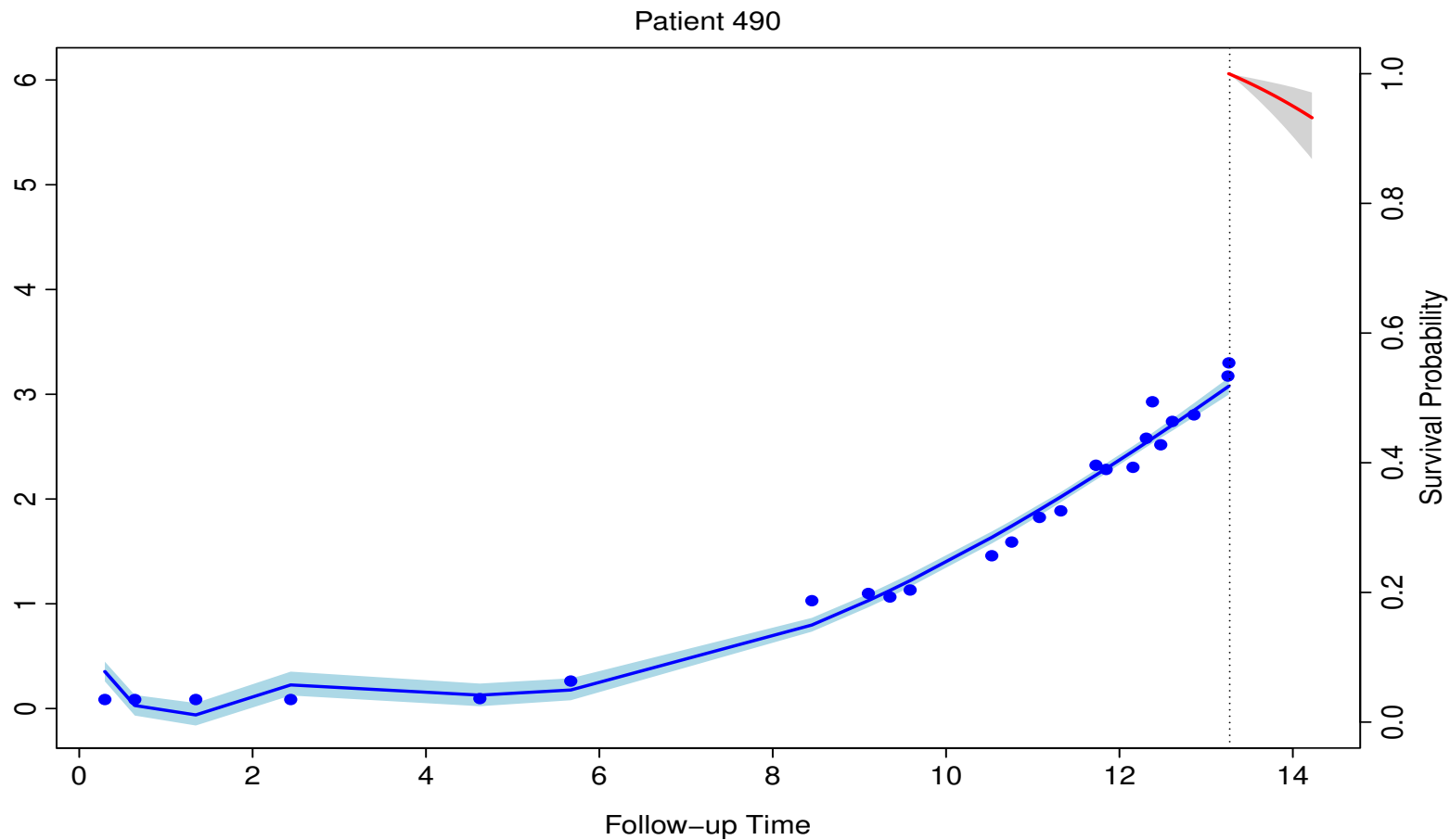
2 Joint Models (cont'd)



2 Joint Models (cont'd)



2 Joint Models (cont'd)



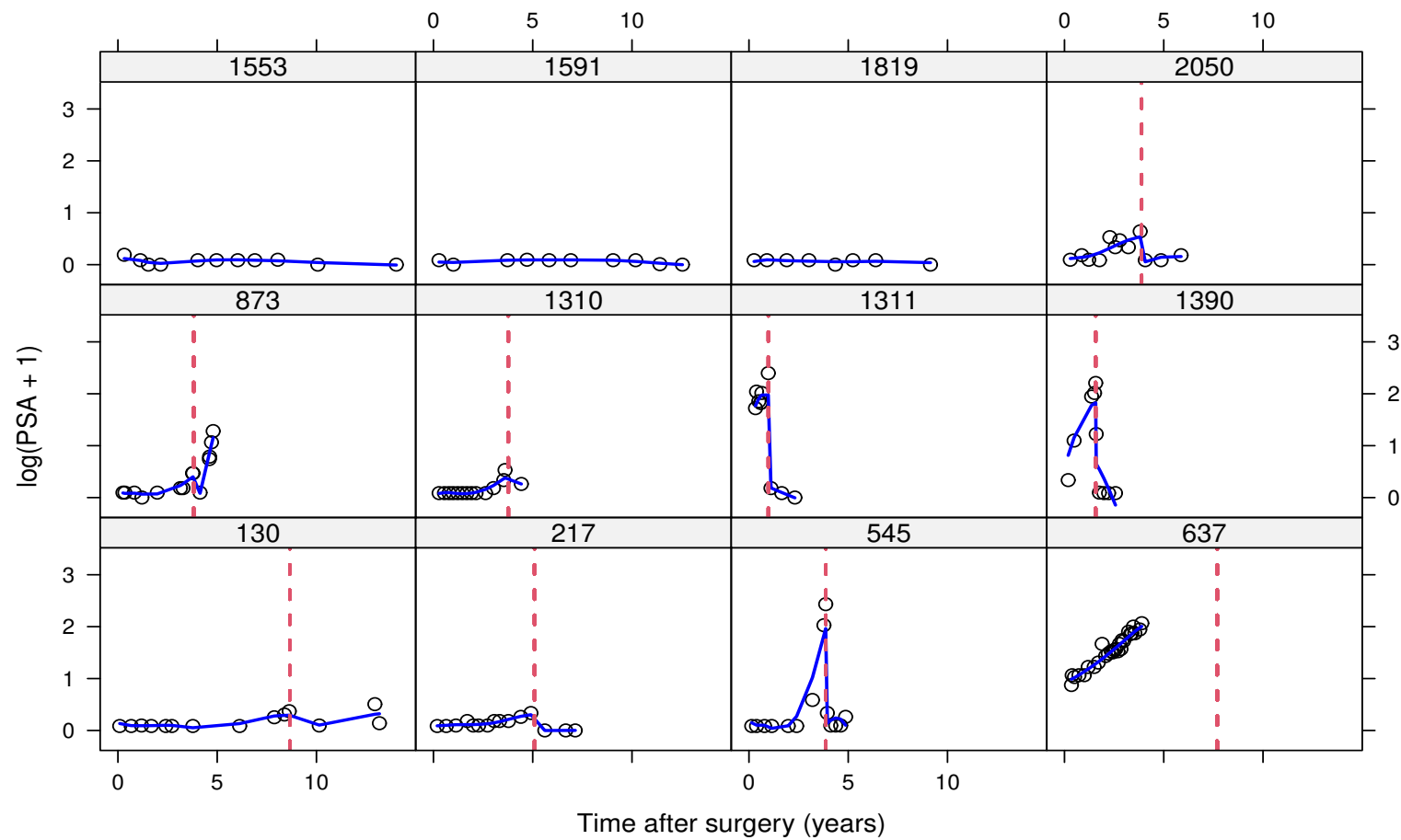
2 Joint Models (cont'd)

- In the context of dynamic predictions,
 - ▷ previous research has shown that predictive accuracy is compromised
 - ▷ when the model does not *adequately* capture the subject-specific trajectories shape

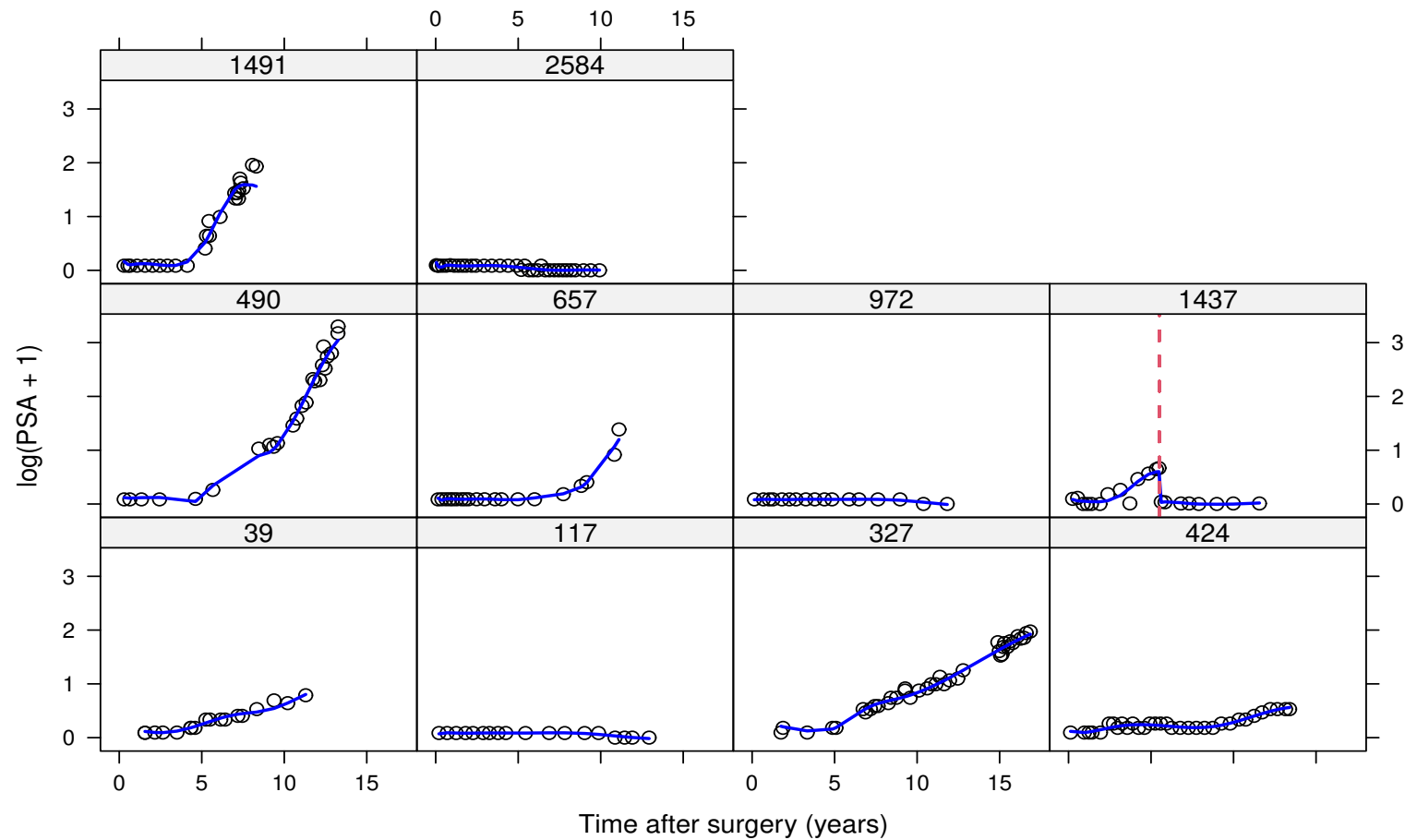
Advice

- ▷ use flexible models, e.g., splines in both fixed- and random-effects parts
- ▷ *increased computational burden*

2 Joint Models (cont'd)



2 Joint Models (cont'd)



3 Functional Forms

**There are different ways to link the longitudinal trajectories
to the risk of an event**

▷ Some standard options are ...

3 Functional Forms (cont'd)

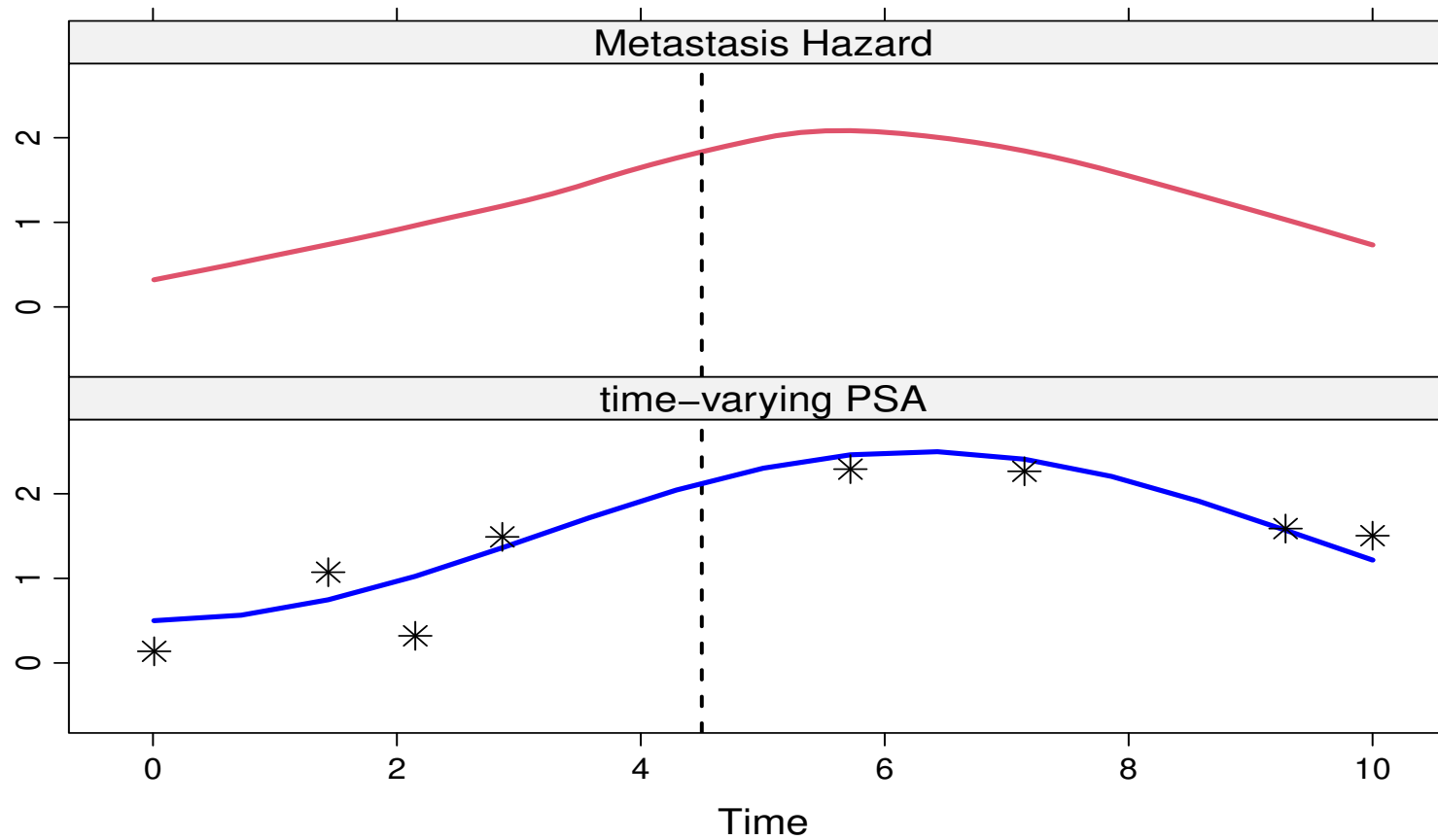
Value: The hazard of metastasis at t is associated with the level of PSA at t :

$$h_i(t \mid \mathcal{H}_i(t, \mathbf{b}_i)) = h_0(t) \exp\{\boldsymbol{\gamma}^\top \mathbf{w}_i + \alpha \eta_i(t, \mathbf{b}_i)\}$$

where

$$\eta_i(t, \mathbf{b}_i) = \mathbf{x}_i^\top(t) \boldsymbol{\beta} + \mathbf{z}_i^\top(t) \mathbf{b}_i$$

3 Functional Forms (cont'd)



3 Functional Forms (cont'd)

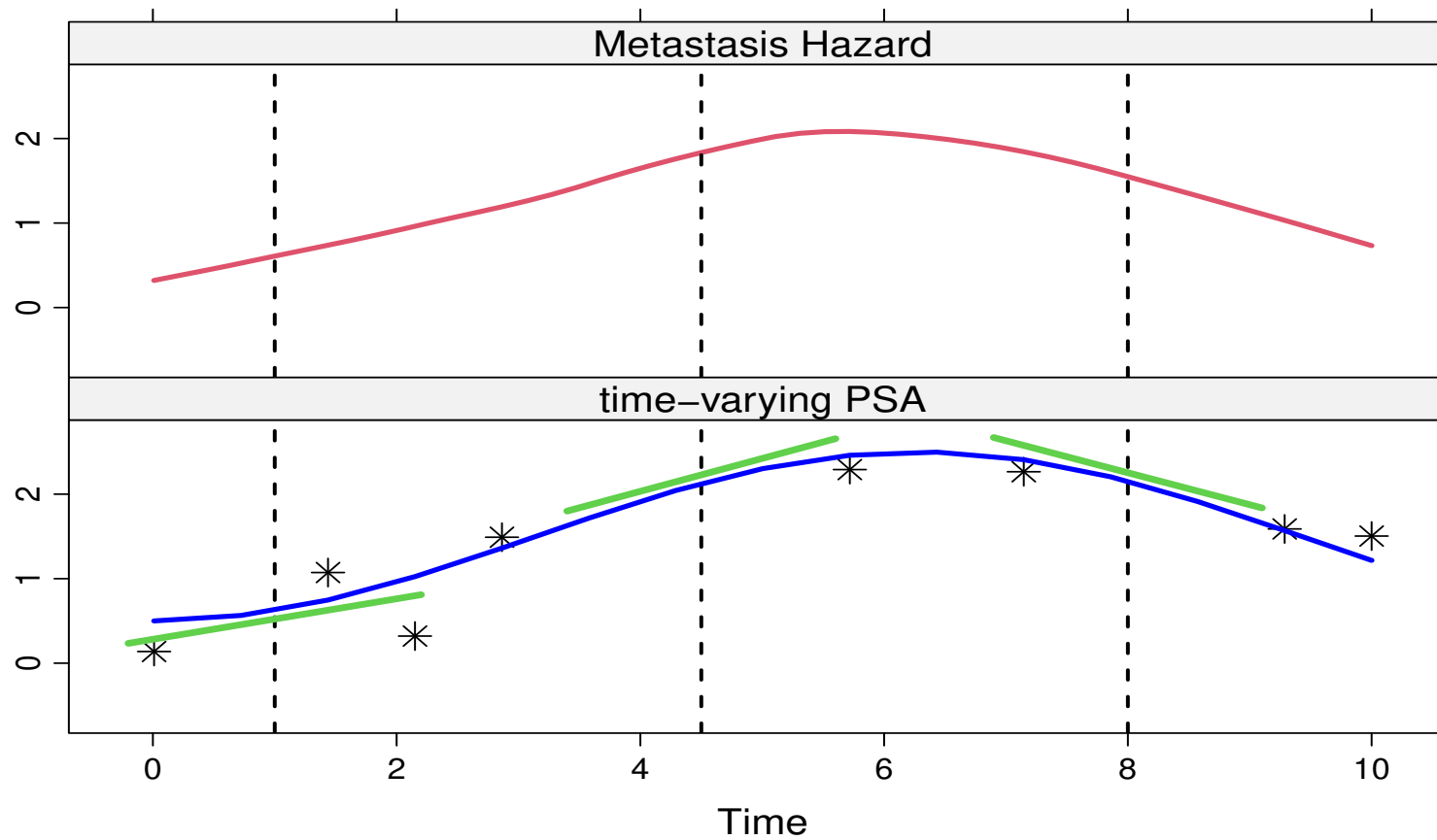
Velocity: The hazard of metastasis at t is associated with the slope of the PSA trajectory at t :

$$h_i(t \mid \mathcal{H}_i(t, \mathbf{b}_i)) = h_0(t) \exp\{\boldsymbol{\gamma}^\top \mathbf{w}_i + \alpha \eta'_i(t, \mathbf{b}_i)\},$$

where

$$\eta'_i(t, \mathbf{b}_i) = \frac{d}{dt} \{\mathbf{x}_i^\top(t) \boldsymbol{\beta} + \mathbf{z}_i^\top(t) \mathbf{b}_i\}$$

3 Functional Forms (cont'd)



3 Functional Forms (cont'd)

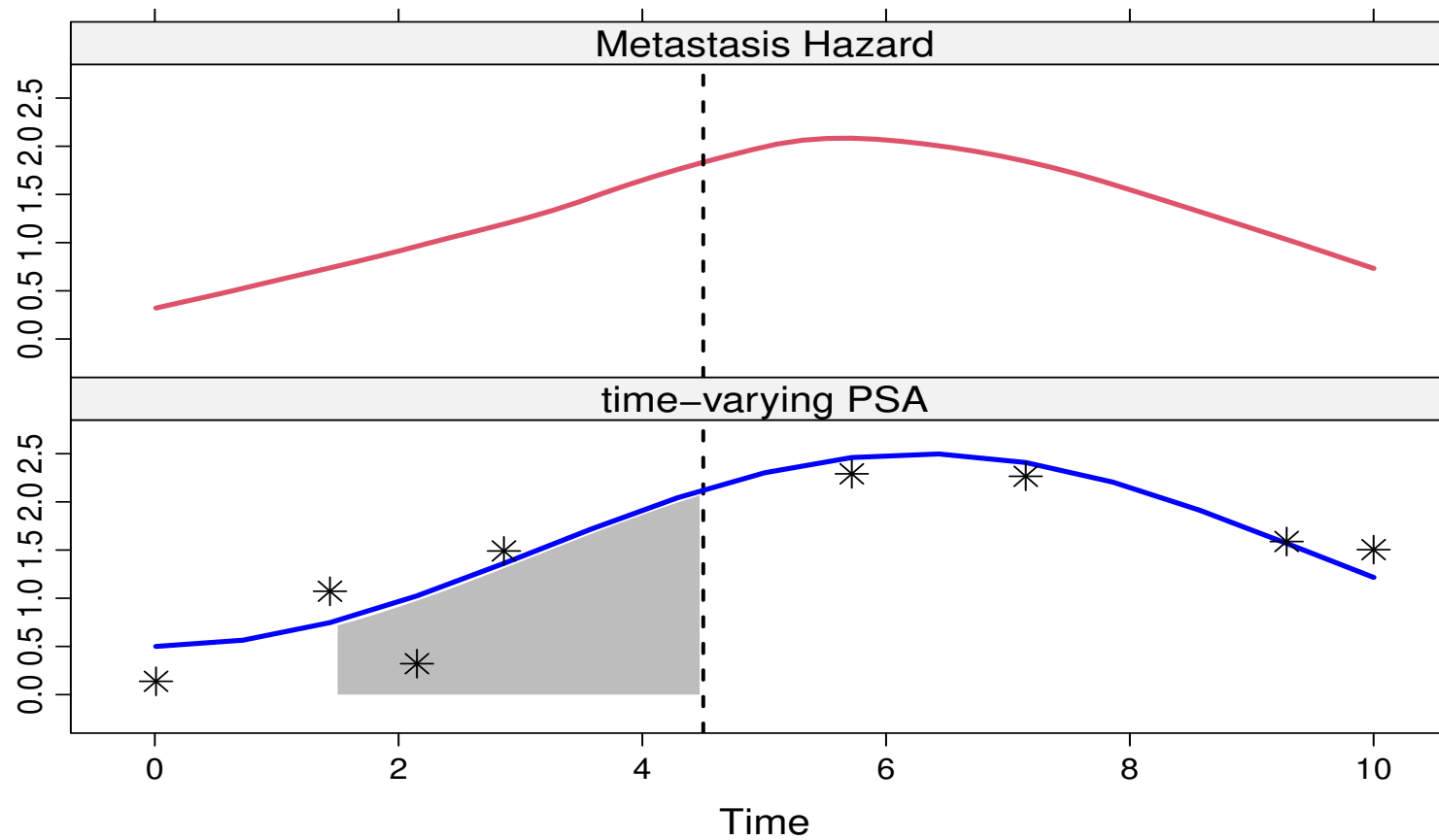
Average Effects:

The hazard of metastasis at t is associated with the average PSA in the interval $(t - \Delta t, t)$:

$$h_i(t \mid \mathcal{H}_i(t, \mathbf{b}_i)) = h_0(t) \exp \left\{ \gamma^\top \mathbf{w}_i + \alpha \frac{1}{\Delta t} \int_{t-\Delta t}^t \eta_i(s, \mathbf{b}_i) \, ds \right\}$$

We account for the observation period

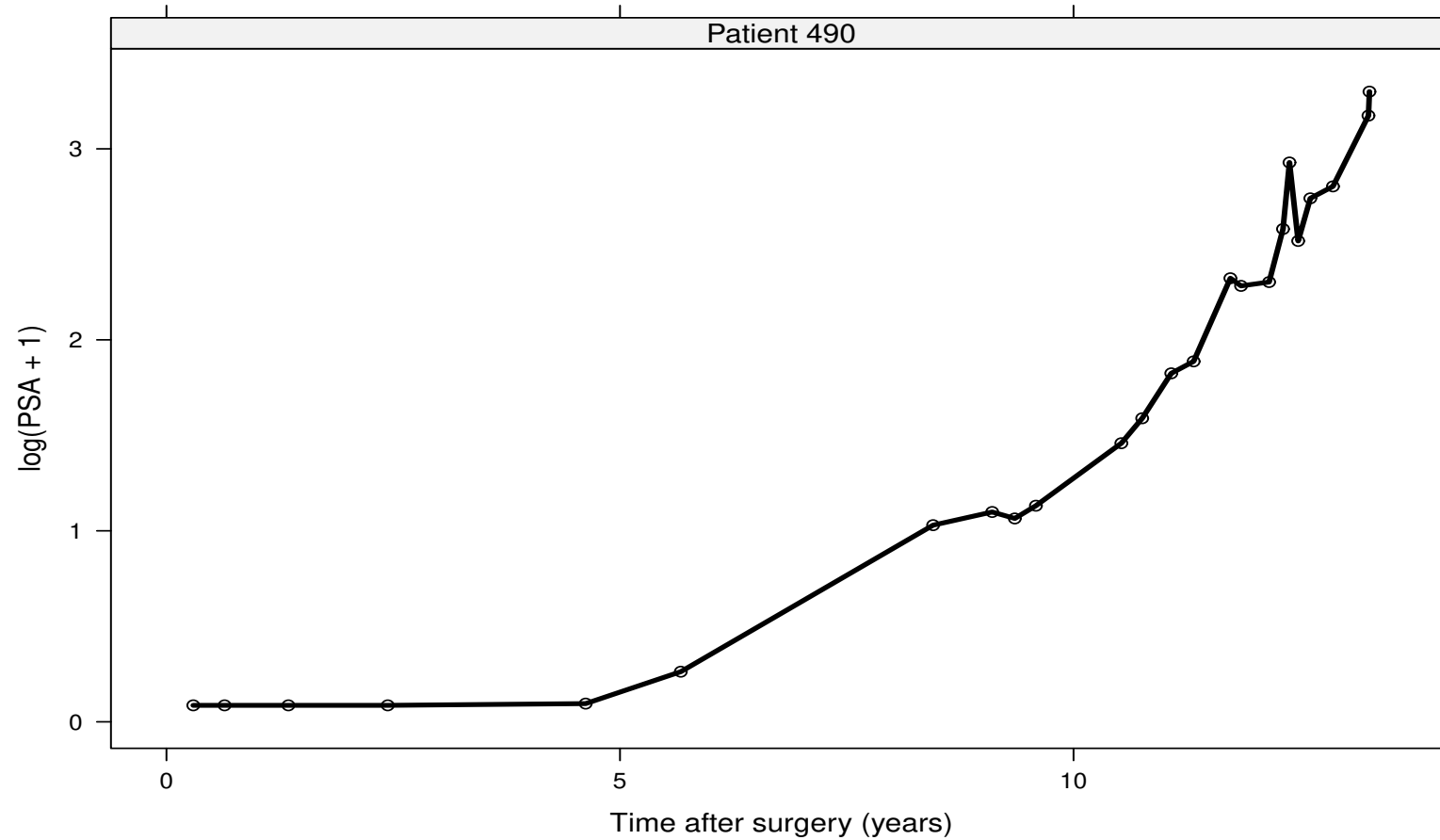
3 Functional Forms (cont'd)



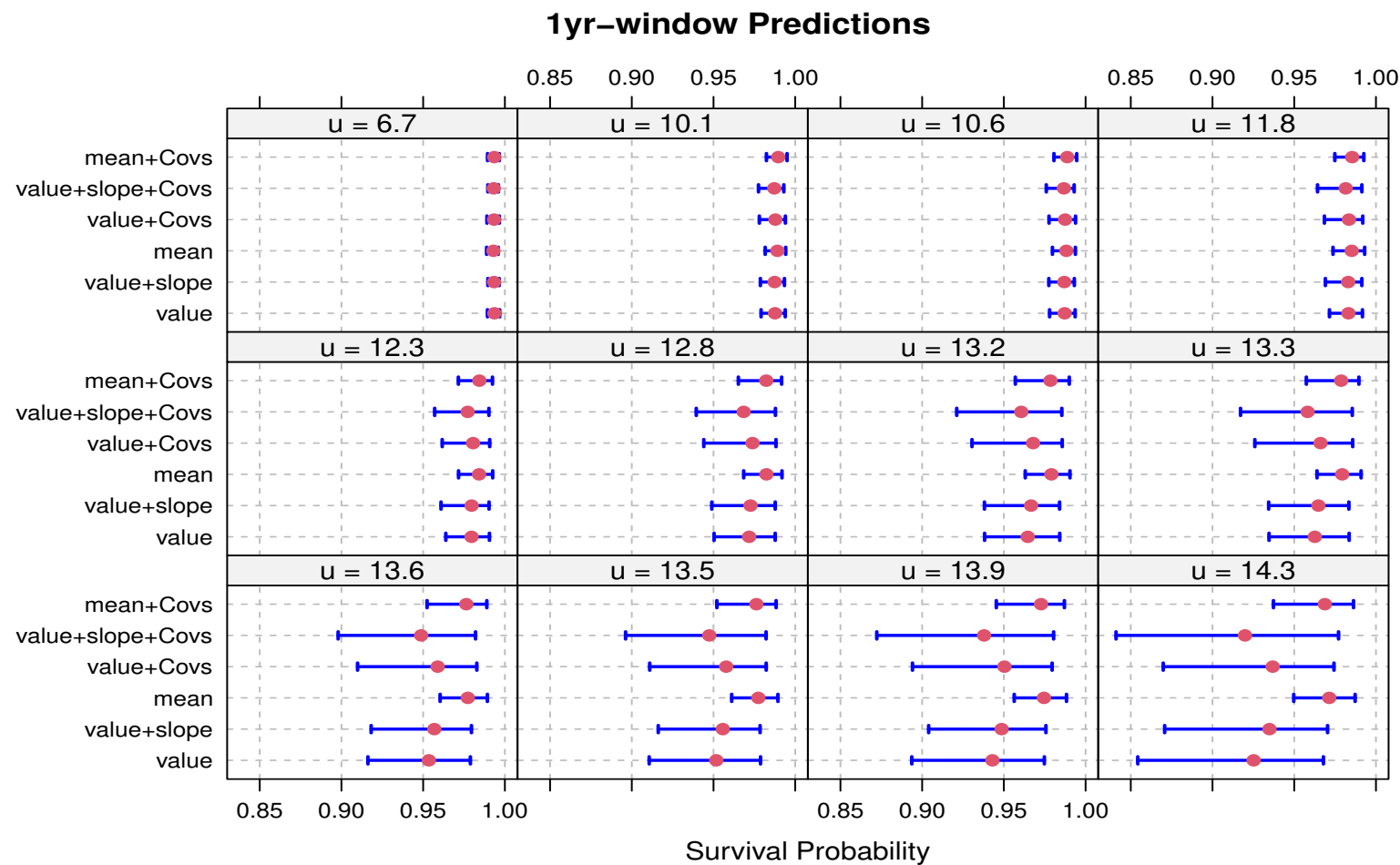
3 Functional Forms (cont'd)

How significant is the choice of the functional form for dynamic predictions?

3 Functional Forms (cont'd)



3 Functional Forms (cont'd)



4 Super Learning

- The selected functional form and time effect for the longitudinal outcome can influence the derived predictions
 - ▷ especially for the survival outcome

How to select between the different functional forms and trajectory shapes?

4 Super Learning (cont'd)

- The standard answer is to employ information criteria, e.g., DIC, WAIC, ...
- However, the longitudinal information dominates the joint likelihood
⇒ will not be sensitive enough wrt predicting survival probabilities
- In addition, will *a single model* be the most appropriate
 - ▷ for all future patients?
 - ▷ for all follow-up times?

4 Super Learning (cont'd)

Solution: *Super Learning*

- ▷ *Consider multiple plausible models with different*
 - * longitudinal outcomes
 - * assumptions for the longitudinal profiles
 - * functional forms
 - * baseline covariates, interaction terms
 - * ...

- ▷ *Obtain the desired predictions from these models*

- ▷ *Combine predictions using weights*
 - * *how to select the weights?*

4 Super Learning (cont'd)

- Previous research: *Bayesian Model Averaging*
 - ▷ Assume we have a library of L models $\mathcal{L} = \{M_1, \dots, M_L\}$
 - ▷ Weights: Posterior probability of a model given the data

$$p(M_l \mid \mathcal{D}_n), \quad l = 1, \dots, L$$

where

$$^* \mathcal{D}_n = \{T_i, \delta_i, \mathbf{y}_i; i = 1, \dots, n\}$$

4 Super Learning (cont'd)

- *Issues with BMA weights*

- ▷ requires calculating the marginal likelihood

$$p(\mathcal{D}_n \mid M_l) = \int \underbrace{p(\mathcal{D}_n \mid \boldsymbol{\theta}, M_l)}_{\text{Likelihood}} \underbrace{p(\boldsymbol{\theta} \mid M_l)}_{\text{Prior}} d\boldsymbol{\theta}$$

⇒ *Computationally demanding*

- ▷ Weights not designed to optimize predictions

- ▷ Not clear if we account for over-fitting

4 Super Learning (cont'd)

- *Issues with BMA weights*

- ▷ The likelihood of a model that fits the data a bit better can have a likelihood value that is several units larger compared to the other models
- ▷ Often one model dominates the weights over the others

4 Super Learning (cont'd)

Alternative Solution: *Super Learning*

- ▷ select weights to optimize prediction metric *of your choice*
- ▷ account for over-fitting using cross-validation

4 Super Learning (cont'd)

How it works:

- ▷ Assume we have a library of L *base-learners* (models) $\mathcal{L} = \{M_1, \dots, M_L\}$
- ▷ Specify the landmark time t , and a relevant future time u , $u > t$
- ▷ Split \mathcal{D}_n in V -folds
- ▷ For $v \in \{1, \dots, V\}$, train the learners in library \mathcal{L} using $\mathcal{D}_n^{(-v)}$

4 Super Learning (cont'd)

How it works:

- ▷ For the subjects in $\mathcal{D}_n^{(v)}$, not used when training the learner, calculate the predictions

$$\hat{\pi}_i^{(v)}(u \mid t, M_l) = \Pr\{T_i^* < u \mid T_i^* > t, \mathcal{Y}_i(t), M_l, \mathcal{D}_n^{(-v)}\}$$

do this for all $v = 1, \dots, V$ to get the *cross-validated predictions*

4 Super Learning (cont'd)

How it works:

- ▷ We define the ensemble of *cross-validated predictions*

$$\hat{\pi}_i^v(u \mid t) = \sum_{l=1}^L \varpi_l(t) \hat{\pi}_i^{(v)}(u \mid t, M_l), \quad v = 1, \dots, V$$

* the weights depend on $t \Rightarrow$ *different weights at different follow-up times*

4 Super Learning (cont'd)

How it works:

- ▷ Select $\varpi_l(t)$ to optimize your *meta-learner* (predictive accuracy metric), e.g.,
 - * Brier Score (*Proper scoring rule*)
 - * Expected Predictive Cross-Entropy (*Proper scoring rule*)
 - * AUC (*Not a proper scoring rule*)
 - * ...

- ▷ Under the constraints
 - * $\hat{\varpi}_l(t) > 0$ for all $l = 1, \dots, L$
 - * $\sum_{l=1}^L \hat{\varpi}_l(t) = 1$

5 UM Data Analysis

A library \mathcal{L} with twelve joint models

- PSA models
 - ▷ M_{l1} : *linear* subject-specific time trends that change after salvage
 - ▷ M_{l2} : the same as M_{l1} + covariates
 - ▷ M_{l3} : *nonlinear* subject-specific time trends that change after salvage
 - ▷ M_{l4} : the same as M_{l3} + covariates
- Baseline covariates: age at surgery, Charlson's index, Gleason score, and baseline PSA

5 UM Data Analysis (cont'd)

A library \mathcal{L} with twelve joint models

- Metastasis models
 - ▷ M_{s1} : value of $\log(\text{PSA} + 1)$
 - ▷ M_{s2} : velocity of $\log(\text{PSA} + 1)$
 - ▷ M_{s3} : average $\log(\text{PSA} + 1)$
- Time varying salvage therapy
- Baseline covariates: the same as in the PSA models

5 UM Data Analysis (cont'd)

- We evaluated predictive accuracy in two time intervals
 - ▷ $(4, 7]$: 2514 patients at risk; 28 metastasis
 - ▷ $(6, 9]$: 1914 patients at risk; 16 metastasis
- Metrics
 - ▷ Integrated Brier Score
 - ▷ Expected Predictive Cross-Entropy

5 UM Data Analysis (cont'd)

Meta-learners

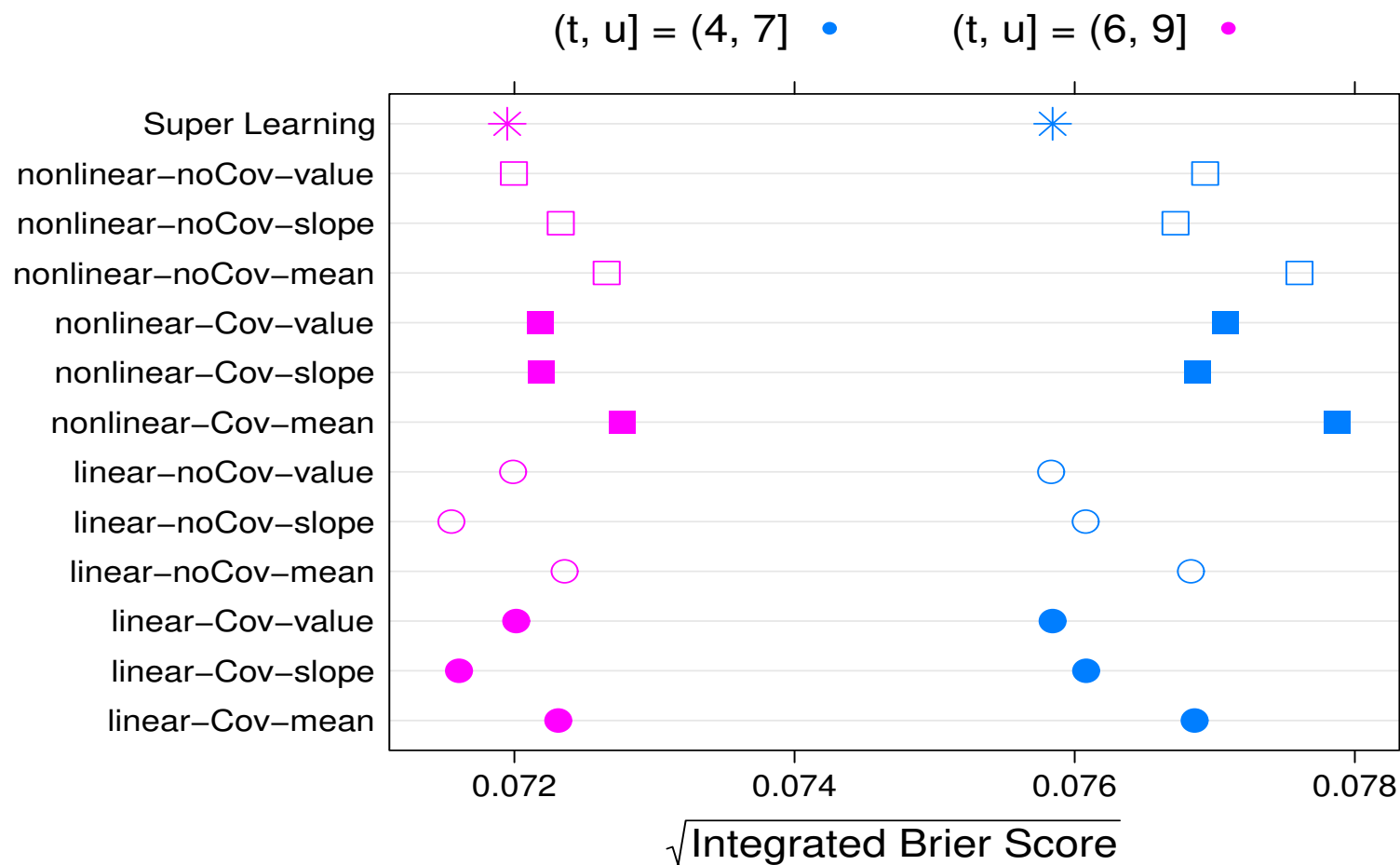
▷ *Integrated Brier Score*

$$\text{IBS}(u, t) = \frac{1}{u - t} \int_t^u E \left\{ \mathbb{I}(t < T_i^* \leq s) - \pi_i(s | t) \right\}^2 ds$$

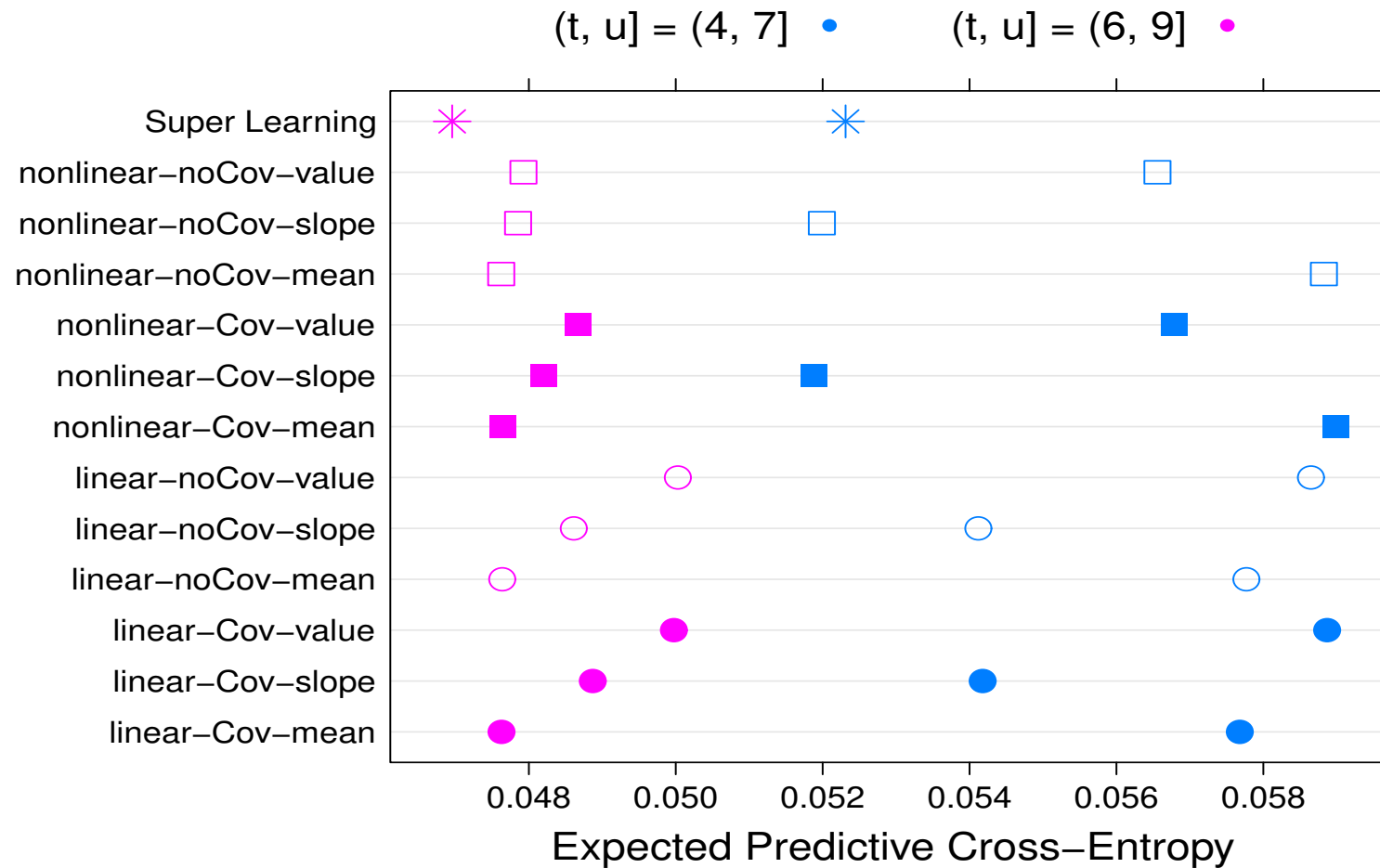
▷ *Expected Predictive Cross-Entropy*

$$\text{EPCE}(u, t) = E \left\{ -\log \left[p \{ T_i^* | t < T_i^* \leq u, \mathcal{Y}_i(t) \} \right] \right\}$$

5 UM Data Analysis (cont'd)



5 UM Data Analysis (cont'd)



5 UM Data Analysis (cont'd)

Observations (also from the simulation study)

- ▷ ensemble Super Learning (eSL) often, *but not always*, outperforms the individual models
- ▷ In some datasets and intervals $(t, u]$, the discrete Super Learner (dSL) beats the eSL

5 UM Data Analysis (cont'd)

Recommendation

Regard eSL as an extra member of the library \mathcal{L} and use CV to select the optimal strategy

- Available in **JMbayes2**

- ▷ cross-validated fitting of models
- ▷ combination of dynamic predictions

https://drizopoulos.github.io/JMbayes2/articles/Super_Learning.html

Thank for your attention!

<https://www.drizopoulos.com/>

7 Choice of the Meta-Learner

We focus on two meta-learners

▷ *Integrated Brier Score*

$$\text{IBS}(t + \Delta t, t) = \frac{1}{\Delta t} \int_t^{t+\Delta t} E \left[\left\{ \mathbb{I}(T_i^* \leq s) - \pi_i(s | t) \right\}^2 \mid T_i^* > t \right] ds$$

▷ *Expected Predictive Cross-Entropy*

$$\text{EPCE}(t + \Delta t, t) = E \left\{ -\log \left[p \{ T_i^* \mid t < T_i^* \leq t + \Delta t, \mathcal{Y}_i(t) \} \right] \right\}$$

7 Choice of the Meta-Learner (cont'd)

- For the estimation of the Brier score, we need to account for censoring in $[t, t + \Delta t)$
 - * inverse probability of censoring weighting
 - * model-based weights

7 Choice of the Meta-Learner (cont'd)

- Brier Score with IPCW

$$\widehat{\text{BS}}_{IPCW}(t + \Delta t, t) = \frac{1}{n} \sum_{i=1}^n \widehat{W}_i(t + \Delta t, t) \left\{ \mathbb{I}(T_i \leq t + \Delta t) - \hat{\pi}_i^v(t + \Delta t | t) \right\}^2$$

where

$$\widehat{W}_i(t + \Delta t, t) = \frac{\mathbb{I}(t < T_i \leq t + \Delta t) \delta_i}{\hat{G}(T_i | t)} + \frac{\mathbb{I}(T_i > t + \Delta t)}{\hat{G}(t + \Delta t | t)},$$

with $\hat{G}(\cdot)$ denoting Kaplan-Meier estimate of the censoring distribution $\Pr(C_i > t)$

7 Choice of the Meta-Learner (cont'd)

- Brier Score with model-weights

$$\begin{aligned}\widehat{\text{BS}}_{\text{model}}(t + \Delta t, t) &= \frac{1}{n_t} \sum_{i: T_i > t} \delta_i \mathbb{I}(T_i \leq t + \Delta t) \left\{ 1 - \hat{\pi}_i^v(t + \Delta t \mid t) \right\}^2 \\ &\quad + \mathbb{I}(T_i > t + \Delta t) \left\{ \hat{\pi}_i^v(t + \Delta t \mid t) \right\}^2 \\ &\quad + (1 - \delta_i) \mathbb{I}(T_i \leq t + \Delta t) \left[\hat{\pi}_i^v(t + \Delta t \mid T_i) \left\{ 1 - \hat{\pi}_i^v(t + \Delta t \mid t) \right\}^2 \right. \\ &\quad \left. + \left\{ 1 - \hat{\pi}_i^v(t + \Delta t \mid T_i) \right\} \left\{ \hat{\pi}_i^v(t + \Delta t \mid t) \right\}^2 \right]\end{aligned}$$

7 Choice of the Meta-Learner (cont'd)

- IPCW

- ▷ *Advantage*: it provides unbiased estimates even when the model is misspecified
- ▷ *Disadvantage*: it requires that the model for the weights is correct
 - * challenging because censoring may depend on the longitudinal outcomes in a complex manner
 - * sensitive to (unobserved) instrument by confounder interactions

7 Choice of the Meta-Learner (cont'd)

- Model-based Weights
 - ▷ *Advantage*: it allows censoring to depend on the longitudinal history (in any possible manner)
 - ▷ *Disadvantage*: it requires that the model is well-specified

7 Choice of the Meta-Learner (cont'd)

- An estimate of $\text{EPCE}(t + \Delta t, t)$ that accounts for censoring

$$\widehat{\text{EPCE}}(t + \Delta t, t) = \frac{1}{n_t} \sum_{i: T_i > t} -\log \left[p\{\tilde{T}_i, \tilde{\delta}_i \mid T_i > t, \mathcal{Y}_i(t), \mathcal{D}_n\} \right]$$

with

- ▷ $\tilde{T}_i = \min(T_i, t + \Delta t)$
- ▷ $\tilde{\delta}_i = \delta_i \mathbb{I}(t < T_i \leq t + \Delta t)$

- Features

- ▷ it allows censoring to depend on the longitudinal history
- ▷ *problem*: it is not written as a function of the predictions

7 Choice of the Meta-Learner (cont'd)

- The conditional predictive log-likelihood

$$\log \left[p \{ \tilde{T}_i, \tilde{\delta}_i \mid T_i > t, \mathcal{Y}_i(t), \mathcal{D}_n \} \right] =$$

$$\tilde{\delta}_i \log [h_i \{ \tilde{T}_i \mid \mathcal{Y}_i(t), \mathcal{D}_n \}] + \log \frac{\Pr \{ T_i^* > \tilde{T}_i \mid \mathcal{Y}_i(t), \mathcal{D}_n \}}{\Pr \{ T_i^* > t \mid \mathcal{Y}_i(t), \mathcal{D}_n \}}$$

▷ the second term is $\log \{ \pi_i(\tilde{T}_i \mid t) \}$

▷ for the first term, we write the hazard function as

$$h_i \{ \tilde{T}_i \mid \mathcal{Y}_i(t), \mathcal{D}_n \} = \frac{p(\tilde{T}_i)}{S(\tilde{T}_i)} = - \frac{\frac{d}{dt} \Pr \{ T_i^* > t \mid \mathcal{Y}_i(t), \mathcal{D}_n \} \Big|_{t=\tilde{T}_i}}{\Pr \{ T_i^* > \tilde{T}_i \mid \mathcal{Y}_i(t), \mathcal{D}_n \}}$$

7 Choice of the Meta-Learner (cont'd)

- We approximate the derivative with a forward difference and we get

$$\widehat{\text{EPCE}}(t + \Delta t, t) =$$

$$-\frac{1}{n_t} \sum_{i: T_i > t} \tilde{\delta}_i [\log\{1 - \hat{\pi}_i^v(\tilde{T}_i + \epsilon \mid \tilde{T}_i)\} - \log(\epsilon)] + \log\{\hat{\pi}_i^v(\tilde{T}_i \mid t)\}$$

that can be used to optimize $\varpi_l(t)$

7 UM Data Analysis (cont'd)

	$(t, t + \Delta t] = (4, 7]$		$(t, t + \Delta t] = (6, 9]$	
	IBS	weights	IBS	weights
SL	0.07584		0.07195	
linear-noCov-value	0.07583	0.00000	0.07199	0.08333
linear-noCov-slope	0.07608	0.00000	0.07155	0.08340
linear-noCov-mean	0.07683	0.00000	0.07236	0.08332
linear-Cov-value	0.07584	1.00000	0.07201	0.08335
linear-Cov-slope	0.07608	0.00000	0.07160	0.08339
linear-Cov-mean	0.07686	0.00000	0.07231	0.08332
nonlinear-noCov-value	0.07693	0.00000	0.07200	0.08334
nonlinear-noCov-slope	0.07672	0.00000	0.07233	0.08331
nonlinear-noCov-mean	0.07760	0.00000	0.07266	0.08329
nonlinear-Cov-value	0.07708	0.00000	0.07218	0.08332
nonlinear-Cov-slope	0.07687	0.00000	0.07219	0.08333
nonlinear-Cov-mean	0.07788	0.00000	0.07277	0.08328

7 UM Data Analysis (cont'd)

	$(t, t + \Delta t] = (4, 7]$		$(t, t + \Delta t] = (6, 9]$	
	EPCE	weights	EPCE	weights
SL	0.05231		0.04696	
linear-noCov-value	0.05865	0.08325	0.05003	0.00002
linear-noCov-slope	0.05412	0.08320	0.04861	0.00000
linear-noCov-mean	0.05777	0.08260	0.04764	0.39649
linear-Cov-value	0.05887	0.08215	0.04997	0.00000
linear-Cov-slope	0.05418	0.08333	0.04887	0.00000
linear-Cov-mean	0.05768	0.08270	0.04763	0.12793
nonlinear-noCov-value	0.05656	0.08337	0.04793	0.00136
nonlinear-noCov-slope	0.05199	0.08517	0.04785	0.44966
nonlinear-noCov-mean	0.05882	0.08296	0.04762	0.00961
nonlinear-Cov-value	0.05679	0.08315	0.04867	0.00000
nonlinear-Cov-slope	0.05188	0.08526	0.04820	0.01327
nonlinear-Cov-mean	0.05899	0.08288	0.04764	0.00166