Joint modeling of longitudinal and survival data

How can we learn about disease
by studying **symptoms** *and* **survival**?

Especially when survival gains due to treatment are small,
improvement in quality of life/symptoms is important to patients.

Joint modeling of longitudinal and survival data

Disease setting: malignant pleural mesothelioma (MPM). This cancer of the pleura (membranes surrounding the lungs) is usually caused by asbestos exposure. Long latency period (20-40 yrs), followed by high mortality.

Other possible settings:
Degradation measurements and time-to-failure (e.g., Lu and Meeker, Technometrics 1993)
Reproductive fertility (daily egg counts) and lifespan in fruit flies (e.g., Hanson et al., LDA 2010)

Joint modeling of longitudinal and survival data

Full details may be found in

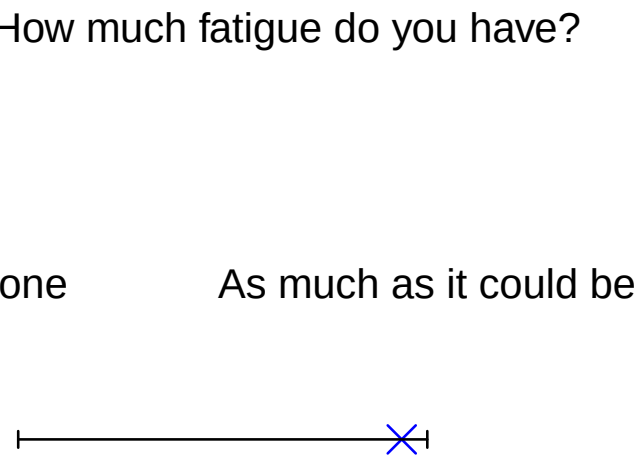
Hatfield LA, Boye ME, Carlin BP. Joint modeling of multiple longitudinal patient-reported outcomes and survival. *J. Biopharmaceutical Statistics* (To Appear), 2011.

and

Hatfield LA, Boye ME, Hackshaw MD, and Carlin BP. Multilevel Bayesian models for survival times and longitudinal patient-reported outcomes with many zeros. *Research Report 2010-029*, Division of Biostatistics, University of Minnesota, 2010.

How do we measure symptoms?

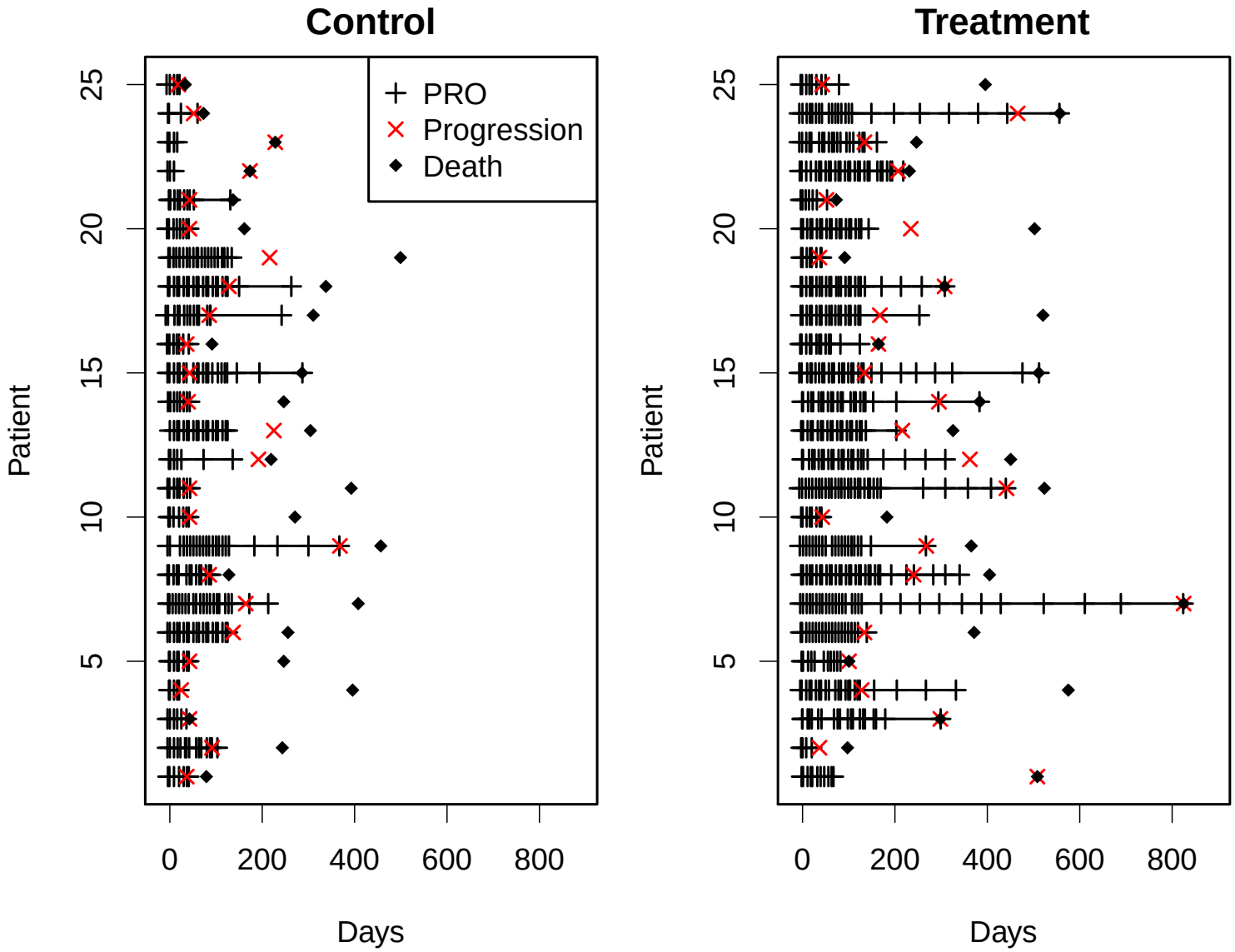
Patient-reported outcomes (PROs) on a visual analog scale.



6 symptoms: anorexia, fatigue, cough, dyspnea, pain, and hemoptysis (which we exclude)

3 global measures: symptom distress, interference with carrying out normal activities, and quality of life

PRO Observation Times



How do we measure survival?

A combined endpoint comprising two possible clinical events– progression of disease and death.

Progression-Free Survival (PFS)

Time from randomization to progression or death (whichever occurs first), where **progression** is defined as a pre-specified increase in size of primary tumor on CT scan

How do we measure survival?

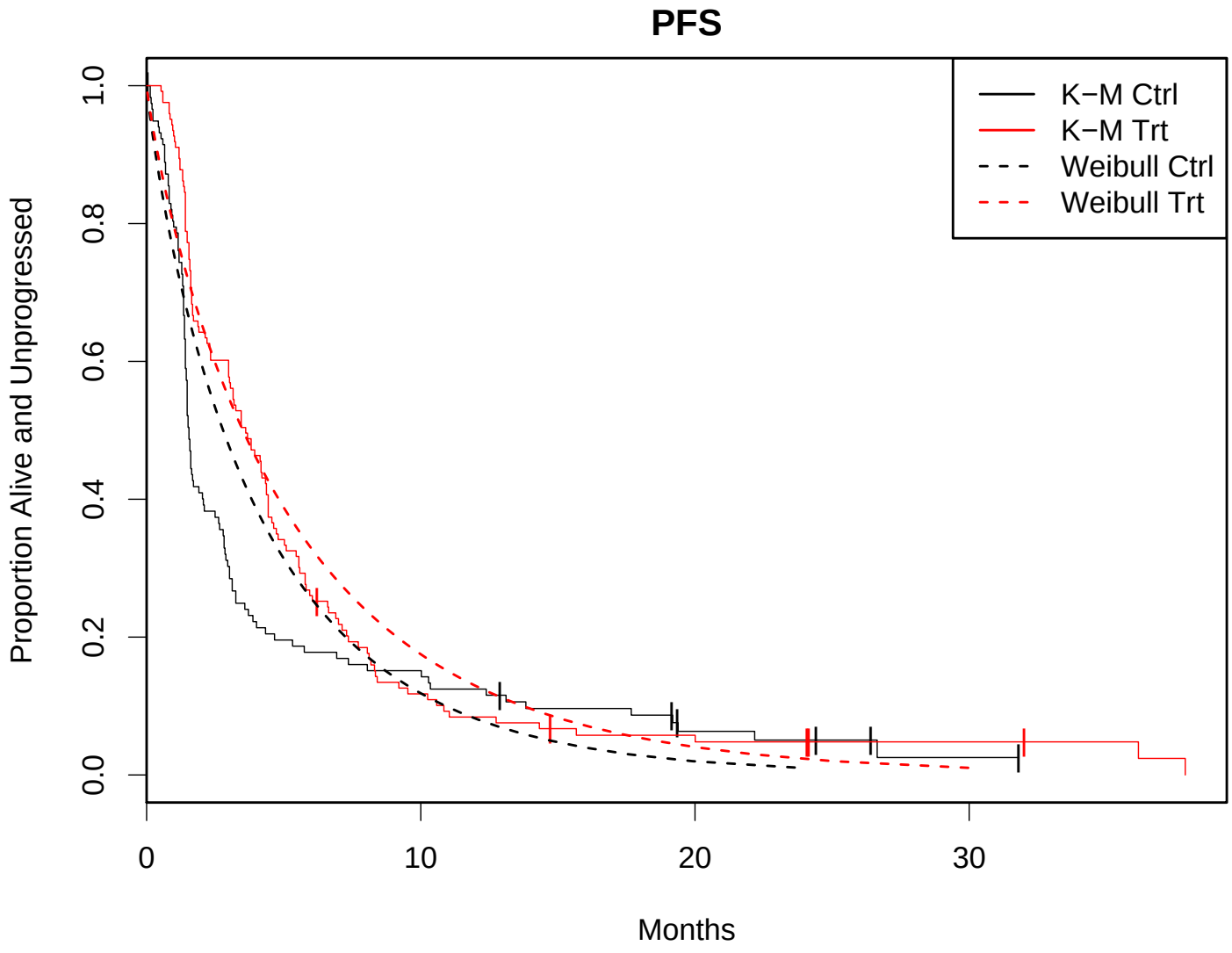
A combined endpoint comprising two possible clinical events– progression of disease and death.

Progression-Free Survival (PFS)

Time from randomization to progression or death (whichever occurs first), where **progression** is defined as a pre-specified increase in size of primary tumor on CT scan

In the absence of PRO data, the **treatment benefit** on PFS was 5.7 months versus 3.9 months, while the **overall survival** difference was not significant (12.1 months versus 9.3).

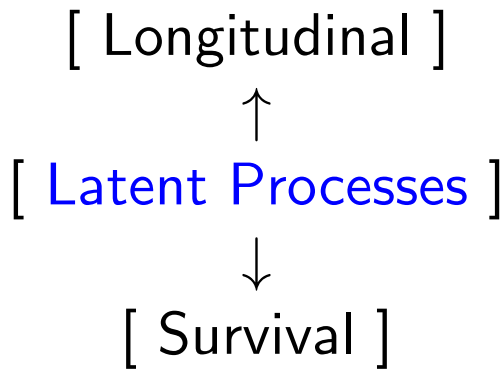
Progression-Free Survival (PFS)



Clinical Questions

- What are the **effects of treatment** on the presence and severity of symptoms and the risk of progression/death?
- How do **individual patients** differ in their disease progression?
- What are the **relationships** between symptoms and survival?

Joint Models: Conceptual Framework



The latent process generates both kinds of observed data.

This idea has a long history in the literature (Tsiatis et al. 1995, Faucett & Thomas 1996). See Brown & Ibrahim (2003) for a recent Bayesian example or Tsiatis & Davidian (2004) for a review.

Building the Model

Model building comprises four major steps:

1. Build a **longitudinal submodel**
2. Build a **survival submodel**
3. Specify the form of the **latent trajectories**
4. **Link the submodels** using these latent parameters

Building the Model

Model building comprises four major steps:

1. Build a **longitudinal submodel**
2. Build a **survival submodel**
3. Specify the form of the **latent trajectories**
4. **Link the submodels** using these latent parameters

First, some notation. For the i^{th} person at time s:

$Y_i(s)$ observed longitudinal outcomes

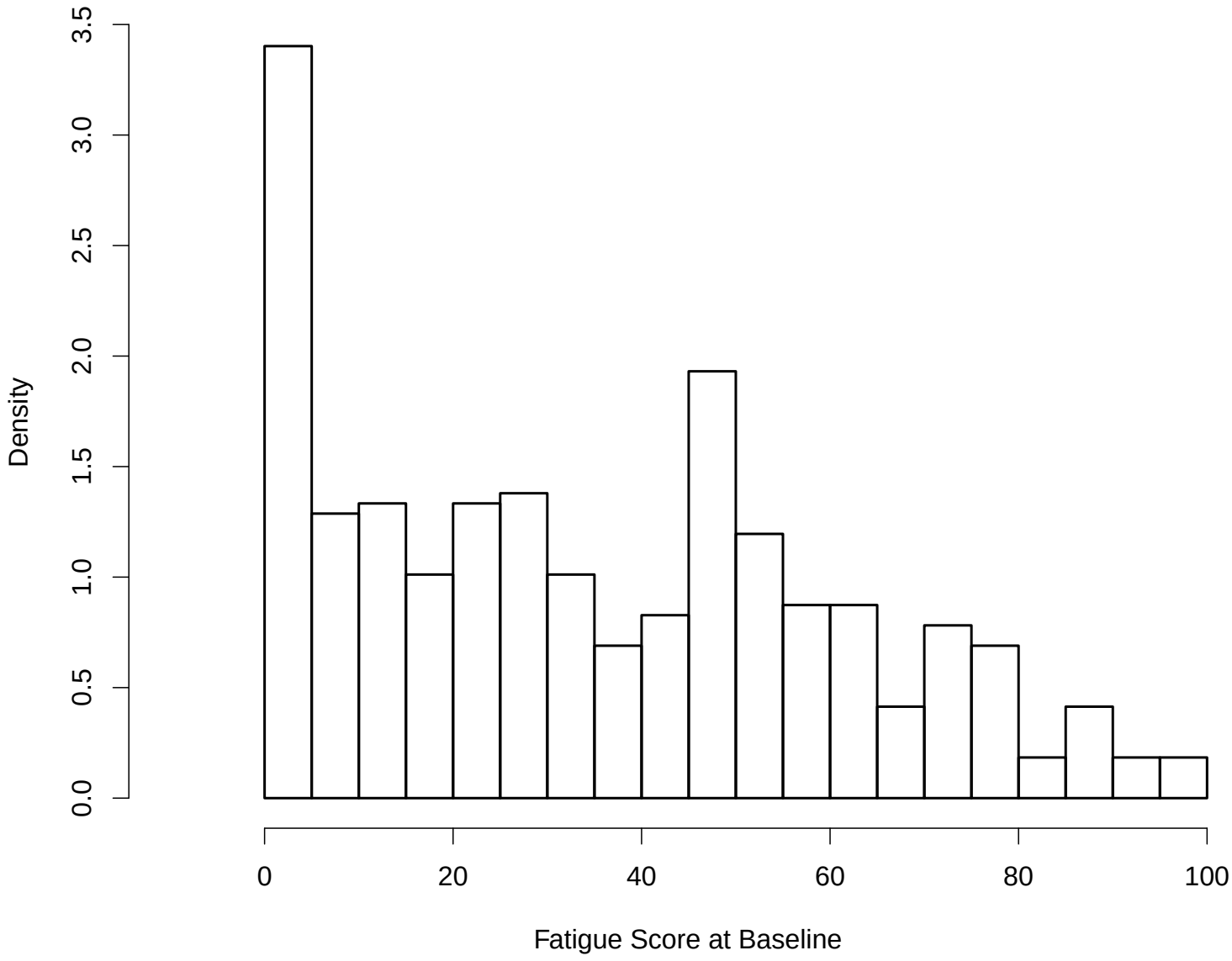
$\mathbf{X}_i(s)$ observed covariates

$U_i(s)$ unobserved (latent) processes

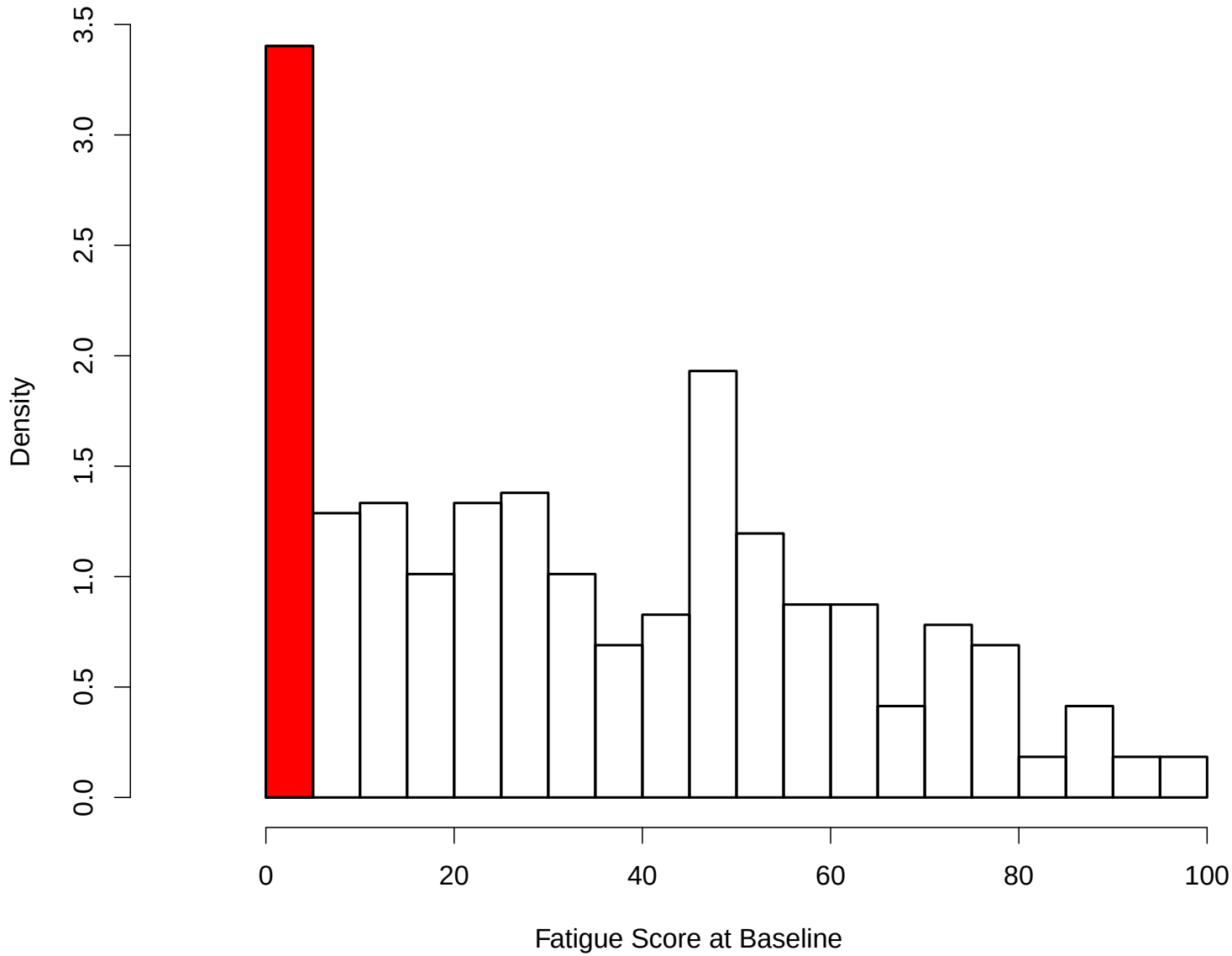
T_i event or censoring time

Next, a couple wrinkles:

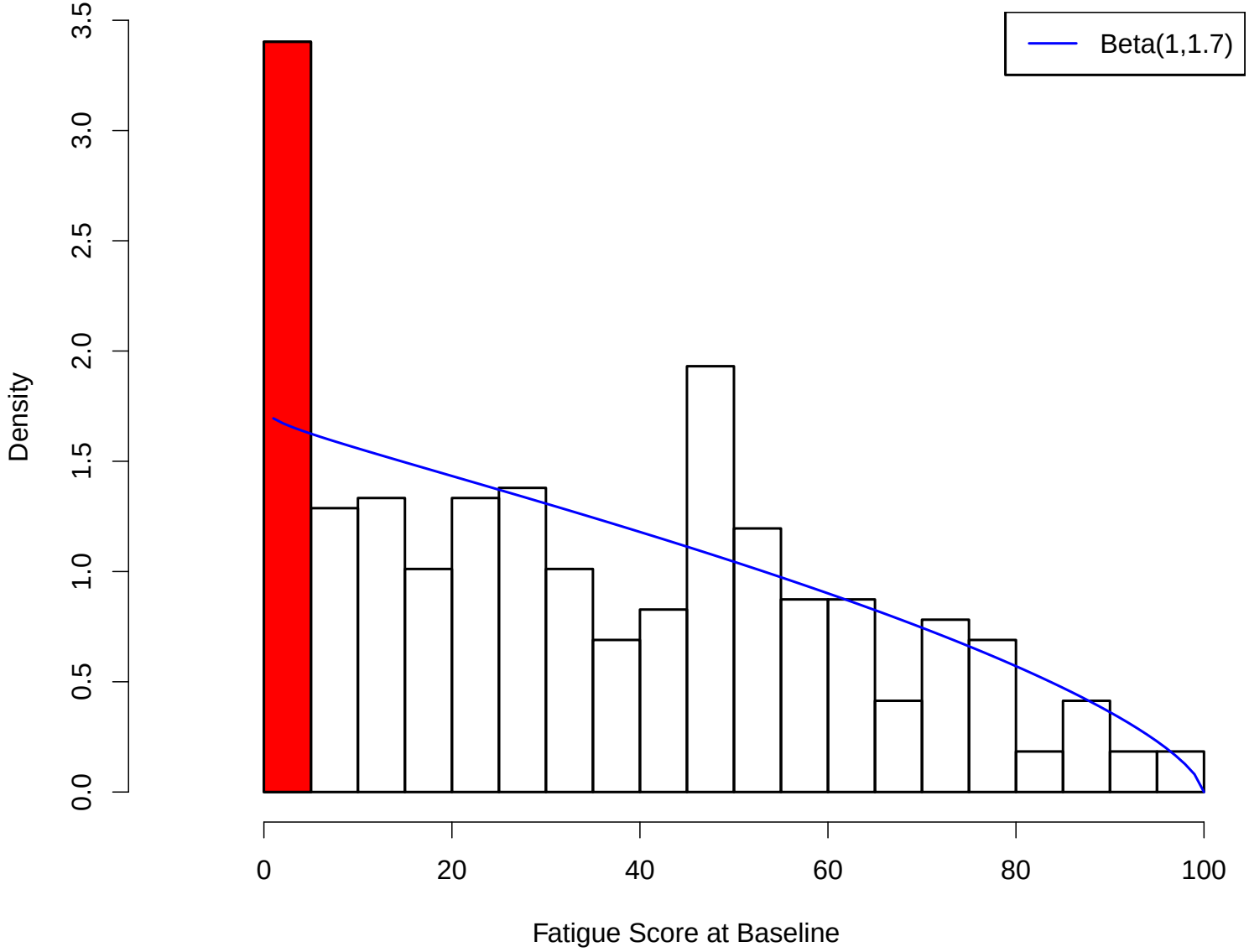
Excess Zeros in PROs



Excess Zeros in PROs



Excess Zeros in PROs



Longitudinal submodel

Break the longitudinal submodel into **two** submodels:
a presence submodel for $Pr[Y_i(s) > 0]$ and
a severity submodel for $E[Y_i(s)|Y_i(s) > 0]$.

Longitudinal submodel

Break the longitudinal submodel into **two** submodels:
a presence submodel for $Pr[Y_i(s) > 0]$ and
a severity submodel for $E[Y_i(s)|Y_i(s) > 0]$.

In the Literature

Count data ("Zero-inflation")

- Binomial (incl. copula joint model Rizopoulos et al. 2008)
- Poisson, etc.

Continuous data ("Spike and Slab Mixture")

- Probit/logistic + lognormal (e.g., Zhang et al. 2006)
- Logistic + beta (our work)

Longitudinal submodel

Zero-Augmented Beta (ZAB) Distribution

$$Y \sim ZAB(\omega, \mu, \phi), \;\; Y \in \{0\} \cup (0,1)$$

$$\omega = \text{ probability of } Y \in (0,1)$$

$$\mu = \text{ mean of } Y \in (0,1)$$

$$\phi = \text{ dispersion of } Y \in (0,1)$$

Longitudinal submodel

Zero-Augmented Beta (ZAB) Distribution

$$
\begin{aligned}
Y &\sim ZAB(\omega, \mu, \phi), \;\; Y \in \{0\} \cup (0,1) \\
\omega &= \text{ probability of } Y \in (0,1) \\
\mu &= \text{ mean of } Y \in (0,1) \\
\phi &= \text{ dispersion of } Y \in (0,1)
\end{aligned}
$$

- $Y \sim ZAB(\omega, \mu, \phi)$ corresponds to $Y = ZB$
- $Z \sim Bernoulli(\omega) \perp B \sim Beta(\mu\phi, (1-\mu)\phi)$
- $E(B) = \mu$, $Var(B) = \frac{\mu(1-\mu)}{\phi+1}$
- $E(Y) = \omega\mu$, $Var(Y) = \omega\mu\left[\frac{\phi\mu+1}{\phi+1} - \omega\mu\right]$

Survival submodel

We assume that the survival times come from a parametric distribution,

$$T_i \sim \mathit{Weibull}(\gamma, \lambda_i) \ ,$$

where λ_i is the **hazard** and γ is a **shape** parameter.

We build a regression model for λ_i that includes the effects of **covariates** and the **latent processes**.

Final joint model

$$
\begin{aligned}
Y_i(s) &\sim ZAB(\omega_i(s), \mu_i(s), \phi) \\
\text{logit}(\omega_i(s)) &= \mathbf{X}_{0i}(s)\boldsymbol{\beta}_0 + U_{0i}(s) \\
\text{logit}(\mu_i(s)) &= \mathbf{X}_{1i}(s)\boldsymbol{\beta}_1 + U_{1i}(s) \\
U_{0i}(s) &= u_{0i1} \\
U_{1i}(s) &= u_{1i1} + u_{1i2}s \\
T_i &\sim \text{Weibull}(\gamma, \lambda_i) \\
\log(\lambda_i) &= \mathbf{X}_{2i}\boldsymbol{\beta}_2 + \alpha_1 u_{0i1} + \alpha_2 u_{1i1} + \alpha_3 u_{1i2}
\end{aligned}
$$

- Intercepts only for probability trajectory: $U_{0i}(s)$
- Intercepts + slopes for severity trajectory: $U_{1i}(s)$
- Simple linear combination of latent effects links long'l and survival submodels

Clinical questions, revisited

How do model parameters address our three analysis goals?

Effects of Treatment

We estimate β_0, β_1, and β_2 for the effect of treatment on the presence of symptoms, severity of symptoms, and risk of progression/death, respectively.

Individual Patients

We estimate two latent trajectories for each patient, governed by intercepts u_{0i1} and u_{1i1} and slope u_{1i2}.

Relationship btw Symptoms & Survival

We estimate the link between latent symptom trajectories and survival, parameterized by α. The magnitude is not interpretable, but sign and non-zero matter.

Computing

BlackBox Component Builder and WBDev together comprise a Component Pascal development environment for implementing custom functions and distributions in WinBUGS

http://www.winbugs-development.org.uk/wbdev.html
http://www.oberon.ch/blackbox.html

Easy to implement using R2WinBUGS in R:

```
fit <- bugs(data=data,inits=init,
  model.file="mymodelfile.txt"',
  ...
  bugs.directory=R2WB$bugsdir,...)
```

Computing - WinBUGS Code

```
# Longitudinal Model
for (j in 1:NJ) {
  LCSS[j] ~ ZeroInflatedBeta(omega[j],mu[j],phi);
  # Probability of non-zero
  logit(omega[j]) <- inprod(beta0[1:8],X[j,1:8]) +
    ranef0[j];
  # Mean of non-zero
  logit(mu[j]) <- inprod(beta1[1:8],X[j,1:8]) +
    ranef1[j];
  # Individual trajectories
  ranef0[j] <- U[u[j],1];
  ranef1[j] <- U[u[j],2] + U[u[j],3]*X[j,5];
} # end of j loop
```

Computing - WinBUGS Code

```
# Survival Model
for (i in 1:N){
  log(lambda[i]) <- inprod(beta2[1:3],X2[i,1:3]) +
    inprod(alpha[1:3],U[i,1:3]);
  SURV[i] ~ dweib(gamma,lambda[i])I(SURV.lb[i],);
  # Subject-specific parameters
  U[i,1:3] ~ dmnorm(meen[],TauU[,]);
} # end of i loop
```

Computing - WinBUGS Code

```
# Priors
beta0[1:8] ~ dmnorm(betamu0[],Sigma0[,])
beta1[1:8] ~ dmnorm(betamu1[],Sigma1[,])
beta2[1:3] ~ dmnorm(betamu2[],Sigma2[,])
phi ~ dgamma(1,inv.scale)
inv.scale <-  1/phi.hat
gamma ~ dgamma(.1,.1)
for (i in 1:3){alpha[i] ~ dnorm(0,.01)}
TauU[1:3,1:3] ~ dwish(R[,],rho);
VarU[1:3,1:3] <- inverse(TauU[,]);
```

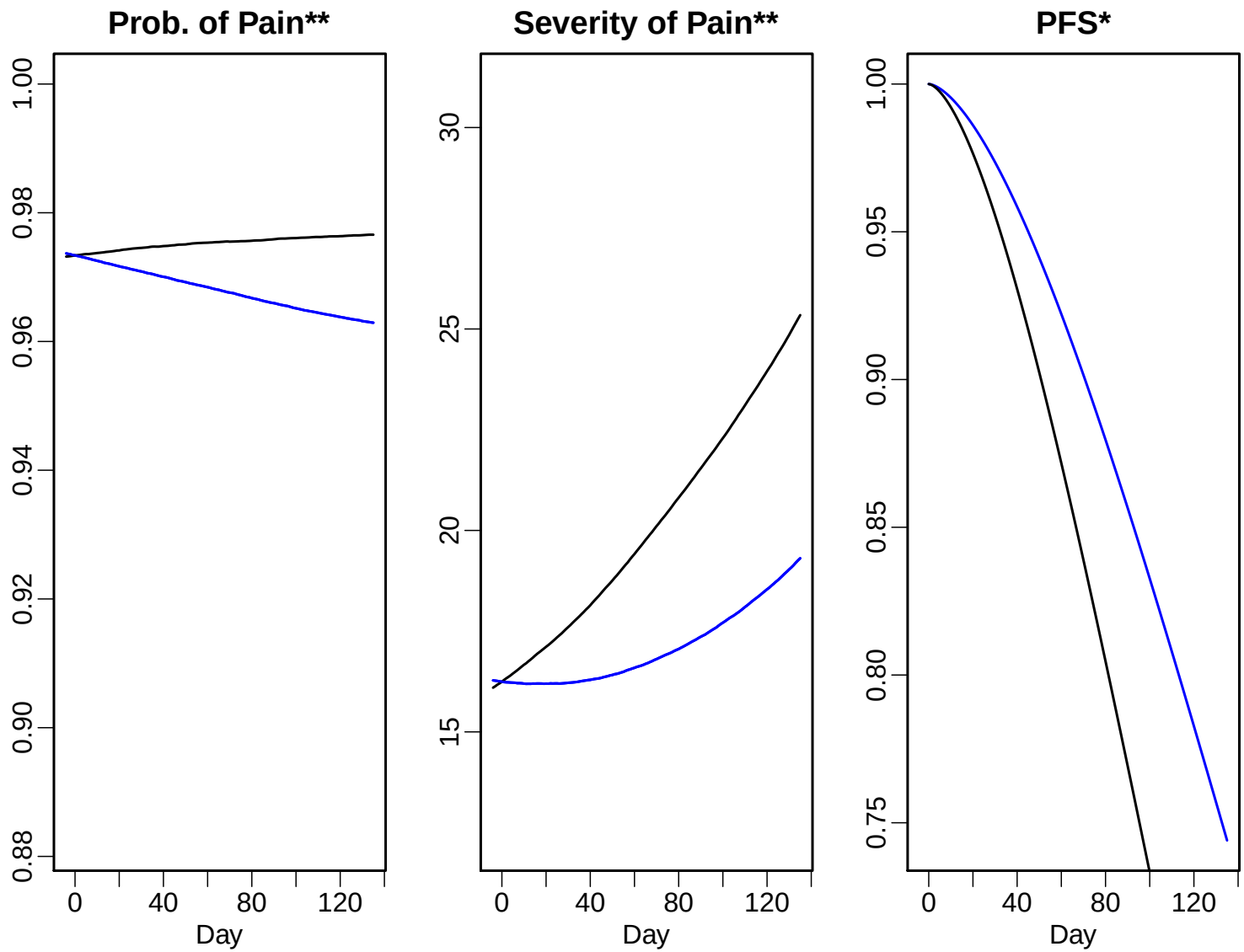
Computing - WBDev Code

```
PROCEDURE LogFullLikelihood
  (node: WBDevUnivariate.Node; OUT value: REAL);
VAR
  omega, alpha, beta, mu, phi, x: REAL;
BEGIN
  omega:=node.arguments[iomega][0].Value();
  mu:=node.arguments[imu][0].Value();
  phi:=node.arguments[iphi][0].Value();
  x := node.value;
  alpha := mu*phi;
  beta := (1-mu)*phi;
```

Computing - WBDev Code

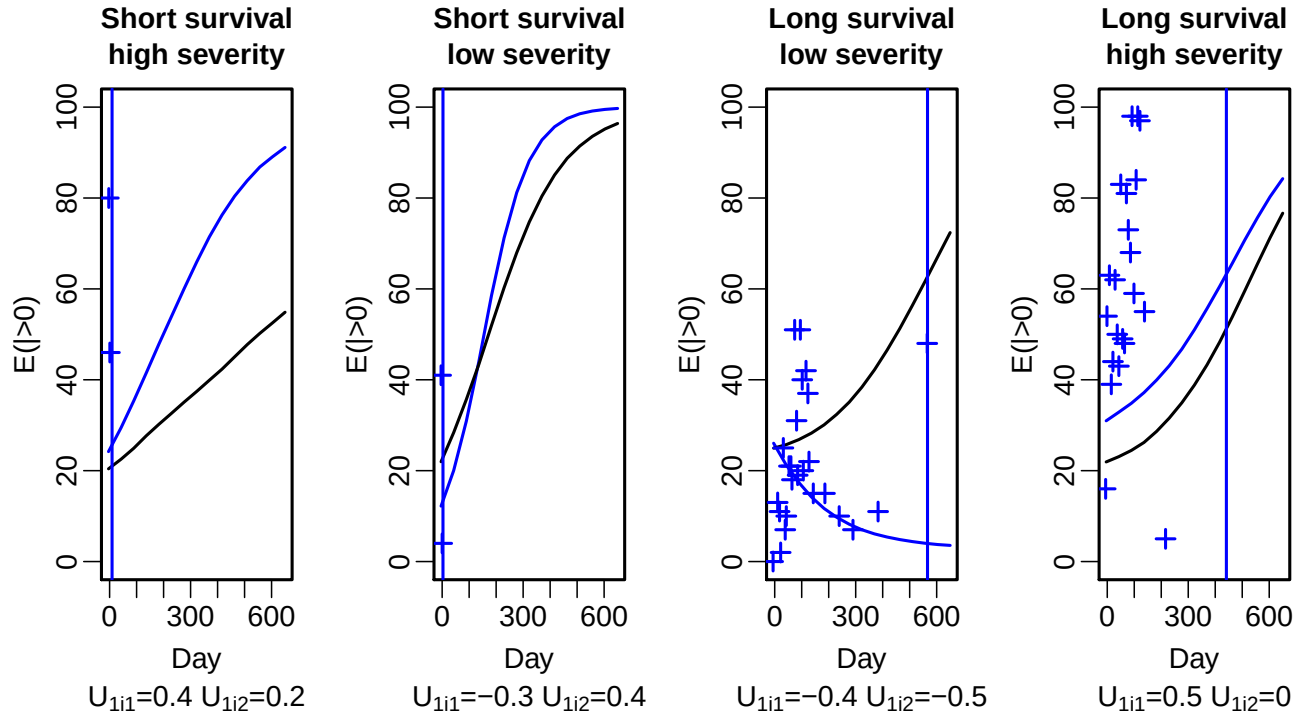
```
    IF x = 0 THEN;
      value := Math.Ln(1-omega);
    ELSIF x > 0 THEN ;
      value := Math.Ln(omega) +
      WBDevSpecfunc.LogGammaFunc(alpha+beta) -
      WBDevSpecfunc.LogGammaFunc(alpha) -
      WBDevSpecfunc.LogGammaFunc(beta) +
      (alpha-1)*Math.Ln(x) + (beta-1)*Math.Ln(1-x);
    END;
  END LogFullLikelihood;
```

Results: Treatment Effects



Fitted group trajectories for treatment (blue) and control (black)

Results: Individual Fitted (Severity) Trajectories



- Fitted individual-level (blue) and population-level (black)
- Vertical bar marks time of progression/death
- Crosses are PRO severity observations