# Hierarchical and Joint Longitudinal and Survival Modeling Using WinBUGS

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presented by

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## Joint Longitudinal and Survival Modeling

Many clinical trials generate both longitudinal (repeated measurement) and survival (time to event) data.

 $\mathbf{Ex:}\ \mbox{In AIDS clinical trials, one measures}$ 

- the number of CD4 cells per  $ml^3$  of blood (longitudinal)
- time until death or disease progression (survival)

The two are obviously correlated (low CD4 is prognostic of poor survival outcome)

Several approaches for *joint* modeling:

- Henderson, Diggle, and Dobson (2000): connect the longitudinal and survival processes with bivariate random effects following a latent bivariate Gaussian process.
- Wang and Taylor (2001): include the longitudinal marker as a time-dependent covariate in the (proportional hazards) survival model.
- Lin et al. (2002): employ a latent class model
  - logistic model for each subject's class membership
  - longitudinal and survival processes are independent given this membership (tho marginally dependent)

#### Longitudinal model

For data  $y_{i1}, y_{i2}, \ldots, y_{in_i}$  from the *i*th subject at times  $s_{i1}, s_{i2}, \ldots, s_{i,n_i}$ , let

$$y_{ij} = \mu_i(s_{ij}) + W_{1i}(s_{ij}) + \epsilon_{ij} ,$$
 (1)

where

- $\mu_i(s) = \mathbf{x}_{1i}^T(s) \boldsymbol{\beta}_1$  is the mean response
- $W_{1i}(s) = \mathbf{d}_{1i}^T(s)\mathbf{U}_i$  incorporates subject-specific random effects (adjusting the main trajectory for any subject)
- $\epsilon_{ij} \sim N(0, \sigma_{\epsilon}^2)$  is a sequence of mutually independent measurement errors.

Typically we assume the random effects are distributed as

$$\mathbf{U}_i \stackrel{iid}{\sim} N(\mathbf{0}, \mathbf{\Sigma})$$

- dates at least to Laird and Ware (1982)
- There are some identifiability issues with  $\sigma_{\epsilon}^2$  and  $\Sigma$  (can't choose "flat" priors for both)
- Often called "mixed" models, since contain both fixed (β<sub>1</sub>) and random (U<sub>i</sub>) effects – SAS Proc MIXED, which does ML/REML and some EB fitting
- Full Bayes-MCMC fitting straightforward in WinBUGS

#### Survival model

Both parametric and nonparametric (Cox) possibilities...

For the former, typically a Weibull or gamma model is assumed, e.g.

$$t_i \sim \mathsf{Weibull}\left(p, \mu_i(t)
ight)$$
 ,

where  $t_i$  is time to event for subject i, p > 0, and

$$\log(\mu_i(t)) = \mathbf{x}_{2i}^T(t)\boldsymbol{\beta}_2 + W_{2i}(t) \ .$$

Here,

- β<sub>2</sub> are the fixed effects corresponding to the (possibly timedependent) explanatory variables x<sub>2i</sub>(t) (which may have elements in common with x<sub>1i</sub>)
- W<sub>2i</sub>(t) is similar to W<sub>1i</sub>(s), including subject-specific covariate effects and an intercept (often called a *frailty*). The event intensity (or *hazard*) at time t is given as

$$\lambda_i(t) = pt^{p-1}\mu_i(t) = pt^{p-1}\exp\left(\mathbf{x}_{2i}^T(t)\boldsymbol{\beta}_2 + W_{2i}(t)\right) , \quad (2)$$

which is monotone in t (decreasing if p < 1, increasing if p > 1) and reduces to the exponential (constant in t) hazard if p = 1.

• Fittable in either SAS (Proc LIFEREG) or WinBUGS

#### Joint model

Link the two models by specifying latent zero-mean bivariate Gaussian process for  $(W_{1i}, W_{2i})^T$ , independent across subjects:

$$W_{1i}(s) = U_{1i} + U_{2i} s, \text{ and}$$
(3)  
$$W_{2i}(t) = \gamma_1 U_{1i} + \gamma_2 U_{2i} + \gamma_3 (U_{1i} + U_{2i} t) + U_{3i}.$$
(4)

- the longitudinal model (3) need not be linear in s
- γ<sub>1</sub>, γ<sub>2</sub>, and γ<sub>3</sub> in the survival model (4) measure the asso- ciation between the two submodels induced by the random intercepts, slopes, and fitted longitudinal value at the event time W<sub>1i</sub>(t), respectively.
- as before we let

$$(U_{1i}, U_{2i})^T \stackrel{iid}{\sim} N(\mathbf{0}, \boldsymbol{\Sigma})$$

while the  $U_{3i}$  are independent frailty terms, i.e., modeled as

$$U_{3i} \stackrel{iid}{\sim} N(0, \sigma_3^2),$$

independent of the  $(U_{1i}, U_{2i})^T$ .

• Fittable in SAS (Proc NLMIXED) or WinBUGS

## Application to ddI/ddC data

- Trial randomized m = 467 eligible HIV-infected patients to receive either didanosine (ddl) or zalcitabine (ddC).
- Data collected: times to death, and CD4 counts at study entry, and again at the 2, 6, 12, and 18 month visits (so that n<sub>i</sub> ≤ 5).
- Boxplots of the CD4 counts over time (Figures 1(a) and (b)) show a high degree of skewness toward high CD4 counts, suggesting a square root transformation.
- Sample sizes at the five time points: (230, 182, 153, 102, 22) for the ddl group and (236, 186, 157, 123, 14) for the ddC group → sharply increasing degree of missing data over time due to deaths, dropouts, and missed clinic visits
- Empirical survival curves (Kaplan-Meier estimates; Figure 1(c)) are very similar during the first six months after randomization. Afterwards, survival in the ddC group is somewhat higher than that in the ddl group through the 18-month visit.







Figure 1: Exploratory plots of longitudinal data and survival data for the ddI/ddc trial.

(c) Survival rates

#### SAS Proc NLMIXED code:

```
title1 'Two Random Effects Joint Model with u1+u2*t term - NLMIXED';
proc nlmixed data=alldata;
    parameters bl0= 8.01 bl1=-0.167 bl2=0.0299 bl3=-0.158
               bl4=-2.31 bl5=-0.131
               a11= 2.0 a12= 0
                                a22=0.4
               bs0= 4.02 bs1=-0.267 bs2=0.14 bs3=-0.77
               bs4=-0.08 r1 = 0.207 r2 =2.51 r3=0;
    if (last) then do;
      linpsurv = bs0 + bs1*randgrp1 + bs2*gender1 + bs3*prevoi1 +
                        bs4*stratum1 + r1*u1 + r2*u2 + r3*(u1+u2*t2death);
      alpha = exp(-linpsurv);
     G_t
          = exp(-alpha*t2death);
     g
            = alpha*G_t;
      llsurv = (death=1)*log(g) + (death=0)*log(G_t);
    end; else llsurv=0;
    v11 = a11*a11;
    v12 = a11*a12;
    v22 = a12*a12 + a22*a22;
                             + (bl1 + u2)*obstime
    linplong = (bl0 + u1)
                                                             +
                bl2*obstime*randgrp1 + bl3*gender1
                                                             +
                                   + bl5*stratum1;
                bl4*prevoi1
    resid = (cd4-linplong);
    if (abs(resid) > 1.3E100) or (s2 < 1e-12) then do;
      111 ong = -1e20;
    end; else do;
       111 \text{ ong} = -0.5*(1.837876 + \text{resid}**2 / s2 + \log(s2));
    end;
    model last ~ general(lllong + llsurv);
    random u1 u2 ~ normal([0, 0],[v11,v12,v22]) subject=patient;
run;
title1;
```

## WinBUGS code:

```
# WinBUGS 1.4 code for joint time-varying model (Model XII in Guo and Carlin paper)
# Written by Xu Guo, 6/26/03
model{
for (i in 1:N) {
    for (j in 1:M) {
       Y[i, j] ~ dnorm(muy[i, j], tauz)
       muy[i, j]<-beta1[1]+beta1[2]*t[j]+beta1[3]*t[j]*randgrp1[i]+</pre>
         beta1[4]*gender1[i]+beta1[5]*prevoi1[i]+beta1[6]*stratum1[i]+U[i,1]+U[i,2]*t[j]
    }
    surt[i] ~ dweib(1,mut[i]) I(surt.cen[i],)
    log(mut[i])<-beta2[1]+beta2[2]*randgrp1[i]+beta2[3]*gender1[i]+</pre>
      beta2[4]*prevoi1[i]+beta2[5]*stratum1[i]+r1*U[i, 1]+r2*U[i, 2]+r3*(U[i,1]+U[i,2]*tee[i])
    U[i,1:2] ~ dmnorm(U0[],tau[,])
   }
tau[1:2,1:2] ~ dwish(R[,], 23)
beta1[1:6] ~dmnorm(betamu1[],Sigma1[,])
tauz~dgamma(0.1, 0.1)
beta2[1:5]~dmnorm(betamu2[],Sigma2[,])
r1<sup>~</sup>dnorm(0, 0.01)
r2<sup>~</sup>dnorm(0, 0.01)
r3<sup>~</sup>dnorm(0,0.01)
}
```

model	$W_1(s)$	$W_2(t)$	$\overline{D}$	$p_D$	DIC <sub>total</sub>
no random effects					
Ι	0	0	9565.5	8.53	9574.0
II	0	$U_3$	9561.1	15.60	9576.7
random intercepts					
III	$U_1$	0	7261.2	429.5	7690.7
IV	$U_1$	$U_3$	7256.3	435.6	7691.9
V	$U_1$	$\gamma_1 U_1$	7222.5	425.8	7648.3
VI	$U_1$	$\gamma_1 U_1 + U_3$	7223.1	433.2	7656.2
random intercepts					
and random slopes					
VII	$U_1 + U_2 s$	0	6866.6	731.9	7598.5
VIII	$U_1 + U_2 s$	$\gamma_1 U_1$	6839.5	728.9	7568.4
IX	$U_1 + U_2 s$	$\gamma_2 U_2$	6859.3	736.4	7595.6
Х	$U_1 + U_2 s$	$\gamma(U_1+U_2)$	6838.6	728.9	7567.4
XI	$U_1 + U_2 s$	$\gamma_1 U_1 + \gamma_2 U_2$	6803.8	744.5	7548.3
XII	$U_1 + U_2 s$	$\gamma_1 U_1 + \gamma_2 U_2 + \gamma_3 W_1(t)$	6959.1	666.1	7625.2

- extra frailty term  $(U_3)$  is not worth it
- Model XI (with random intercepts and slopes and two different association parameters) is best
- Model XII (adds time-varying component  $W_1(t)$  to the survival model) is not worth it: higher DIC, and  $\gamma_3$  is insignificant (95% posterior credible interval (-0.43, .26)).

Consistent with earlier finding: exponential model (time-constant baseline hazard) is adequate for this very ill population.

#### Comparison of separate and joint models

- In both cases, in the longitudinal submodel only *Time* and *PrevOI* are "Bayesianly significant" at level 0.05, while only *PrevOI* is significant in the survival submodel.
- Posterior estimates of the association parameters in the joint analysis are negative and significantly different from zero → strong evidence of association between the two submodels, and both the initial level and slope of CD4 count is negatively associated with the hazard of death.
- Figure 2 plots the estimated posterior density of the median survival time of this hypothetical male patient who is AIDS-negative at study entry and intolerant of AZT. In both the separate (panel a) and joint (panel b) analyses, this patient's survival is clearly better if he receives ddC instead of ddl. However, the joint analysis increases the estimated median survival times by roughly 50% in both groups.



Figure 2: Median survival time for a hypothetical patient (male, negative AIDS diagnosis at study entry, intolerant of AZT): (a) estimated posterior density of median survival time of the patient from separate analysis; (b) estimated posterior density of median survival time of the patient from joint analysis.

#### Comparison of separate and joint models (cont'd)

Figure 3 compares the estimated posterior median survival time distributions for two hypothetical patients:

- 1. Patient 450: ddl group, male, AIDS positive at baseline, previously failed AZT (poor prognosis)
- 2. Patient 454: ddl group, male, AIDS negative at baseline, intolerant of AZT (better prognosis)

Both were still alive at the end of the study, censored at days 571 and 591, respectively. Figures 3(b) and (c) compare the posterior median survival time distributions of the joint model with two separate models (with and without frailty terms  $U_3$ )

- Again, no need to include  $U_3$ ; separate analysis curves are virtually identical
- Joint and separate results differ much more markedly than in Figure 2, significantly increasing the survival time for Patient 450, and decreasing it for Patient 454.
- Joint model also *reverses* the separate conclusion: Patient 450, with the "good" CD4 trajectory but "bad" covariates (AIDS positive, AZT failure) now predicted to survive much longer (and vice-versa for Patient 454)!



Figure 3: Observed data and estimated posteriors of median survival time for two patients, ddI/ddC study: a) observed longitudinal data for Patients 450 and 454; b) estimated posterior densities for Patient 450; c) estimated posterior densities for Patient 454.

## Comparison with SAS Proc NLMIXED

- Estimation of the random effects is via empirical Bayes, with associated standard errors obtained by the delta method. Approximate 95% prediction intervals can then be obtained by assuming asymptotic normality.
- For the median survival times of Patients 450 and 454, under Model XI we obtained point estimates of roughly 72.3 and 22.4, respectively, in rough agreement with Figure 3.
- However, the asymmetry of the posteriors in this figure (which are similar to the likelihood, due to our vague priors) suggests traditional confidence intervals based on asymptotic normality and approximate standard errors will not be very accurate.
- Exact results (and corresponding full posterior inference) as available from Figures 3 and 2 still require the fully Bayesian-MCMC (WinBUGS) approach.

Thus the joint Bayesian approach appears to offer significantly improved and enhanced estimation of median survival times and other parameters of interest, as well as simpler coding and comparable runtimes!

## Discussion

- $\star$  Bayesian approach seems both simpler *and* easier here!
- \* Extension to semiparametric (i.e. Cox) survival models is not so obvious in WinBUGS: fittable via counting process approach (the "Luek" example), but connection to the longitudinal frailties requires some thought.
- \* DIC is a convenient model choice tool here (already standard in WinBUGS) and properly accounts for shrinkage of parameters in the hierarchical model. BUT
  - 1. just a "score"; differences in DIC can not be compared to a chi square table
  - 2. Monte Carlo variability in DIC not easy to estimate (delta method approximation is poor); just replicate a few times?
  - see discussion of Spiegelhalter et al. (2002, JRSS-B) or recent work of Celeux et al. (2006, Bayesian Analysis) for alternate, perhaps more robust definitions of DIC.

For more info and references:

http://www.biostat.umn.edu/~brad/