Establishing a Predictive Survival Model for Patients with Leukemia Adjusting for the Random Effect of Pre Leukemia

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EXTENDED ABSTRACT

Myelodysplastic syndrome (MDS), sometimes referred to as pre-leukemia or smoldering leukemia, is a group of diseases usually characterized by failure of the bone marrow to produce enough normal blood cells. In about one-third of patients, the disease transforms into acute leukemia. In high-risk MDS, the bone marrow contains too many immature blood cells known as blasts. Patients with high-risk MDS survive for an average of six to 12 months. We have taken data from a large clinical trial and re-examined it considering the pre-leukemia as a random event in a Weibull distribution model. We have taken the intercept, stress effect and shape parameter of the distribution to be random effects as well with realistic prior distributions based on previous shapes of the survival experience of subjects with this disease. We demonstrate how the model performs under relevant clinical conditions. The conditions are all tested using a Bayesian statistical approach allowing for the robust testing of the model parameters under various stress conditions which we introduce into the model. The convergence of the parameters to stable values are seen in trace plots which follow the convergence patterns This allows for precise estimation for determining clinical conditions under which the survival pattern will change. We give a numerical example of our results.

The major platform for the theoretical development follows the Bayesian methodology and the multiple parameter Weibull model with random effects having carefully chosen hyper parameters. Wew have done the basic infrastructure for the analysis using the commercially available WinBugs software employing the Markov Chain Monte Carlo (MCMC) methodology. The BUGS language allows a concise expression of the model to denote stochastic (probabilistic) relationships and to denote deterministic(logical) relationships. The stochastic parameters , however specified, may be given proper but minimally informative prior distributions, while the logical expression for the variance in the model allows the standard deviation (of the random effects distribution) to be estimated. Fixed effect model approaches are also handled rather well with the software. As seen in the WinBugs manual by Spiegelhalter et. al (2003) also at www.mrc.bsu.cam.ac.uk/bugs/winbugs/manual14.pdf, the WinBUGS software uses compound documents, which comprise various different types of information (formatted text, tables, formulae, plots, graphs, etc.) displayed in a single window and stored in a single file for application to the problem at hand. This manual describes the WinBugs software, an interactive Windows version of the BUGS program for Bayesian analysis of complex statistical models using MCMC techniques. We have been careful to apply only the models that WinBugs handles thus avoiding possibly spurious results with untested models as one is so warned.

INTRODUCTION

High speed computations with user friendly software has facilitated ease in the computations of complex models. This has been the case with Bayesian solutions to problems involving cumbersome analytic calculations in the prior to posterior framework which are often stalled at some point as closed form analytic solutions do not exist. Thus numeric solutions are called for. This is especially the case in introducing several parameters with random effects having their own hierarchical modeling pattern as is seen in Gelman et al (2004). One makes use of this capability in the present application to a random effects model in a clinical setting. We now describe the clinical setting for our approach. A randomized clinical trial was undertaken to compare the therapeutic effectiveness of two regimens in acute myelogenous leukemic (AML) patients. See Vogler et al (1992). From December 1985 to January 1989, 230 patients were registered from 16 institutions in the multi center trial. The survival for all patients who were assessable for evaluation on the two treatment arms was compared. There was no statistically significant difference between the groups. The entire sample was considered as homogeneous and one pursues the question as to whether one can model the overall survival taking into account the Myelodysplastic syndrome (MDS). This is sometimes referred to as pre-leukemia or smoldering leukemia, and is a group of diseases usually characterized by failure of the bone marrow to produce enough normal blood cells. One is especially interested in determining how this variable and its history impacts on predicted survival once one takes into account the stress of the actual onset white blood count (WBC) at the start of the medical intervention. In addition the Pre leukemia or MDS is incorporated as a random effect in the model. In our case it will range from 1 (mild syndrome) to 5 (severe syndrome). The Weibull reliability model of Meeker and Escobar (1998) and the random effects approach of Ashby et al (2003) are considered. Ashby et al (2003) have also listed a Web guide to the WinBugs computational approach to this challenge at stat.bus.utk.edu/techrpts/2003/2003-01.pdf.

THE MODEL

In the past the MDS was considered a fixed effect in the survival model as seen in Vogler et al (1992). The MDS is assumed as a random effect for our purposes. We will show how it, as well as other clinical parameters, fit into the model. The model cumulative distribution function (CDF) is

$$F(t)=1-\exp[-(t/\eta)^{\beta}] \text{ , } t>=0, \beta>0 \text{ and } \eta>0, \quad (1)$$

where

$$\log(\eta)=\beta_0 + \beta_1\log(s) + \varphi_k \text{ , } k=1,..5.$$

$$\varphi_k \sim \text{Normal}(0, 1/\sigma^2), k=1,...,5.$$

In equation (1) t is the survival time in months, s is the stress or white cell count and φ_k is the random MDS effect with k=1 to 5 as the five levels of severity. In this case the vague priors by Ashby et al (2003) will suffice for this purpose, except for a slight modification of the hyper shape parameter of the sample shape parameter, β. They are:

$$\beta_0 \sim \text{Normal}(0,0.001), \quad \beta_1 \sim \text{Normal}(0,0.001)$$

$$\beta \sim \text{Gamma}(1,0.3) \text{ and} \quad (2)$$

$$\tau=(1/\sigma^2) \sim \text{Gamma}(0.001,0.001).$$

Our goal will be to apply this model with parameter estimates to our data and then to model the predicted survival based on various stress or onset WBC considerations.
Some sensitivity was applied to test the robustness of these priors especially for the variance parameters of the Gamma and normal from 0.001 to 0.01, but is not presented here.

THE DATA

As mentioned above, we have a sample from 230 AML patients upon which to build our model. The primary endpoint was survival with fixed effect variable onset WBC and random effect MDS for each subject. The objectives of the study were (1) to compare the efficacy and toxicity of two treatments and to make comparisons of survival and remission or

response induction in previously untreated AML. The focus is on the survival question. Previously untreated patients older than 14 years with diagnoses AML were eligible. The diagnosis was confirmed by morphology and
histochemic stains and reviewed by one of the investigators. Patients were required to have a normal cardiac ejection fraction as
determined by the normal value at each of the 17 participating institutions or medical centers in the United States. The randomization plan was generated prospectively and was restricted to incorporate stratification parameters including age and performance status which is an abbreviated activity of daily living scale. The overall survival comparison of the two therapies yielded a p-value of 0.5342. Thus by traditional statistical standards treatment had no effect on the survival comparisons. The data is thus pooled with a median survival of about 9.5 months and a range of 0.03 months to 67.75 months. The onset WBC median was 8400 with a range of 1100 to 424,200. We want to proceed with building a predicted survival model based on the Weibull model in (1) to determine how stress or onset WBC effects the survival duration for subjects with this disease.

BUILDING THE MODEL

Based on our data set described above,
we now detail applying the WinBugs software to solving for equation (1) with standard graphics and summary statistics.
Two chains of initial values were incorporated into the data to attempt the conversion to the four estimates in our model. The names in parentheses are the names of the variables in the WinBugs program for ease of interpretation and differentiation from each other when we examine the output and present graphical results. For the first chain we had β_0 (intercept)=18.1, β_1 (beta.stress)=-23.1, β (r=shape)=1.21 and τ (taub)= 1.0. For the second chain we had a simpler set of initial estimates set at β_0 (intercept)=15, β_1 (beta.stress)=-1.0, β (r=shape)=1.0 and τ (taub)= 1.0. The trace plots which map the conversion through the iterations give the pattern for both sets of starting values for each chain. The intercept trace is seen in Figure 1

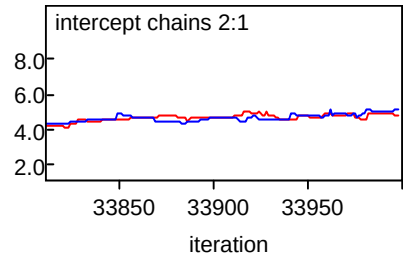

Figure1. Trace plot for the intercept .

Note the conversion at about 34000 iterations (not seen very well at the end of the plot). Figures 2 to 4 below give similar results for the beta.stress, r and taub variables.

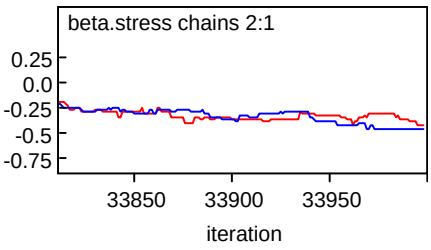

Figure 2. Trace plot for beta.stress

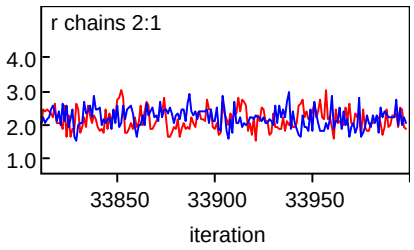

Figure 3. Trace plot for r (shape parameter)

Note that for the next, parameter in Figure 4, the taub parameter, yields what appears to be a very close correspondence of the two chains in their convergence patterns. This is due primarily to the scale of the plot. Also as with the shape parameter above the two chains were able to follow a very close convergence. It appears that all the parameters were fairly stable in the iteration process.

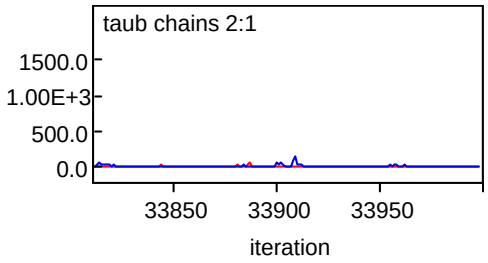

Figure 4. Trace plot for τ (taub)

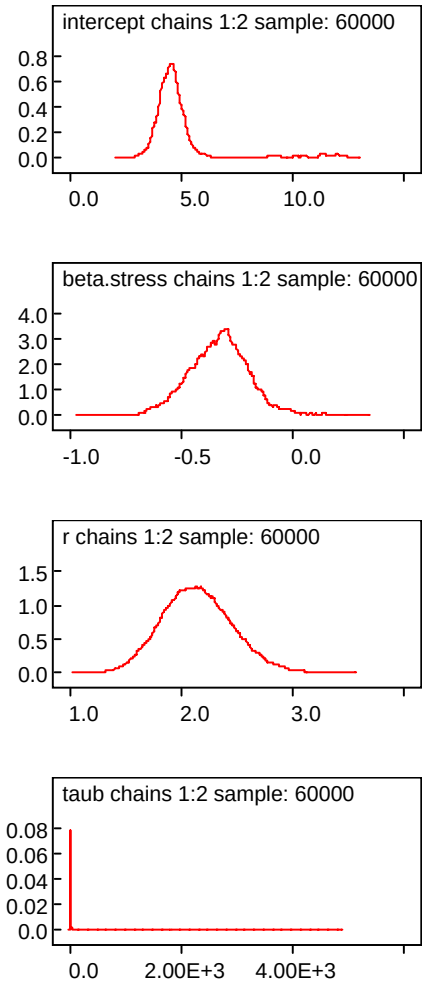

Figure 5. Densities for intercept, beta.stress, r and taub.

One can see from Figure 5 that the parameter densities are given for 60000 simulated samples. The actual mean parameter values with their confidence limits (CL) are seen in Table 1.

Parameter	Mean	95% CL
Intercept	5.001	3.49, 11.52
beta.stress	-0.3285	-0.61, -0.05
r (shape)	2.148	1.57, 2.81
taub	12.94	0.014, 46.98

Table 1. Parameters and 95% confidence limits

Note in Table 1 that these values pretty much approximate the modes of the parameter densities in Figure 5. Also note the width of the confidence limit for taub or the parameter, τ, in equation 1 indicating a good amount of variation in the random component, MDS, in this investigation.

THE PREDICTIVE MODEL

The task now is to take the parameter estimates from Table 1 and insert them into the model of equation (1) to determine the survival prediction at various values of stress. We will also examine how the median of the predictive survival varies for differing values of the stress or onset WBC. This is seen in the next Table 2.

Quantile or Mode of Stress	Stress or WBC Count	Median Survival (Months)
Mode	1100	12.65
0.25	2500	9.65
0.50	8400	6.50

Table 2. Association of stress with survival in the random effects model.

One thus sees from Table 2 the consistency of the association between the stress and median survival. As one increases the stress or WBC, which generally is a reasonable prognosis for survival, then we see the decreasing median survival in the

sample from the random effects model. In the actual data set the correlation of WBC with survival was -0.1171, p=0.079. If one ignores the stress factor then the Weibull model here yields a predicted median survival of 10.25 months, which is close to the actual empirical median of 9.5 months. The actual predictive survival curves for a stress of 8400 and 1100 are seen in Figures 6 and 7.

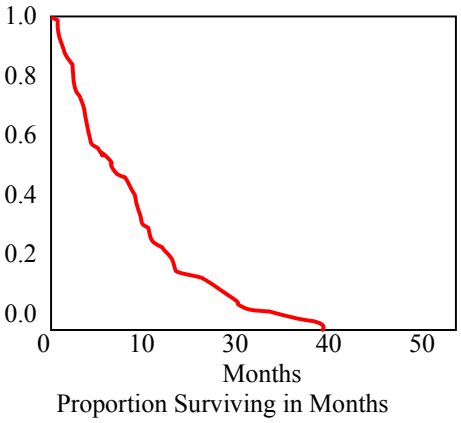

Figure 6. Predicted survival for stress factor =8400. Median=6.5 months.

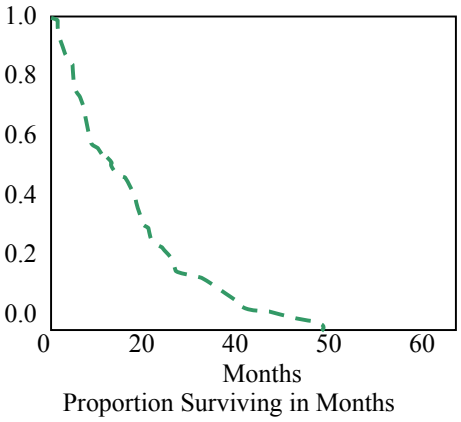

Figure 7. Predicted survival for stress factor =1100. Median=12.65 months.

CONCLUSIONS

We have attempted to show that one can assume an underlying random effects model with a parametric distribution such as the Weibull and apply this methodology in a clinical or biological setting. We really set out to do this with the added caveat that assuming vague prior information one can then further extend the methodologic application to the Bayesian framework. Thus there is a lot to consider when attempting this approach. The data comes from an actual database. That's a given. The next step was to assume a reasonable model for the data. The Weibull fits many time to event or lifetime data applications. The parametric estimation using the random effects was enhanced by the available software, WinBugs, which is specific to Bayesian applications and easy to handle in the random effects environment since random effects automatically assumes some underlying probability distribution. Thus this fits naturally into the Bayesian mindset. Also one is not overly committed to assigning subjective priors which some may consider as unrealistic as we were cautious to place rather largely dispersed vague priors on the parameters of interest. The WinBugs software allows one to break away from the temptation of assigning just normal models to parameters of interest as the use of other distributions such as the Gamma in our case can be easily applied as well. 0ne also has the flexibility of simulating results as one is likely to do in a numerical environment.
Being provided with visuals of the convergence patterns and the underlying density structure of the parameters of interests allows one to logically determine if the convergence is following a logical pattern and not deviating wildly as one goes through the iterations. Having to conduct this exercise for different initial values or chains in our case is yet a further enhancement of the tools available and another check on the consistency of the functional patterns of the variables over the iterative domain.

We note our results were consistent with the science in that when accounting for the randomness of the MDS the stress or onset WBC is inversely related to survival prognosis in this group of subjects. After having done all this analysis one wants to be

assured that outcomes are consistent with common knowledge of the discipline one is involved in.

A word on the ease of the use of this software may be in order. One has to know the underlying model one would attempt in the analysis, provide the data and then the initial values for the parameters of interest. That is all that is required. However, not to be lulled into a false sense of security, it is wise with larger data sets to take a random sample of the observations as a split test sample and check for the consistency of that result with the remainder of the data set. Jackknifing and bootstrapping samples are also suggested as well. We in fact took a subset of our data here to check for its consistency with not only the previous analysis in 1992 but with our current analysis as well. Also one should do a sensitivity analysis for logical ranges of the hyper parameters in the Bayesian model to check for the robustness of the results. Although it was done on a limited basis here, it was done throughout the course of this analysis. We hope that the reader(s) find these last few words of recommendation helpful and we look forward to applying more complex Bayesian models to past and future biological and environmental problems of interest.

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