Stats 756 - Assignment 1

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Question 1:

Adaptive clinical trials are clinical trials that can be modified during operation based on incoming results. Some examples of adaptations are adaptive randomization, sample size reassessment, dropping doses, dropping treatments, early stopping, and more. It is important that the adaptations are predefined, approved, and documented before the trial begins to avoid ad hoc changes that are biased to a particular conclusion. The main benefits of adaptive clinical trials are efficiency of time, efficiency of resources, maximization of beneficial treatments, and minimization of harmful treatments. This can greatly reduce the time and effort required to approve beneficial treatments to market and can reduce the burden subjects must endure. One downside of adaptive clinical trials is the weakening of conclusions. Clearly, if there are too many or too significant adaptations, the evidence might not even relate to the original hypothesis. Thus, it is important to make clear what exactly can be inferred given the adaptations. This can also make adaptive trials more complex. Furthermore, preliminary results might be misleading so it can be detrimental to adapt a trial prematurely based on signals that will level off in time.

Question 2:

The main disadvantage of early stopping of an experiment is it weakens its conclusions. For example, adverse effects that arise many years after a treatment might not be detected due to early stopping. Moreover, promising treatments at the beginning of a study might level off or degrade with respect to the other treatments or controls by the end of the study. As such, prematurely switching subjects to an ostentatious treatment can be quite nefarious. Early stopping might also lead to erroneous estimates of the treatment effect due to fluctuating sample sizes. One major advantage of early stopping is the efficient use of resources, namely, time and money. Another advantage of early stopping is switching subjects to a successful treatment or away from a detrimental treatment i.e., maximize subject benefit and minimize subject burden. However, the decision to make such switches is delicate. In the extremes, it is clear that the option to switch subjects on or off a treatment is warranted, i.e. if the treatment has obvious and immediate positive/negative effects it is warranted to switch subjects on/off the treatment. In practice, one needs to critically evaluate the evidence with respect to a cost benefit rubric that has undergone ethical analysis.

Question 3:

Given

	Illness State		
Test Result	Yes	No	Total
Positive	154 (TP)	584 (FP)	738 (t_3)
Negative	18 (FN)	2108 (TN)	2126 (t_4)
Total	172 (t_1)	2692 (t_2)	2864 (t)

we calculate the following measures:

Exact prevalence $= \frac{t_1}{t} = \frac{172}{2864} \approx 0.06$

Sensitivity $= \frac{TP}{t_1} = \frac{154}{172} \approx 0.90$

False Negative Rate $= \frac{FN}{t_1} = \frac{18}{172} \approx 0.10$

Specificity $= \frac{TN}{t_2} = \frac{2108}{2692} \approx 0.78$

False Positive Rate $= \frac{FP}{t_2} = \frac{584}{2692} \approx 0.22$

Probability of Positive Test $= \frac{t_3}{t} = \frac{738}{2864} \approx 0.26$

Probability of Negative Test $= \frac{t_4}{t} = \frac{2126}{2864} \approx 0.74$

Positive Predictive Value $= \frac{TP}{t_3} = \frac{154}{738} \approx 0.21$

Negative Predictive Value $\frac{TN}{t_4} = \frac{2108}{2126} \approx 0.99$

Accuracy $\frac{TP+TN}{t} = \frac{154+2108}{2864} \approx 0.79$

Positive Likelihood Ratio $= \frac{\text{Sensitivity}}{1-\text{Specificity}} = \frac{154/172}{1-2108/2692} \approx 4.13$

Negative Likelihood Ratio $= \frac{\text{1 - Sensitivity}}{\text{Specificity}} = \frac{1-154/172}{2108/2692} \approx 0.13$

Regret Given Positive Test $= \frac{FP}{t_3} = \frac{584}{738} \approx 0.79$

Posterior Probability of Illness given Positive Test $= \frac{TP}{t_3} = \frac{154}{738} \approx 0.21$

Posterior Probability of Illness given Negative Test $= \frac{FN}{t_4} = \frac{18}{2126} \approx 0.0085$

Question 4:

Given $F(t) = 1 - \left[1 - \lambda(\frac{t}{\sigma})^{1/\alpha}\right]^{1/\lambda}$ we have $S(t) = 1 - F(t) = \left[1 - \lambda(\frac{t}{\sigma})^{1/\alpha}\right]^{1/\lambda}$. Then we calculate the hazard function as follows:

$$h(t) = -\frac{\mathrm{d}}{\mathrm{d}t}\log S(t)$$

$$= \left(\frac{-1}{\lambda}\right)\frac{\mathrm{d}}{\mathrm{d}t}\log\left[1 - \lambda\left(\frac{t}{\sigma}\right)^{1/\alpha}\right]$$

$$= \left(\frac{-1}{\lambda}\right)\left(\frac{1}{1 - \lambda\left(\frac{t}{\sigma}\right)^{1/\alpha}}\right)(-\lambda)\left(\frac{1}{\alpha}\right)\left(\frac{t}{\sigma}\right)^{\frac{1}{\alpha}-1}\left(\frac{1}{\sigma}\right)$$

$$= \frac{\left(\frac{t}{\sigma}\right)^{1/\alpha-1}}{\alpha\sigma\left(1 - \lambda\left(\frac{t}{\sigma}\right)^{1/\alpha}\right)},\ \alpha > 0,\ \sigma > 0,\ \lambda \leq 0,\ t \geq 0$$

To investigate its behaviour, we analyze its derivative.

$$h'(t) = \frac{1/\alpha - 1}{\sigma}\left(\frac{t}{\sigma}\right)^{1/\alpha-1}\alpha\sigma\left(1 - \lambda\left(\frac{t}{\sigma}\right)^{1/\alpha}\right) - \frac{-\lambda\alpha\sigma}{\alpha\sigma}\left(\frac{t}{\sigma}\right)^{1/\alpha-1}\left(\frac{t}{\sigma}\right)^{1/\alpha-1}/\alpha^2\sigma^2\left(1 - \lambda\left(\frac{t}{\sigma}\right)^{1/\alpha}\right)^2$$

$$= \frac{\left(\frac{t}{\sigma}\right)^{1/\alpha-2}}{\alpha^2\sigma^2\left(1 - \lambda\left(\frac{t}{\sigma}\right)^{1/\alpha}\right)^2}\left(1 - \alpha + \alpha\lambda\left(\frac{t}{\sigma}\right)^{1/\alpha}\right)$$

Fixing $h'(t) = 0$ with the variable constraints implies the critical point $t_c = \left(\frac{\alpha - 1}{\alpha\lambda}\right)^{\alpha}\sigma$, $\lambda \neq 0$.

The sign of h' depends on the second term since the first is always non-negative. First, let's consider when $\lambda = 0$ since this is where the critical point vanishes. We have the following three cases independent of σ:

1. $\lambda = 0 \wedge \alpha \in (0, 1) \implies h$ is increasing
2. $\lambda = 0 \wedge \alpha = 1 \implies h$ is constant
3. $\lambda = 0 \wedge \alpha \in (1, \infty) \implies h$ is decreasing

If $\lambda < 0$ we have the following two cases independent of σ:

1. $\lambda < 0 \wedge \alpha \in [1, \infty) \implies h$ is decreasing
2. $\lambda < 0 \wedge \alpha \in (0, 1) \implies h$ is increasing on $(0, t_c)$ and decreasing on (t_c, ∞) with max at t_c

Question 5:

Let $Y = \log(T) \sim \text{logistic}(\nu, \tau)$ with $f_Y(y) = \left(\frac{1}{\tau}\right) \frac{e^{(y-\nu)/\tau}}{(1+e^{(y-\nu)/\tau})^2}, \ -\infty < y < \infty, \ \tau > 0.$

Since exp is a monotonic function, we have that the density of $T = e^Y$ is given by

$f_T(t) = f_Y(\log(t)) \left| \frac{\mathrm{d}}{\mathrm{d}t} \log(t) \right|$

$= \left(\frac{1}{\tau}\right) \frac{e^{(\log(t)-\nu)/\tau}}{(1+e^{(\log(t)-\nu)/\tau})^2} \left(\frac{1}{t}\right)$

$= \left(\frac{1}{\tau}\right) \frac{t^{1/\tau} t^{-1} e^{-\nu/\tau}}{(1+(te^{-\nu})^{1/\tau})^2}$

$= \frac{\alpha t^{\alpha-1} \beta^\alpha}{(1+(t\beta)^\alpha)^2}, \ \alpha = \frac{1}{\tau}, \beta = e^{-\nu}, t \geq 0$

Thus, T follows the log-logistic distribution.

Question 6:

Let $f_T(t) = \dfrac{\alpha t^{\alpha-1}\beta^\alpha}{(1+(t\beta)^\alpha)^2},\ \alpha > 0,\ \beta > 0,\ t \geq 0$. Then the survival function is given by:

$$S(t) = \int_t^\infty \alpha\beta^\alpha \frac{u^{\alpha-1}}{(1+(u\beta)^\alpha)^2}\, du$$

$$= \frac{-1}{1+(u\beta)^\alpha}\Big|_t^\infty$$

$$= \frac{1}{1+(t\beta)^\alpha}$$

The hazard function and its derivative are given by:

$$h(t) = \frac{f(t)}{S(t)} = \frac{\alpha t^{\alpha-1}\beta^\alpha}{1+(t\beta)^\alpha}$$

$$h'(t) = \alpha\beta^\alpha \left[(\alpha-1)(t^{\alpha-2})(1+(t\beta)^\alpha)) - (t^{\alpha-1})(\alpha\beta)(t\beta)^{\alpha-1}\right] / (1+(t\beta)^\alpha)^2$$

$$= \frac{\alpha\beta^\alpha t^{\alpha-2}}{(1+(t\beta)^\alpha)^2}(\alpha - 1 - (t\beta)^\alpha)$$

Setting $h'(t) = 0$ along with the variable constraints results in the critical value $t_c = \dfrac{(\alpha-1)^{1/\alpha}}{\beta}$. In the derivative, $\frac{\alpha\beta^\alpha t^{\alpha-2}}{(1+(t\beta)^\alpha)^2}$ is non-negative since $\alpha, \beta > 0, t \geq 0$. This means the sign is dependent on $(\alpha - 1 - (t\beta)^\alpha)$. If $\alpha < 1$ the term is negative $\implies h' < 0 \implies h$ is decreasing. If $\alpha > 1$ then this term is positive until t_c, 0 at t_c, and negative after t_c. This means h is increasing on $(0, t_c)$, decreasing on (t_c, ∞), and hits a maximum at t_c.

Question 7:

Let $S(t) = \dfrac{1}{1+(t\beta)^\alpha}, \alpha > 0\, \beta > 0.$

a) The odds of failure before t is given by:

$$\text{odds}(t) = \frac{1-S(t)}{S(t)} = \left(1 - \frac{1}{1+(t\beta)^\alpha}\right)(1+(t\beta)^\alpha) = (t\beta)^\alpha$$

b) The odds ratio of two individuals with different β is given by:

$$\frac{\text{odds}_1(t)}{\text{odds}_2(t)} = \frac{(t\beta_1)^\alpha}{(t\beta_2)^\alpha} = \left(\frac{\beta_1}{\beta_2}\right)^\alpha$$

c) Let $\alpha = 1.5$ $\beta = 0.05$.

The median survival time is

$$S(M) = 1/2 \iff \frac{1}{1+(M\beta)^\alpha} = 1/2 \iff (M\beta)^\alpha = 1 \iff M = \frac{1}{\beta} = 20 \text{ days.}$$

Hazard reaches a max at $t_c = \dfrac{(\alpha-1)^{1/\alpha}}{\beta} = 12.6$ days.

The probability of surviving until t_c is $S(t_c) = \dfrac{1}{1+(t_c\beta)^\alpha} = 0.67.$

Question 8:

a) Below are the results of the Weibull(α, θ) fit.

Table 1: Weibull(α, θ) fit.

Parameter	**Estimate**	**Std Error**
α (shape)	1.240485	0.1533419
θ (scale)	986.951680	127.1394093

b) Below are the results of the Exponential(λ) fit.

Table 2: Exponential(λ) fit.

Parameter	**Estimate**	**Std Error**
λ (rate)	0.001080945	0.0001648426

As a scale parameter we have $\theta = 1/\lambda = 925.1163$. To decide if the exponential is adequate, we perform a likelihood ratio test.

$$H_0 : \alpha = 1 \quad \text{v.s.} \quad H_1 : \alpha \neq 1$$

$$\Lambda = -2(\ell_{\text{Exponential}} - \ell_{\text{Weibull}}) = -2(-336.6865 + 335.3089) = 2.7552 \sim \chi^2(1)$$

The resulting p-value is 0.0969 so we fail to reject H_0 at a significance level of 0.05. Therefore, the exponential fit is adequate.

c) The sample mean of the lifetime data is 925.1163 days after diagnosis and the sample median is 702 days. The estimates from the exponential fit are mean 925.1163 days and median $(925.1163)\log(2) = 641.241755$ days.

Question 9:

Below are the results of the Weibull(α, θ) fits and the survival curves. There is a clear difference in survival time by class. We can see that glioblastoma (G) is a much more sinister class than astrocytoma (A) with its probability of survival always below and decreasing faster. Around 3 years in, the probability of survival is near zero for G whereas it is around 20% for A.

Table 3: Weibull(α, θ) fits.

Parameter	**Estimate**	**Std Error**
α_A(shape)	1.246698	0.2599469
θ_A(scale)	103.710697	22.2381582
α_G(shape)	1.297593	0.1786429
θ_G (scale)	50.203334	7.5750090

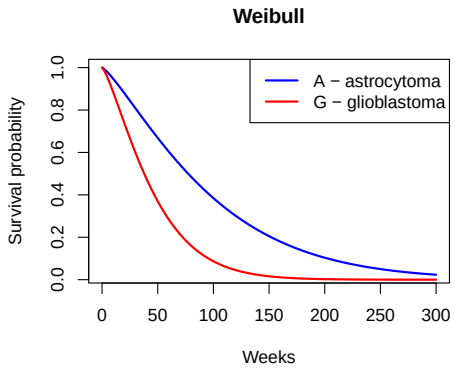

Figure 1: Astrocytoma v.s. glioblastoma survival curves (Weibull)

b) Below are the results of the Gamma(β, δ) fits and survival curves. We see the same behaviour between classes as Weibull with only slight deviations in steepness.

Table 4: Gamma(β, δ) fits.

Parameter	**Estimate**	**Std Error**
β_A (shape)	1.41907359	0.454023508
δ_A (rate)	0.01455384	0.006275429
β_G (shape)	1.77484557	0.43014403
δ_G (rate)	0.03873289	0.01118796

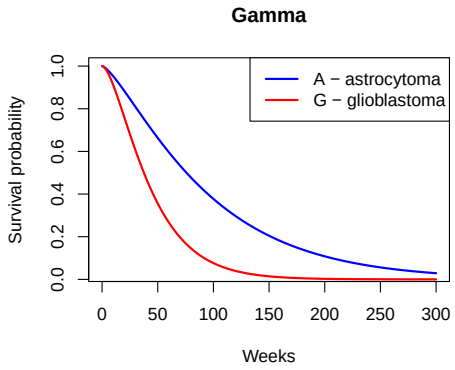

Figure 2: Astrocytoma v.s. glioblastoma survival curves (Gamma)

c) Below are the Lognormal(μ, σ) fits and survival curves. Again, we see similar behaviour between classes with slight deviations in steepness.

Table 5: Lognormal(μ, σ) fits.

Parameter	**Estimate**	**Std Error**
μ_A	4.237560	0.2552585
σ_A	1.052227	0.2035696
μ_G	3.5216666	0.1429222
σ_G	0.7830066	0.1056521

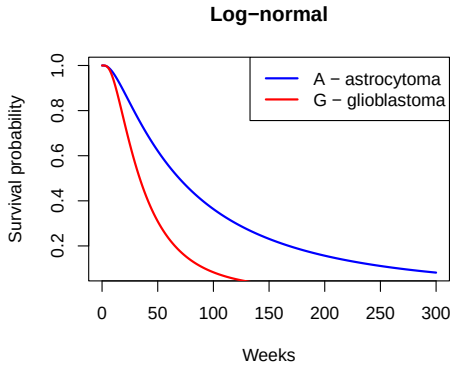

Figure 3: Astrocytoma v.s. glioblastoma survival curves (Log-normal)

d) The AIC values are summarized below as well as a plot comparing survival curves by distribution and class. The results indicate that we should model A with the gamma distribution and G with the log-normal distribution as they have the minimal AICs.

Table 6: AIC values.

Distribution	**AIC**
$\text{Weibull}_{\text{A}}$	161.1606
Gamma_{A}	161.0825
$\text{Log-normal}_{\text{A}}$	161.7356
$\text{Weibull}_{\text{G}}$	272.7754
Gamma_{G}	271.0473
$\text{Log-normal}_{\text{G}}$	267.0044

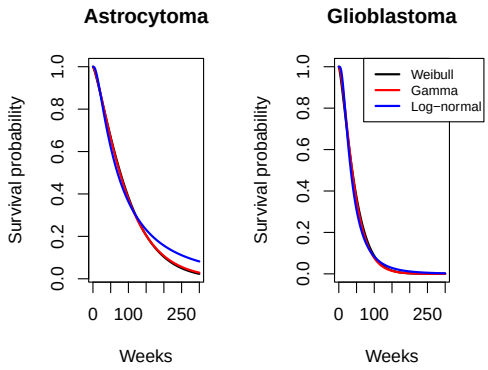

Figure 4: Survival curves by distribution and class.

Question 10:

Below are the results of the Weibull(α, θ) fits and the survival curves. There is a clear difference in survival time by class. We can see that Hodgkin's lymphoma (HL) starts above other lymphoma (NHL) but crosses around 40 days with near 80% probability of survival. After the intersection, HL falls rapidly within hundreds of days whereas NHL falls moderately over a couple thousand days.

Table 7: Weibull(α, θ) fits.

Parameter	**Estimate**	**Std Error**
α_{HL} (shape)	0.5141875	0.1682407
θ_{HL}(scale)	1225.489897	1006.063239
α_{NHL}(shape)	0.8337323	0.2186612
θ_{NHL} (scale)	337.9529238	135.2249786

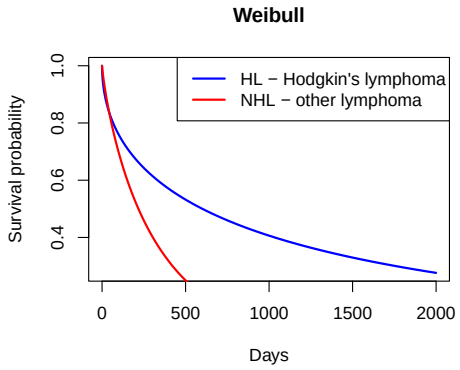

Figure 5: Hodgkin's lymphoma v.s. other survival curves (Weibull)

b) Below are the results of the Gamma(β, δ) fits and the survival curves. We see the similar behaviour as Weibull except they intersect around 50 days.

Table 8: Gamma(β, δ) fits.

Parameter	**Estimate**	**Std Error**
β_{HL} (shape)	0.452713326	0.1819825
δ_{HL}(scale)	0.0002816492	0.0001362174
β_{NHL}(shape)	0.858037542	0.2678785785
δ_{NHL} (scale)	0.002396881	0.0008789946

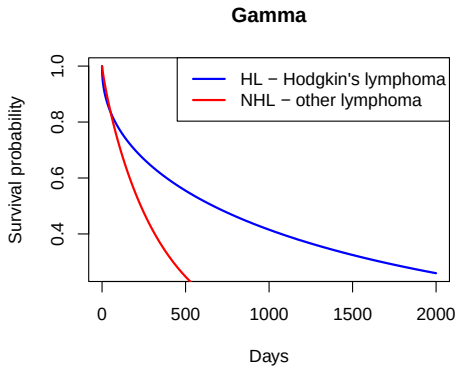

Figure 6: Hodgkin's lymphoma v.s. other survival curves (Gamma)

c) Below are the results of the Lognormal(μ, σ) fits and the survival curves. Again, we see similar behaviour except they intersect near 60 days.

Table 9: Lognormal(μ, σ) fits.

Parameter	**Estimate**	**Std Error**
μ_{HL} (shape)	6.228303	0.7671443
σ_{HL}(scale)	2.328399	0.7161220
μ_{NHL}(shape)	5.241862	0.3762819
σ_{NHL} (scale)	1.245615	0.3113745

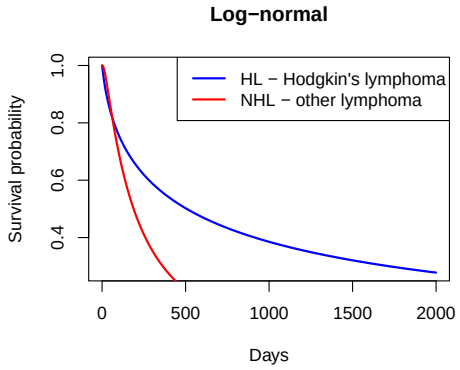

Figure 7: Hodgkin's lymphoma v.s. other survival curves (Log-normal)

d) The AIC values are summarized below as well as a plot comparing survival curves by distribution and class. The results indicate that, we should model HL and NHL with log-normal as it has the minimal AIC in both classes.

(Note: For HL, I scaled the dataset down to fix a convergence issue and then scaled the parameters back appropriately for each distribution. I compared the HL models based on the scaled down AIC.)

Table 10: AIC values.

Distribution	**AIC**
$\text{Weibull}_{\text{A}}$	73.80355
Gamma_{A}	74.78211
$\text{Log-normal}_{\text{A}}$	71.36015
$\text{Weibull}_{\text{G}}$	126.6898
Gamma_{G}	127.0669
$\text{Log-normal}_{\text{G}}$	123.7113

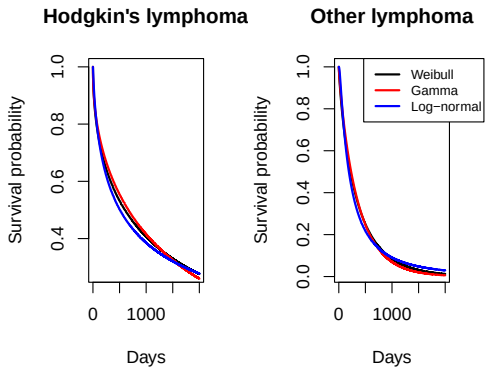

Figure 8: Survival curves by distribution and class.