Exponential Model Extended for Neurologic Studies

Ramalingam Shanmugam[1], Alfred A. Bartolucci [2], Karan P. Singh[2]

1. Department of Mathematics, University of Colorado, Denver, CO. USA
2. Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL. USA

At some point in time during a post-surgery period an anesthesiologists may intervene using a medication to quicken a patient's conscious-recovery time. An assessment of such intervention methods has clinical importance. One performs an extension of the exponential model to address this issue. The model derived is the intervened exponential model (IED). Statistical properties of this new model, expressions to estimate the model parameters, and a test statistic procedure to verify conjectures about the intervention efforts are derived. Other concepts such as the hazard function and its relevance to this model are introduced and examined. An illustrative example is pursued to demonstrate this procedure.

1.0 Background and Motivation

Before a patient undergoes surgery it is customary for the anesthesiologist to sedate the patient who then loses either partial or complete consciousness for a random amount of time which is to exceed the surgery time. One of the post surgery health procedures is to cause the patient to recover consciousness completely. For some reasons, if this recovery does not occur on its own before a medically suggested time, the anesthesiologist intervenes by medicating the patient with a dose of anti-sedation drug to speed up the patient's conscious recovery. Of interest to the anesthesiologist is an assessment of such intervention efforts. This article extends the exponential model to address this interest.

An analogous situation arises in neurological studies. There has been an interest in the medical community (Lamarre et al, 1983 and Commenges and Seal, 1985) involved in brain research studies about the total (behavioral) reaction time, X for a patient who is subjected to some stimulus drug. In this study the random variables Y and Z denote respectively the time for stimulus to reach the neuron cells and the time for neurons to activate the necessary movements. In an experiment like this, although neuron activities are continuously monitored, there is a latent variable which is much of individualistic, and it is primarily based on the patient's physiology. An often asked question is how much effect does those patient's physiologic characteristics or metabolism have on the neuronal response time?

2.0 The Intervened Exponential Distribution

Let Y denote the random amount of time a patient might be unconscious due to an anesthetic drug. The surgery team would prefer to have Y exceed an amount of time $\tau>0$ which may either be known when it is decided by the medical team or an unknown when it is to be disease complication dependent. At any rate we assume that Y follows a truncated exponential model,

$$f(y|\theta,\tau)=\frac{1}{\theta}e^{-[y-\tau]/\theta};\tau<y<\infty,\theta>0. \quad (1)$$

It is easy to recognize that $\tau+\theta=E[Y]$, the expected time for a patient to be in an unconscious state. At some point in time during the post surgery period, if on its own the patient's conscious-recovery does not occur, then the medical team might intervene by medicating the patient with an extra anti-sedation drug to speed up the recovery. Suppose that on the average these efforts result in $E[Z]=\rho\theta$ where Z and $\rho\theta$ denote respectively the random remaining time to completely recover consciousness and an "intervention function" of θ. In the brain research study application, Z denotes a random amount of time for neuronal response to movement. We assume here that the intervention function is a linear type where $\rho>0$ is an intervention effect. Thus ρ is interpreted as being a percent reduction in the conscious-recovery time. We also assume that the random variable Z follows an exponential model:

$$g[z|\theta,\rho]=\frac{1}{\rho\theta}e^{-\frac{z}{\rho\theta}};z>0,\rho\geq 0,\theta>0. \quad (2)$$

Suppose that data on only X=Y+Z, the total unconscious time of the patient is available for statistical analysis. Assuming that Y and Z are independent random variables, we derive the probability density function [pdf] of X as :

$$f[x|\rho,\theta,\tau]=\int_{\tau}^{x}f[u|\theta,\tau]g[x-u|\theta,\rho]du.$$

That is

$$f[x|\rho\neq 1,\theta,\tau]=\left[\frac{e^{-\frac{(x-\tau)}{\rho\theta}}-e^{-\frac{(x-\tau)}{\theta}}}{(\rho-1)\theta}\right] \quad (3a)$$

and

$$f[x|\rho=1,\theta,\tau]=\frac{(x-\tau)}{\theta^2}e^{-(x-\tau)/\theta}. \quad (3b)$$

This new model is called the intervened exponential distribution, [IED]. The sample [observable] space for x is $x>\tau>0$, and the parametric space of the model is in the positive quadrant of a three dimensional sphere such that $\{(\rho,\theta,\tau)|\ \rho>0,\ \theta>0,\tau>0\}$. In an event that the intervention efforts were most effective [i.e. the patient instantaneously recovers consciousness at the time of the medical intervention], ρ will be equal to zero, and in which case the random times X and Y are the same and hence the IED becomes the usual exponential model in (1). When $\rho=1$ the situation is static in the sense that the intervention efforts have not altered the patient's conscious recovery rate, θ. For $\rho>1$ the situation is adversarial in the anesthetic example.

Using the characteristic function we obtain the mean, μ_x, and variance σ_x^2 of the IED in (3),which are:

$$\begin{aligned}\mu_x&=\tau+(\rho+1)\theta\\ \sigma_x^2&=(\rho^2+1)\theta^2\end{aligned} \quad (4)$$

The mode is:

$M_x=\tau+\frac{\rho\theta}{\rho-1}\ln|\rho|$ and the median is

$$X_{0.5}=\tau-\frac{\rho\theta}{\rho+1}\ln[1/2].$$

3.0 Parameter Estimation

Consider a random sample X_1 , X_2 ,......X_n of size n ≥ 2 from an IED population in (3). Then, its log likelihood function is non-zero if and only if the minimum of the observations, $X_{(1)} > \tau$. Hence the maximum likelihood estimate, MLE, of the threshold parameter, τ, is $X_{(1)}$. To estimate the other parameters, θ and ρ, we consider the transformation of the data, $U_i = X_i - X_{(1)}$ for i-1,2,...,n. It is easy to see that the log likelihood function $\psi(u_1, u_2, \ldots, u_n)$ of the transformed data for $\rho \neq 1$ is

$$\sum_{i=1}^{n} \psi[u_i] = \sum_{i=1}^{n} [\ln|e^{-\frac{u_i}{\rho\theta}} - e^{-\frac{u_i}{\theta}}| \quad (5)$$
$$-n \ln|\rho - 1| - n \ln \theta]$$

Note that $E[U]=(\rho-1)\theta$ and $Var[U]=(\rho^2+1)\theta$. Differentiating separately with respect to θ and ρ in [5], and equating them to zero, we obtain the MLE of the model parameters. After some derivation we have for the case that $\rho>1$ the two equations to be solved simultaneously,

$$\sum_{i=1}^{n} u_i e^{\frac{-u_i(\rho-1)}{\rho\theta}} \left[1 - e^{-\frac{u_i(\rho-1)}{\rho\theta}}\right]^{-1} = \frac{n\theta}{(\rho-1)} \quad (6)$$

and

$$\sum_{i=1}^{n} u_i \left[1 - e^{\frac{u_i(\rho-1)}{\rho\theta}}\right]^{-1} = \frac{n\rho^2\theta}{(\rho-1)} \quad . \quad (7)$$

For the case of $\rho<1$ we have

$$\sum_{i=1}^{n} u_i \left[1 - e^{\frac{-u_i(1-\rho)}{\rho\theta}}\right]^{-1} = \frac{n\theta}{(\rho-1)} \quad (8)$$

and

$$\sum_{i=1}^{n} u_i e^{\frac{-u_i(1-\rho)}{\rho\theta}} \left[1 - e^{\frac{-u_i(1-\rho)}{\rho\theta}}\right]^{-1} = \frac{n\rho^2\theta}{(1-\rho)} . \quad (9)$$

4.0 Testing Whether Effective Intervention Took Place

A zero value for ρ is indicative of a completely successful medical intervention, whereas $\rho=1$ is to be interpreted as the status quo in a conscious recovery rate of a patient. Of interest to the medical team is whether effective intervention took place. That is of interest to test H_0: $\rho=1$ versus H_1: $\rho<1$ based on a random sample X_1 , X_2 , ...X_n of size n from IED as in (3). Since the incidence rate , θ, is unknown in a real life situation, the testing of ρ is not straight forward. For this purpose we employed the Neyman's (1959) $C[\alpha]$ test procedure and also use it to find a confidence interval estimate for the effectiveness of the medical intervention. Using this procedure and an approximate version of the MLE for θ which is

$$\hat{\theta} = \frac{\bar{u}}{(\rho-1)}, \quad (10)$$

where $\bar{u} = \sum_{i=1}^{n} u_i / n$ we have an asympotic test statistic based on the chi square distribution. One has to be especially careful in this case assuming asymptotic theory. The reason is more pronounced in that we are starting out with a positively skewed distribution given the truncated exponential assumption.

Thus given these assumptions the statistic takes the form:

$$\chi^2_\rho = \frac{(\rho+1)\sum_{i=1}^{n}(u_i-\bar{u})^2}{\bar{u}(n+1)(\rho^2+1)} \qquad (11)$$

which is chi square with one degree of freedom under a hypothesized value of ρ. So for a large sample we have for the null hypothesis that ρ=1 the statistic:

$$\chi^2_{\rho=1} = \frac{\sum_{i=1}^{n}(u_i-\bar{u})^2}{\bar{u}(n-1)} \quad . \qquad (12)$$

In the case of small sample sizes the statistic should be computed using simulation.

We can also derive an asymptotic 100(1-α)% confidence interval for ρ. Note that

$$\Pr[\chi^2_{\frac{\alpha}{2}} < \chi^2_\rho < \chi^2_{1-\frac{\alpha}{2}}] = 1-\alpha \qquad (13)$$

in which χ^2_ρ is as specified in (11) and $\chi^2_{\frac{\alpha}{2}}$ is the $100_{\alpha/2}$th percentile from the chi square distribution on 1 degree of freedom. Thus arranging terms accordingly we obtain a 100(1-α)% confidence interval for ρ, the intervention effect which is specified in the statement,

$$\Pr[L-1 < \rho < U-1] = 1-\alpha \qquad (14)$$

where

$$L = \left(1 - \frac{\sum_{i=1}^{n}(u_i-\bar{u})^2}{\bar{u}(n-1)\chi^2_{1-\frac{\alpha}{2},1df}}\right)^{-1} \qquad (15)$$

$$U = \left(1 - \frac{\sum_{i=1}^{n}(u_i-\bar{u})^2}{\bar{u}(n-1)\chi^2_{\frac{\alpha}{2},1df}}\right)^{-1} \quad .$$

(16)

5.0 Illustrative Example

Two small sets of data were used to illustrate this technique. Each had about 8 data points. These were the transformed times, U_i, i=1,...,n for n=8. Admittedly these are small sample sizes. However, they demonstrate the IED technique quite nicely. The MLE's of θ and ρ were derived using expressions (6) to (9). We then computed the chi square values with 95% confidence limits on the parameter, ρ, from expressions (11) and (13).Table 1 gives the values of $\bar{u}, \hat{\theta}, and\ \hat{\rho}$. Table 2 gives the χ^2 value with the 95% confidence limits on ρ. In the first study we have a very small $\hat{\rho}$, indicating the possibility of a successful intervention. The chi square value is quite small, but not quite under the lower chi square limit. However, the lower tail of the confidence limit does include 0. In the second study the value of the MLE for ρ is quite close to one indicating the status quo and certainly one would not reject the null that ρ=1.

6.0 Conclusions

One can see that from this newly derived intervened exponential distribution that it certainly has application to the intervention we have proposed. The shortcoming of this technique is the derivations required to isolate the intervention parameter, ρ. Also some large sample approximations are required to derive a number of the results. However, the maximum likelihood procedure works very nicely for this model as does the chi square distribution. We have not had the opportunity to apply this to additional data sets, but expect to do so. Also this technique will lend itself very nicely to a Bayesian treatment, especially in the case of deriving the marginal posterior of ρ for inference on that intervention parameter. This work is currently ongoing.

Study	$\hat{\theta}$	$\hat{\rho}$
1	1.849	0.005
2	0.503	0.999

Table 1. Estimated Parameter Values of The Intervened Exponential Model.

Study	Parameter	Lower	Upper
1	ρ	0.000	0.289
2	ρ	0.593	1.404

Table 2. 95% Confidence Limits on ρ.

7.0 References

Commenges, D. and Seal, J., The analysis of neuronal discharge sequences: Change point estimation and comparison of variances. *Statistics in Medicine*, 4, 91-104, 1985.

Lamarre, Y., Busby, L.,and Spidalieri, G., Fast ballistic arm movements triggered by visual, auditory, and somesthetic stimuli in the monkey. I. Activity of precentral cortical neurons. *J Neurophysiology*, 50, 1343-1358,1983.

Neyman, J., Optimal asymptotic tests of composite hypotheses, in *Probability and Statistics: The Harold Cramer Volume,* New York. John Wiley Press. 1959.