ESTIMATION AND FORECASTING AGE GROUPS WISE SURVIVAL OF CABG PATIENTS (KALMAN FILTER SMOOTHING APPROACH)

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ABSTRACT: *In this paper we present a new approach (Kalman Filter Smoothing) to estimate and forecast, Age Groups wise, survival of Coronary Artery Bypass Graft Surgery (CABG) patients. Survival proportions of the patients are obtained from a lifetime representing parametric model (Weibull distribution with Kalman Filter approach). Moreover, an approach of complete population (CP) from its incomplete population (IP) of the patients with 12 years observations/ follow-up is used for their survival analysis [23]. The survival proportions of the CP obtained from Kaplan Meier method are used as observed values* y_t *at time t (input) for Kalman Filter Smoothing process to update time varying parameters. In case of CP, the term representing censored observations may be dropped from likelihood function of the distribution. Maximum likelihood method, in-conjunction with Davidon-Fletcher-Powell (DFP) optimization method [8] and Cubic Interpolation method is used in estimation of the survivor's proportions. The estimated and forecasted, Age Groups wise survival proportions of CP of the CABG patients from the Kalman Filter Smoothing approach are presented in terms of statistics, survival curves, discussion and conclusion.*

KEYWORDS: CABG Patients, Complete and Incomplete populations, Weibull& distribution, Kalman Filter, Maximum Likelihood method, DFP method, Estimation and Forecasting of Survivor's Proportions.

INTRODUCTION

The Coronary Artery Disease (CAD) is a chronic disease, which progresses with age at different rates. CAD is a result of built-up of fats on the inner walls of the coronary arteries. Thus, the sizes of coronary arteries become narrow and as a result the blood flow to the heart muscles is reduced / blocked. Therefore, the heart muscles do not receive required oxygenated blood, which leads to the heart attack. CAD is a leading cause of death worldwide (see William, Stephen, Thomas and Robert [36], John [18], Hansson [14], and Sun and Hong [33]). The medical scientists; Goldstein, Adams, Alberts, Appel, Brass, Bushnell, Culebras, Graba, Gorelick& Guyton [11] and Jennifer [17] are of the opinion that CABG is an effective treatment option for CAD patients. The medical research organizations like Heart and Stroke Foundation Canada [16], American Heart Association [2] and Virtual Health Care Team Columbia [35] have classified risk factors of CABG patients as modifiable (Hypertension, Diabetes, Smoking, High Cholesterol, Sedentary Lifestyle and Obesity) and non-modifiable (Age, Gender and Family History-Genetic Predisposition). An analytical study with respect to these risk factors has been carried out by medical scientists [38].

The researchers [36] carried out the survival study on incomplete population (progressive censoring of type 1) of CABG patients comprising 2011 patients using Kaplan Meier method [20]. The patients were grouped with respect to Male, Female, Age, Hypertension, Diabetes, and Ejection Fraction, Vessels, Congestive Heart Failure, Elective and Emergency Surgery. The patients were undergone through a first re-operation at Emory University hospitals from 1975 to 1993(see William [36]. The patients were observed / followed up for 12 years. In the article [32] we proposed a procedure, to make an *IP*, a *CP*.

The Weibull distribution model - one of the existing/current survival model has been used for survival analysis by Cohen [6], Gross and Clark [13], Bunday [5], Crow [7], Klein &Moeschberger [24], Lawrencce [28],Abrenthy [1], Lawless [27], and Lang [25]. In particular, the survival study of chronic diseases, such as AIDS and Cancer, has been carried out using Weibull distributions by Bain and Englehardt [3], Khan & Mahmud [21 & 22], Klein &Moeschberger [24], Lawless [27] and Swaminathan and Brenner [34]. Lanju & William [26] used Weibull distribution to human survival data of patients with plasma cell and in response-adaptive randomization for survival trials respectively. We [32] have carried out survival analysis of CABG patients by parametric estimations-classical approach, in modifiable risk factors (Hypertension and Diabetes).

Kalman Filter Smoothing Approach (New Approch). The dynamic linear model (DLM) and Kalman Filter (KF) equations have been described by Harrison and Steven [15]. According to the researchers, Dan [8] and Greg [12] Kalman Filter is a mathematical technique, used to estimate the state of a process by minimizing error of estimation. Kalman Filter extracts signals from a series of incomplete and noisy measurements. It removes noises from the process parameters and retains useful information. Kalman filter estimates the state of a dynamic linear model through its recurrence equations which minimizes the variance of estimation error. To implement Kalman filter, observed values as dependent variables are required for updating the process parameters. Though, since time of introduction, the Kalman Filter has been subject of research for engineering processes see Frank [10], however the KF methodology has been applied extensively in medical research/ life-testing studies / survival analysis; for example, Meinhold and Singpurwalla [31] proposed a new method for inference and extrapolations in certain dose–response, damage-assessment, and accelerated-life-testing studies, using Kalman-filter smoothing. Anatoli, Kenneth and James [4]indicated that various multivariate stochastic process models have been developed to represent human physiological aging and mortality. These researchers considered the effects of observed and unobserved state variables on the age trajectory of physiological parameters. The parameters of the distribution used were estimated based on an extension of the theory of Kalman filters to include systematic mortality selection. Ludwig [29] considered models for discrete time panel and survival data; and used a generalized linear Kalman filter approach.

In our study, Kalman filter technique is applied to estimate parameters of Weibull probability distribution using Diabetic and Non Diabetic CABG patient's data sets. For construction of KF equations, survivor function of the probability distribution is linearized by transformation of double-log. The procedure to construct linear form of the survivor function, as advocated by researchers (see Meinhold and Singpurwalla, [30]; Gross and Clark, [13]; Kalbfleisch and Prentice) is followed. Survival proportions for complete population of Diabetic CABG patients obtained from Kaplan Meier method are used as observed values y_t at time *t*, for updating the time varying parameters of the distribution. After defining the updating system of parameters of a probability distribution with KF approach (discussed in the methodology), the parameters are estimated at each time *t* by maximizing likelihood function of double-lognormal distribution, through Davidon-Fletcher-Powel method of optimization [9]. Since, in KF approach the observed values are from complete population, therefore, censored part is excluded(dropped) from log-likelihood function. The survival proportions obtained by the probability distributions with KF approach are presented with respect to Age Groups (I,II,III and IV**)** wise of CABG patients**.**

METHODOLOGY

For the estimation of survival proportions Kaplan Meier [20] proposed a method and latter discussed by William [36] and Lawless [27] i.e. $S(t)=\prod_{j:t_j<t}(1-\frac{d_j}{n_j})$, where d_j and n_j are the number of items failed (died individuals / patients) and number of individuals at risk at time t_j respectively, that is, the number of individuals survived and uncensored at time t_{j-1}.This method may be applied to both censored and uncensored data, see Lawless [27]. In case of censored individuals (items) the analysis is performed on IP. Khan, Saleem& Mahmud [23] proposed that the censored individuals c_j may be taken into account. The inclusion of splitted-censored individuals, c_j proportionally $\left[(1-\frac{d_j}{n_{j-1}-c_j})\times c_j \ \ and \ (\frac{d_j}{n_{j-1}-c_j})\times c_j\right]$ into known survived, n_j and died individual's d_j respectively make populations complete. Thus the survival analysis may be performed on the*CP* from its*IP*. The input in the DLM and KF equations/ process. In this study the observed values (survival proportions) are denoted by $Y_t \in (0,1)$, where Y_t may take value $y_1, y_2, y_3, ..., y_t$ at time $t_1, t_2, t_3, ..., \text{t}$. Harrison and Stevens [15] described the DLM which may be reproduced as system of following two equations:

Observation Equation: $$Y_t = F_t\theta_t + \ e_t\,,\ \{e_t \sim N(0,\sigma^2_{e_t}\} \qquad (1)$$

System Equation: $\theta_t = G\theta_{t-1} + w_t, \{w_t \sim N(0, W_t)\}$ (2)

Where Y_t and θ_t are of arbitrary dimensions. Y_t is a scalar, θ_t is vector of process parameters at time t, F_t is matrix of independent variables, known at time$t$, G is known system matrix (identity matrix), e_t is error term, a difference between observed and expected value y_t *and* $\hat{y}_t$ respectively at time t. $\sigma^2_{e_t}$ is the variance of e_t . It is assumed that e_t has Gaussian distribution with mean 0 and variance $\sigma^2_{e_t}$. The system equation describes the change which occurs when process parameter changes from preceding value θ_{t-1} to current value θ_t and W_t is the variance of disturbance term w_t .According to Harrison and Stevens (1976), it is assumed that distribution of the parameter vector θ_t at time t = 0 *i.e.* θ_0 prior to the first observation y_1 is in the form of normal probability distribution with mean say m_0 and variance C_o i.e. $\theta_0 \sim N(m_o, C_o)$. If the observed values; y_t, $t = 1, 2, 3, \ldots$ are described through DLM, then the posterior distribution of parameter vector θ_t is also normally distributed with mean say m_t and variance C_t i.e. $\theta_t \sim N(m_t, C_t)$.Whereas, the values of m_t and C_t are recursively obtained as:

$\hat{y}_t = F_t G m_{t-1}$; $e_t = y_t - \hat{y}_t$; $R_t = G C_{t-1} G' + W_t$; $\sigma_{y_t}{}^2 = F_t R_t F_t' + \sigma^2_{e_t}$; $A_t = R_t F_t' (\sigma_{y_t}{}^2)^{-1}$. The Kalman filter equations are: $m_t = G\, m_{t-1} + A_t\, e_t$ and $C_t = R_t - A_t\, \sigma_{y_t}{}^2 A_t'$ (for detail see Harrison and Stevens [15]). $\sigma_{y_t}{}^2$ is variance of y_t and A_t is a matrix which update m_t & C_t at each time t recursively.

The KF equations of Weibull probability distribution models are constructed by linearzing survival function of the distribution with transformation; double-log. The parameters of the probability distributions are estimated at each time t, by maximizing log-likelihood function of lognormal distribution (which is transformed form of Weibull distribution), through the Davidon-Fletcher-Powel method of optimization. For the entire system, the parametric space at each time point t is $\Phi = (m_t, C_t, W_t)$. Specification of starting values of the parameters is a common difficulty in implementing Kalman Filter. Practitioners have to check the sensitivity of the final results with different sets of assumed values (see Meinhold and Singpurwalla, [31]. After obtaining the prior values of the parameters of the probability distributions at timet = 0, the values $\Phi = (m_t, C_t, W_t \text{ for } t = 1, 2, 3, \ldots)$ are obtained recursively by using the Kalman filter updating equations.

2 (a). DROPPING A TERM OF LIKELIHOOD FUNCTION

Since, in the Kalman filter approach the observed values are from complete population, therefore, censored part is dropped from the log-likelihood function. To find maximum likelihood estimates we take negative log-likelihood function of the distribution. A subroutine for maximizing log-likelihood function of each distribution along with KF process is developed in FORTRAN program. The subroutine in-conjunction with the DFP optimization method is used to find the optimal initial estimates of the mean and variance parameters included in the model, m_0, C_0 *and* W_0, from final iteration of the program.

3. FORECASTING. For outside sample period (forecasting), due to non-availability of dependent values y_t) we stop the process of updating the mean parameters. Therefore, values of these optimal mean parameters remain constantand are utilized for updating the variance parameters for outside sample period, using the KF equations. The survival proportions y_t's of these probability distributions are estimated.

4. CONSTRUCTION OF KF EQUATIONS OF WEIBULL DISTRIBUTION

Since the values of survival proportions Y_t (observed values) lies in the interval (0, 1), expected value, $E(Y_t)$ of a probability distribution should also lie in the interval (0, 1). Keeping in view the natural process of deaths with the passage of time, it is assumed that $E(Y_t)$ as a function of *t* is monotonically decreasing. These researchers, Meinhold and Singpurwala [29] considered a quantity $E(Y_t) = e^{-\alpha_t t^{\beta_t}}$ (α_t *and* $\beta_t >$ 0) which is a nonlinear, monotonically decreasing function of *t* and is survival function, $S(t)$ of the Weibull distribution. Moreover, the form $e^{-\alpha_t t^{\beta_t}}$ (where α_t and β_t are scale and shape time varying parameters respectively in KF approach) has property with respect to linearity; may be linearized by taking its double logarithm. The linear form is a requirement for filtering techniques. Thus to implement KF a random quantity $Y_t^* = \ln\{-\ln(Y_t)\}$ is defined, which require that Y_t^* has a Gaussian density with expectation μ_t and variance $\sigma_{y_t}^2$. This implies that the random quantity Y_t^* must have double-lognormal distribution with *pd f*(at y_t) of the form:

$$f(y_t) = \left[\frac{1}{\sqrt{2\pi\sigma_{y_t}^2}\, y_t(-\ln y_t)}\right]\left[\exp\{-\frac{1}{2\sigma_{y_t}^2}(\ln(-\ln y_t) - \mu_t)^2\}\right].$$

Now, $E(Y_t^*) = \ln(-\ln(S(t))$

$= \ln(-\ln(e^{-\alpha_t t^{\beta_t}}))$

$= \beta_t \ln t + \ln \alpha_t$

$= [1 \quad \ln t][\ln \alpha_t \quad \beta_t]'$

$= [1 \quad \ln t][\gamma_t \quad \beta_t]'$, setting $\gamma_t = \ln \alpha_t$

$$Y_t^* = [1 \quad \ln t\ ][\gamma_t \quad \beta_t]' + e_t\ ;\ \{e_t \sim N(0, \sigma_{e_t}^2)\} \qquad (3)$$

The corresponding system equation is:

$$[\gamma_t \quad \beta_t]' = I_2\,[\gamma_{t-1} \quad \beta_{t-1}]' + w_t\ ;\{w_t \sim N(0, W_t)\} \qquad (4)$$

Comparing equations (3) and (4) with (1) and (2), we find that:

$F_t = [1 \quad \ln t]$, $\theta_t = [\gamma_t \quad \beta_t]'$; $\theta_{t-1} = [\gamma_{t-1} \quad \beta_{t-1}]'$ and $G = I_2$

where I_2 is an identity matrix of order. 2×2.

To find maximum likelihood estimates we consider negative log-likelihood function say $l(\Phi)$) of the double-lognormal distribution, given as:

$l(\Phi) = \sum l_t$, $l_t = f_{t_i} \ln(f(y_t))$

Where, y_t and f_{t_i} are observed values from CP and f_{t_i} number of failures at time t_i respectively and l_t may be obtained as: $l_t = f_{t_i}\left[[\ln\sqrt{2\pi}\, y_t(-\ln y_t) - a_t + \frac{(\delta_t)^2}{2}\right]$

For derivation of l_t and its partial derivatives, see appendix A.

A subroutine for maximizing log-likelihood function of the double-lognormal distribution along with KF process (subroutine) is developed in FORTRAN program. The subroutine in-conjunction with DFP optimization method is used to find the optimal initial estimates of the parameters included in the model, m_0, C_0 *and* W_0, from final iteration of the program.

The optimal initial estimates of parameters obtained by maximizing the log-likelihood function are given below in table 1.

Table 1. Survival Proportions y_t and Survival Proportions using Weibull Distribution $\hat{y}_t$ of Age Groups I,II,III and IV of CABAG Patients

Years (t)	**Age Groups**							
	I		**II**		**III**		**IV**	
	y_t	$\hat{y}_t$	y_t	$\hat{y}_t$	y_t	$\hat{y}_t$	y_t	$\hat{y}_t$
0	1	1	1	1	1	1	1	1
1	0.925	0.983	0.927	0.982	0.868	0.935	0.824	0.945
2	0.896	0.957	0.905	0.953	0.842	0.870	0.782	0.871
3	0.892	0.925	0.880	0.919	0.812	0.807	0.745	0.792
4	0.842	0.890	0.853	0.882	0.786	0.748	0.708	0.714
5	0.813	0.852	0.819	0.843	0.720	0.692	0.663	0.638
6	0.804	0.813	0.793	0.803	0.675	0.640	0.595	0.567
7	0.796	0.774	0.758	0.762	0.630	0.591	0.511	0.500
8	0.771	0.734	0.742	0.721	0.551	0.546	0.434	0.439
9	0.717	0.694	0.716	0.681	0.487	0.504	0.434	0.384
10	0.679	0.655	0.675	0.641	0.424	0.465	0.300	0.334
11	0.633	0.617	0.624	0.602	0.365	0.429	0.300	0.290
12	0.579	0.579	0.595	0.564	0.332	0.395	0.147	0.250

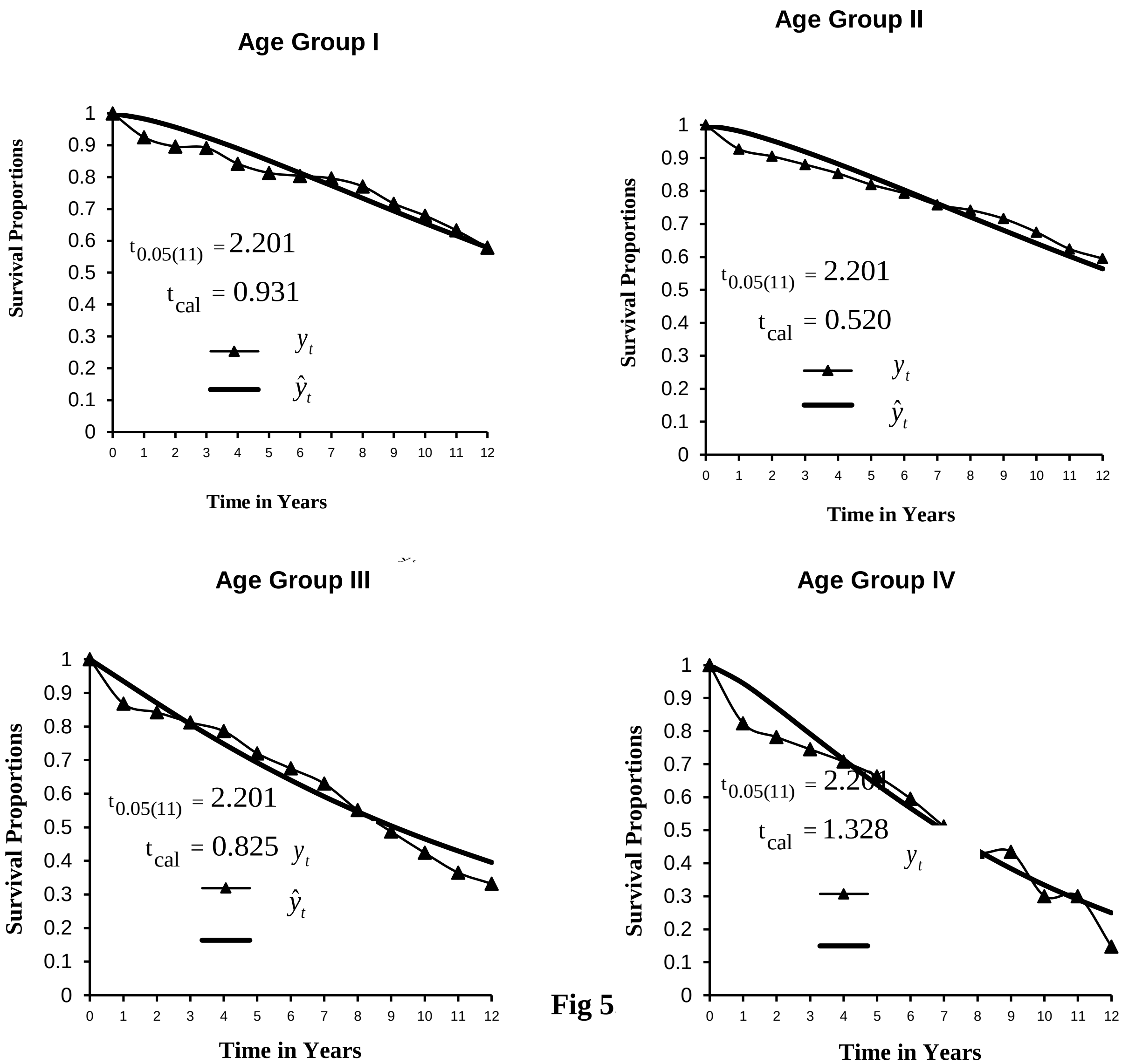

Fig 5

DISCUSSION

The graphs of observed survival proportions from the complete population y_t and expected survival proportions $\hat{y}_t$ of age groups I,II,III and IV of CABG patients indicate that the behavior of $\hat{y}_t$ for age groups I and II of CABG patients is like linear through out the sample period and $\hat{y}_t$ remain around and closer to y_t. Whereas, the behavior of $\hat{y}_t$ for age groups III and IV of CABG patients is like an arc, although $\hat{y}_t$ remain around y_t. Survival Proportions y_t and 12 years estimated with 3 Years forecasted Survival Proportions of CP of Age Groups I and II of CABG Patients Obtained by Kalman Filter Approach $(\hat{y}_t)_{KF}$ is given in Table 2.

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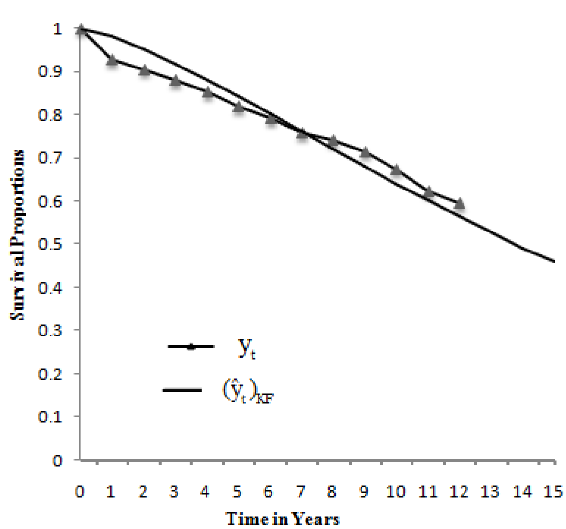
Table 2. Survival Proportions y_t and 12 Years Estimated with 3 Years Forecasted Survival Proportions of *CP* of Age Groups I and II of CABG Patients Obtained by Kalman Filter Approach $(\hat{y}_t)_{KF}$.

Years (t)	Age Groups			
	I		**II**	
	y_t	$(\hat{y}_t)_{KF}$	y_t	$(\hat{y}_t)_{KF}$
0	1	1	1	1
1	0.925	0.983	0.927	0.982
2	0.896	0.957	0.905	0.953
3	0.892	0.925	0.880	0.919
4	0.842	0.890	0.853	0.882
5	0.813	0.852	0.819	0.843
6	0.804	0.813	0.793	0.803
7	0.796	0.774	0.758	0.762
8	0.771	0.734	0.742	0.721
9	0.717	0.694	0.716	0.681
10	0.679	0.655	0.675	0.641
11	0.633	0.617	0.624	0.602
12	0.579	0.579	0.595	0.564
13		0.543		0.528
14		0.508		0.492
15		0.474		0.459

Age Group I **Age Group II**



Conclusion

As per linearity point of view, in comparison with data of age groups III and IV, the data of age groups I and II of CABG patients has been adequately modeled with Kalman Filter approach. Therefore, forecast of age groups I and II of CABG patients is reliable outside the sample observations. Thus, the linearity aspect achieved through the Kalman Filter Smoothing Approach helps in reliable forecasting and distinguish it from classical / existing method of survival analysis. The approach may be applied for other probability distributions by linearzing their Survival or Hazard function.

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Appendix -A

THE DOUBLE-LOGNORMAL DISTRIBUTION

Consider *p.d.f* of log-normal distribution:

$f(y_t) = \frac{1}{\sqrt{2\pi}\sigma_{y_t} y_t} \times \exp\{-\frac{1}{2\sigma_{y_t}{}^2}(\ln y_t - \mu_t)^2\}$, Where μ_t and σ_{y_t} are parameters of the distribution.

Let $\frac{1}{\sigma_{y_t}} = \eta_t$ and $a_t = \ln(\eta_t)$ then $\exp(a_t) = \eta_t$ or $e^{a_t} = \eta_t$, therefore we may write:

$$f(y_t) = \frac{e^{a_t}}{\sqrt{2\pi} y_t} \times \mathrm{e}^{\frac{[(\ln y_t - \mu_t) e^{a_t}]^2}{2}}$$

Setting $\delta_t = [(\ln y_t - \mu_t) e^{a_t}]$, we may write as: $f(y_t) = \frac{e^{a_t}}{\sqrt{2\pi} y_t} \times \mathrm{e}^{\frac{(\delta_t)^2}{2}}$

To find maximum likelihood estimates (as discussed in chapter 2, section 2.9) we consider negative log-likelihood function say $l(\Phi)$ of the double-lognormal distribution, given as: $l(\Phi) = \sum l_t$,

Where $l_t = f_{t_i} \ln(f(y_t))$, by excluding the censored part since observed values y_t are from complete population, f_{t_i} are the number of failures (died) at time t_i and l_t may be obtained by replacing value of $f(y_t)$ .We get l_t as:

$$l_t = f_{t_i}\left[[\ln\sqrt{2\pi} y_t - a_t + \frac{(\delta_t)^2}{2}\right]$$

For partial derivatives, differentiating equation (5.16) with respect to δ_t *and* a_t, we get

$$\frac{\partial l_t}{\partial \delta_t} = f_{t_i}\delta_t(-e^{a_t})$$

$$= f_{t_i}\delta_t(-e^{a_t})$$