



Design of Survival-Hazard and Mathematical Model for High Osmolarity Glycerol Protein using Parametric and Nonparametric Methods

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ABSTRACT: Survival and Hazard probabilities are two different related probabilities for describing survival data. The aim of the investigation of the survival function is to evaluate and compare the survival values of different groups. This paper proposes a Survival/Hazard model and Mathematical model for HOG/p38/MK2 which is one of the MAPK pathways. In Survival/Hazard Model, probability, cumulative distribution function, survival and hazard plots were plotted for Weibull, Exponential, Lognormal and Logistic functions for maximum likelihood (ML) and least square (LS) estimates. Anderson darling statistics (AD) values using ML estimate and correlation values using LS estimate were calculated. In Mathematical Model, AD values are calculated using ML and LS technique for Normal, Kalpan Meier and Herd Johnson approaches for different distribution functions. For Survival/Hazard model, Weibull distribution yields the best results while for mathematical model 0ng/ml of TNF, 100ng/ml of EGF and 0 ng/ml of insulin concentration for Weibull, and Normal distribution function shows remarkable results. No paper till yet worked on such type of problem.

Keywords: HOG/p38/MK2 protein, parametric tests, non-parametric tests, Anderson darling statics value, distribution functions

I. INTRODUCTION

Survival methods integrate data from both uncensored & censored observations as it estimates the main parameters of models [1]. Observations are known as censored if the data and information regarding the survival time are insufficient. Censored data that is non-informative and random is mainly used in order to avoid bias in survival analysis. Time to event and event status (event occur or not) are the two parts for the dependent variable in survival analysis. The response of survival analysis is termed as survival time or event time [2,3]. Survival analysis technique is mainly used to analyze the collected data. It is also defined as a set of a technique for investigating data where the net result is the time until the occurrence of an event of interest. Survival time is a positive number, but ordinary linear regression (OLR) is not the best alternative unless these times are first transfigured in a way that removes the limitation. OLR cannot successfully handle the monitoring of the censoring. For explaining the distribution of time event, two functions are estimated: the hazard function and the survival function. The survival function expresses the probability of surviving up to the time and the hazard function gives the perspective that the event will occur per unit time (assuming that an individual has survived for the particular defined time).

Mitogenic (MAP) kinase [4-7] is one of the important pathways which lead to cell survival [8]. It occurs due to pro-survival proteins [9-10]: epidermal growth factor (EGF) [11-13] and insulin [14-15] and pro-apoptotic protein: Tumor necrosis factor (TNF) [16-18]. MAPK is further categorized into three main groups consisting (a)

extracellular signal-regulated kinase (ERK) pathway which is mediated by mitogenic and differentiation signals, (b) stress-activated protein kinase (SAPK)/ Jun N-terminal kinases (JNK) pathway which respond to stress and inflammatory cytokines; and (c) high osmolarity glycerol (HOG)/p38/MK2 which is activated in response to endotoxins, osmotic stress, and inflammatory cytokines [19].

Survival function estimation is a major component of survival analysis. The survival function if depends on covariance values is a challenging problem. A model is proposed which let us know the time origin of a patient having a particular type of cancer: HT carcinoma cells. The time origin of particular cancer can be time point of diagnosis. To study particular cancer we are working on MK2/ p38/HOG protein that is one of the mitogenic (MAPK) pathways leading to survival/ death. This paper aims to analyze Survival/Hazard Model and Mathematical Model. In Survival/Hazard model, probability density function (pdf), Cumulative Distribution Function (CDF), survival and hazard plot using parametric tests for various distribution functions were plotted for Maximum Likelihood (ML) and Least Square (LS) estimates and adjusted Anderson Darling statics (AD) and correlation values are calculated respectively [20, 21]. Survival and hazard plots were also plotted for Non-parametric tests using Kalpan Meier method. In Mathematical Model the AD values using Normal, Kalpan Meier and Herd Johnson methods for ML and LS approach for various distribution functions are calculated.

Organization of this article is as follows: Section 2 explains the materials and methods which explains the two proposed models. Section 3 explains the results and

discussions of the proposed models which are followed by the conclusion and future work.

II. MATERIALS AND METHODS

In this paper, data is taken from Gaudet *et al.* which consists of different proteins but we are concentrating only on the HOG/ p38/ MK2 pathway. If HOG is present (digitally 1) it leads to cell survival and if it is absent (digitally zero) it leads to cell death/apoptosis [22, 23]. The data is for 0-24 hrs and each distribution is further categorized in 13 different parts. We have used ten different concentrations levels (ng/ml) of EGF, insulin, and TNF- α for cell death/ cell survival for HT-29 human colon carcinoma cells. Fig 1 shows the signal communication network triggered by TNF/ EGF/ Insulin. Red colored boxes signify proteins leading to cell death/apoptosis, green colored boxes signifies proteins leading to cell survival, and blue colored are the marker proteins. The data were normalized to the maximum. All the simulations were carried out in Statistica 11 software in Intel (R) Core™, 3.30 processor, 64-bit operating system. Fig. 2 shows the proposed methodology for designing the different model using HOG protein.

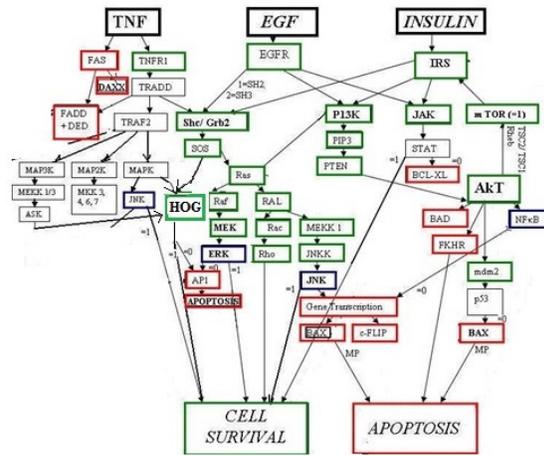


Fig. 1. Different pathways leading to activation of HOG [4].

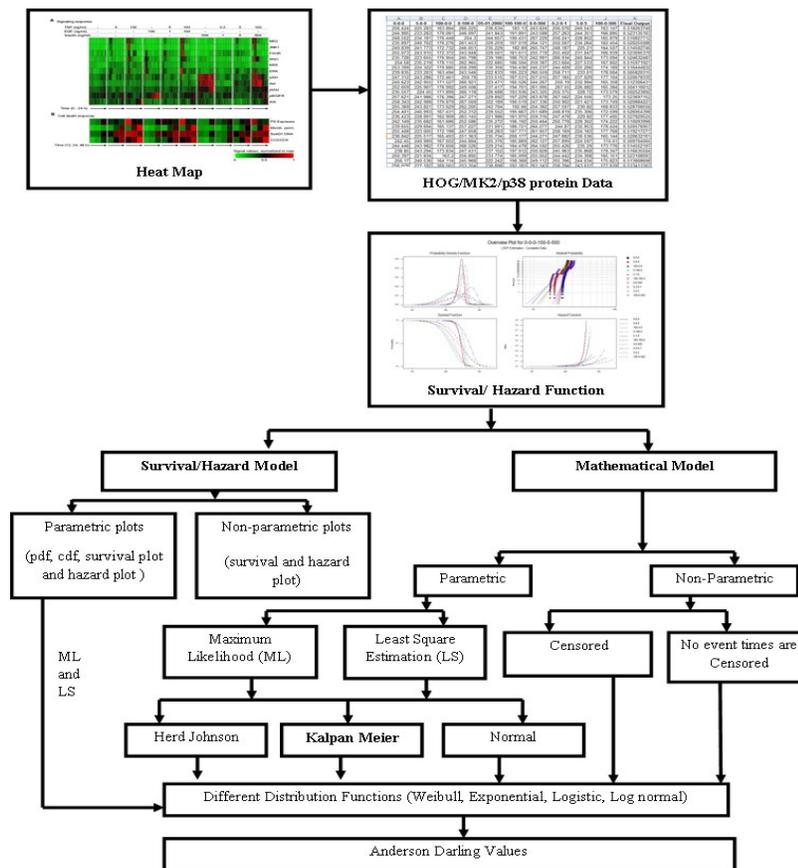


Fig. 2. Proposed Methodology for designing of Computational Model.

In this paper Survival/Hazard Model and Mathematical Model are proposed that are tabulated in Table 1. In the Survival/Hazard model (SHM), survival and hazard functions are calculated using parametric and nonparametric tests while in the Mathematical model (MM), AD values are calculated for different distribution functions. In SHM, pdf, CDF, survival and hazard plots

are plotted for parametric and non-parametric using different distribution functions. In MM, AD values are calculated for different distribution functions using normal, Kalpan Meier and Herd Johnson approach for ML and LS technique. While in nonparametric tests censored and uncensored events are used where Kalpan Meier is used for different distribution functions.

Table 1: Different proposed experiments performed on HOG protein.

Experiment 1	Survival /Hazard Model : Parametric and Non-parametric plots for Survival and Hazard probabilities using different Distribution Functions
Experiment 2	Mathematical Model : Calculation of AD values using Normal, Kalpan Meier and Herd Johnson methods for ML and LS approach for various distribution functions

A. Survival /Hazard Model

Survival and hazard probability are two different related probabilities for describing survival data. The survival probability is also called as survival function expressed as $S(t)$ and hazard probability $h(t)$ is calculated using pdf and CDF for different distribution at $T \geq 0$. Table 2 shows the different calculated functions with their notations used in this paper. The aim of the investigation of survival function is to compare and evaluate survival values of different groups. The use of the survivor function is the prediction of quartiles of the survival time. If the data is highly skewed than the median of the data is preferable over the mean as a measure of centrality. We can easily estimate $S(t)$, if we assume every subject follows the same survival function.

Table 2: Different calculated functions and their notations.

S.No.	Different calculated functions	Notations
1	probability density function or lifetime probability distribution	$f(t)$
2	cumulative distribution function or lifetime distribution function	$F(t)$
3	Survival Probability	$S(t)$
4	Hazard Probability	$h(t)$
5	Cummulative Hazard function	$H(t)$

Survival probability is the probability that an individual survives from the origin to a particular future time t . Survival function is the probability that the survival time is at least and is also the inverse of Lifetime distribution function expressed as $F(t)$.

$$S(t) = P(T \geq t) = \int_t^{\infty} f(u) du = 1 - F(t) \tag{1}$$

$F(t)$ is the probability of failure before a time t . This value can also be obtained by taking CDF of $f(t)$. The differential of $F(t)$ is equal to probability distribution.

$$F(t) = P(T \leq t) \tag{2}$$

$$f(t) = \frac{d}{dt} F(t) = F'(t) \tag{3}$$

$f(t)$ is the probability of the failure time occurring at exactly time t (for all values of t) expressed in Eq. (4).

$$f(t) = \lim_{dt \rightarrow 0} \frac{P(t \leq T < t + dt)}{dt} \tag{4}$$

The hazard probability is the probability that an individual under observation for a time t has an event for that time. Hazard function is the immediate death rate for an individual who has survived for time t . Hazard is a measure of risk, it is not a probability or density. Greater the hazard between time t_1 and t_2 , more is the failure risk of that time interval. Hazard function explains how the rate of event is happening. The hazard function can be solved by using Baye's Rule expressed by Eq. (5)

$$\lambda(t) dt = h(t) dt = \lim_{\Delta t \rightarrow 0} P(t \leq T < t + dt / T \geq t) \tag{5}$$

$$= \frac{P(t \leq T < t + dt \& T \geq t)}{P(T \geq t)} \tag{6}$$

$$= \frac{P(t \leq T < t + dt)}{P(T \geq t)} \tag{7}$$

Replace the numerator of Eq. (7) by Eq. (4) and denominator part by Eq. (1), we get

$$= \frac{f(t) dt}{S(t)} \tag{8}$$

Hazard function is useful in survival analysis as it describes the method in which the instantaneous probability of failure for an individual changes with time. The integral of hazard function yields Cumulative Hazard Function (CHF), Λ and is expressed by Eq. (9). As the hazard function is not a probability, likewise CHF is not probability. However it is also a measurement of risk.

$$H(t) = \Lambda(t) = \int_0^t \lambda(u) du = -\log S(t) \tag{9}$$

The greater the value of $\Lambda(t)$, more is the failure risk by time t . Survival function can be expressed by Eq. (10) in terms of CHF.

$$S(t) = \exp(-H(t)) \tag{10}$$

Parametric and Non-parametric plots for Survival and Hazard probabilities using different distribution functions have to be calculated. For different distribution functions if T is continuous than the survival probability, hazard probability, pdf, CDF and cumulative hazard function are calculated as per Table 3 while if it is discrete than the calculations are done as per Table 4.

Table 3: Different functions when T is continuous (positive value).

Survival probability	$S(t) = \Pr(T \geq t)$ where $S(0) = 1$ and $S(\infty) = 0$
Cumulative density Function	$F(t) = 1 - S(t) = \Pr(T < t)$
Probability density function	$f(t) = F'(t) = -S'(t)$
Hazard probability	$h(t) = f(t) / S(t)$
Cumulative Hazard function	$H(t) = \int_0^t h(\mu) d\mu$

Table 4: Different functions when T is discrete (taking values $t_1 < t_2 < \dots$).

Survival probability	$S(t) = \sum f_i I(t_i \geq t)$ where $I(A) = \begin{cases} 1 & \text{if A is true} \\ 0 & \text{otherwise} \end{cases}$
Cumulative density Function	$F(t) = 1 - S(t) = \sum f_i I(t_i < t)$
Probability density function	$f(t) = \begin{cases} f_i & \text{if } t = t_i \\ 0 & \text{otherwise} \end{cases}$ where $f_i = Pr(T = t_i)$
Hazard probability	$h(t) = f(t) / S(t)$
Cumulative Hazard function	$H(t) = \sum h(t_i) I(t_i \leq t)$

B. Mathematical Model

If we assume that our data follows the parametric distribution than parametric distribution analysis is used, while if the data is not parametric distributed than non-parametric analysis is used. Parametric distribution analysis is further divided into two methods: ML and LS. ML is evaluated by maximizing the likelihood function for each set of distribution parameters. LS are evaluated by fitting a regression line to the points in a probability plot. The line is formed by regressing time (X) to failure (Y). For each ML and LS method Kaplan Meier, Herd Johnson and normal methods were used to find the Anderson darling value of different distribution functions. Herd Johnson and Kaplan Meier estimators of $R(x)$ are known as product limit estimators [21]. The Anderson darling statics is used to measure the area between the nonparametric step function and fitted curve for the distribution. We can also say that AD is a squared distance that is weighted more likely to occur in the peaks of the distribution. AD is used for the comparison of the fit for the particular distribution. Lower the value of AD better the fitting distribution. AD explains

how far the plot points fall from the fitted line in a PP or how the data follow a particular distribution. In general, Kalpan Meier method is used to get AD values. The p -value for these statistics is not calculated. AD values using Normal, Kalpan Meier and Herd Johnson methods for ML and LS approach for various distribution functions has to be calculated.

III. RESULTS AND DISCUSSIONS

A Survival/Hazard model and mathematical model is designed for HOG protein using survival/ hazard plots and adjusted AD statistics for ML and LS approach for different distribution functions.

A. Survival/Hazard Model

Survival analysis is used to depict the data in which the time to event data or time event is of interest. If the distribution of the survival time follows known probability distribution it is known as parametric method. Parametric and non parametric plots for survival and Hazard probabilities for various distribution functions are calculated. Exponential, Weibull Lognormal and Logistic distributions are some important functions.

- (a) **Exponential** (Exp (λ)): Parameter λ has all the positive values and if $\lambda = 1$ than the distribution is unit standard exponential.
- (b) **Weibull distribution** (λ, γ): If $\gamma = 1$ yields exponential distribution, $\gamma > 1$: hazard function increases from zero (at time zero) to infinity (at time zero) and $\gamma < 1$: hazard function decreases from infinity (at time zero) to zero (at time infinity).
- (c) **Log-normal distribution**: Lognormal (μ, σ^2) $\sim \exp\{N(\mu, \sigma^2)\}$
- (d) **Logistic distribution**: It is obtained as a combination of Gompertz distribution with a gamma distributed variable when mean and variance are equal to one.

Table 5: pdf, CDF, survival, hazard and CHF for different distribution functions.

	pdf	CDF	Survival Function	Hazard Function	CHF
Weibull Distribution Function	$\lambda \gamma t^{\gamma-1} e^{-(\lambda t)^\gamma}$	$1 - e^{-(\lambda t)^\gamma}$	$e^{-(\lambda t)^\gamma}$	$\lambda \gamma t^{\gamma-1}$	λt^γ
Exponential Distribution Function $T \sim \text{Exp}(\lambda)$	$\lambda e^{-\lambda t}$ for $\lambda > 0$	$1 - e^{-\lambda t}$	$e^{-\lambda t}$	λ (constant)	λt
Log normal Distribution Function	$\frac{\varphi\left(\frac{\log(t) - \mu}{\sigma}\right)}{t \sigma}$	$\theta\left(\frac{\log(t) - \mu}{\sigma}\right)$		$f(t) / F(t)$	
Logistic Distribution Function	$a b t^{b-1} (1 + a t^b)^{-2}$		$(1 + a t^b)^{-1}$	$\frac{a b t^{b-1}}{1 + a t^b}$	$\ln(1 + a t^b)$

Kalpan Meier method is mainly used to estimate the survival probability in non parametric estimator. It can be used to obtain univariate descriptive statistics for survival data, including the median survival time, and compare the survival experience for two or more groups of subjects. The main equation of function with its survival function, hazard function, CDF, pdf is tabulated in Table 5. Fig. 3, Fig. 4, Fig. 5, Fig. 6 and Fig. 7 shows the pdf, distribution function, survival function and hazard function for ML estimator of Normal, Exponential, Lognormal, Logistic and Weibull distribution respectively.

Fig. 8, Fig. 9, Fig. 10, Fig. 11 and Fig. 12 shows the pdf, distribution function, survival function and hazard function for LS estimator of Normal, Exponential, Lognormal, Logistic and Weibull distribution respectively. 95% confidence interval limits are very close to the estimated line, therefore we have simulated a dataset with a large sample size.

The four plots describe the survival/failure rate of HOG at ten different combinations of TNF/ EGF/Insulin. With the different plots, we can decide how much more likely the HOG will survive/fail when used in any of the ten combinations using different distribution function for ML and LS estimator [22].

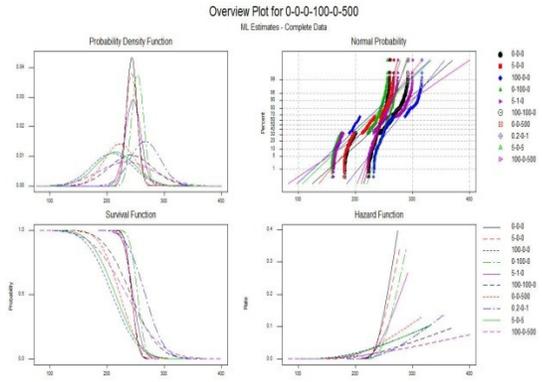


Fig. 3. The different plots for ML estimate using Normal function.

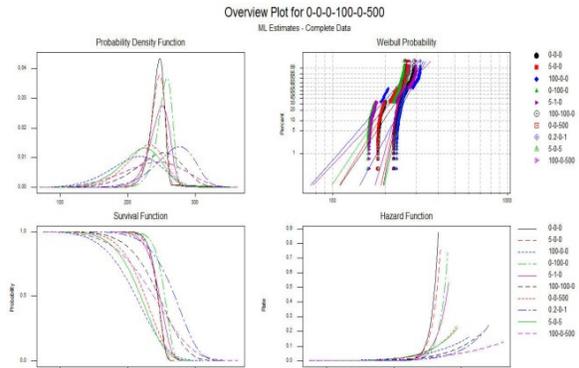


Fig. 7. The different plots for ML estimate using Weibull function.

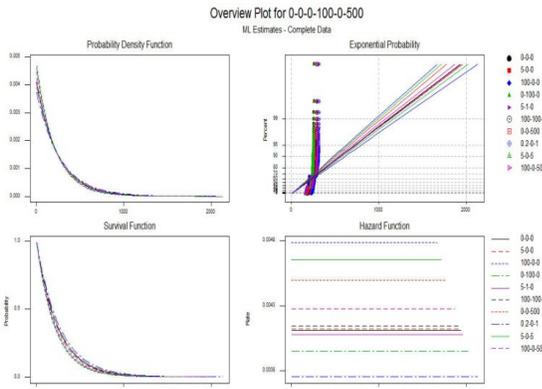


Fig. 4. The different plots for ML estimate using Exponential function.

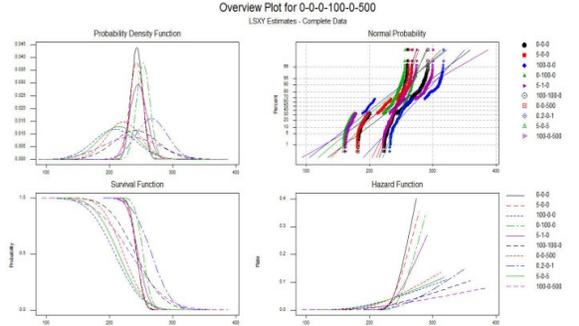


Fig. 8. The different plots for LS estimate using Normal function.

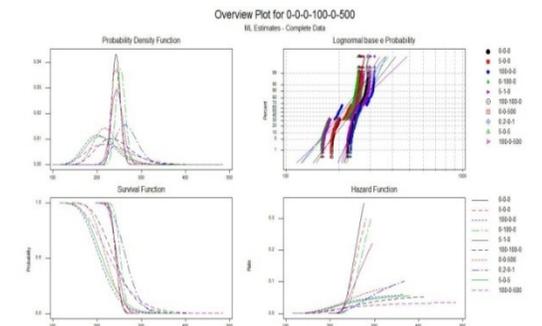


Fig. 5. The different plots for ML estimate using Log normal function.

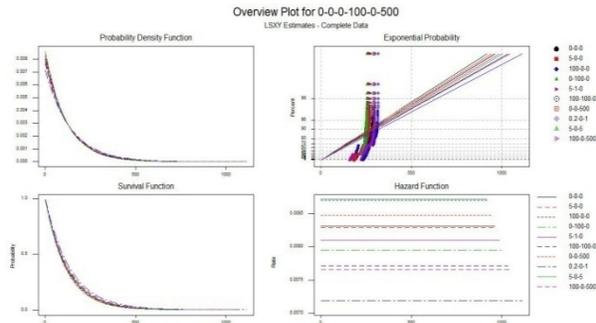


Fig. 9. The different plots for LS estimate using Exponential function.

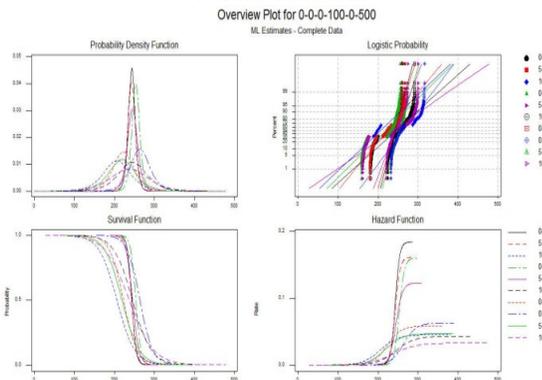


Fig. 6. The different plots for ML estimate using Logistic function.

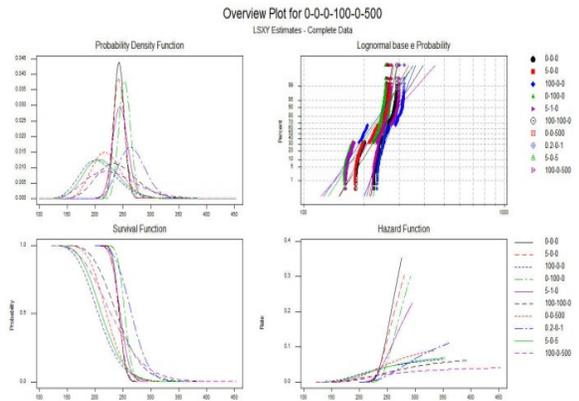


Fig. 10. The different plots for LS estimate using Log normal function.

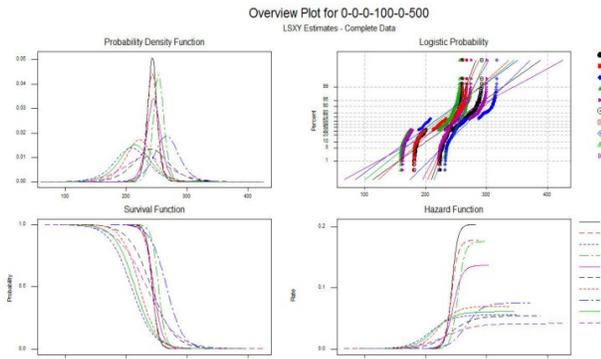


Fig. 11. The different plots for LS estimate using Logistic function.

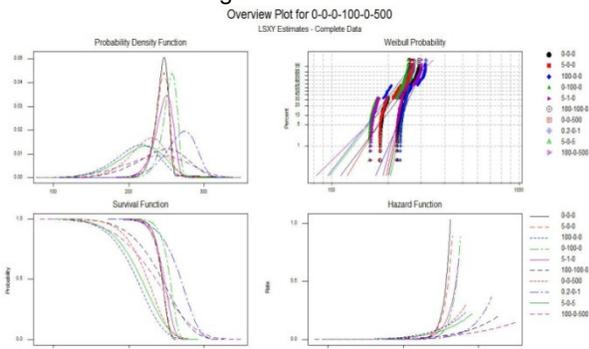


Fig. 12. The different plots for LS estimate using Weibull function.

The four curves in Fig. 3 to Fig. 12 represent parametric plots. *Subplot 1* is the pdf, that displays the curve which describes the distribution of our data; *sub plot 2* shows the probability plot, which displays the CDF vs. failure time; *sub plot 3* shows the parametric survival plot, that shows the survival function vs. failure time and *sub plot 4* depicts the parametric hazard plot, that shows the hazard function vs. failure time. Parametric survival and hazard plots are based on a fitted distribution and therefore the curves are smooth.

Fig. 13 and Fig. 14 shows the ML and LS estimate plot for Weibull, Lognormal, Exponential and Normal distribution function. From Fig. 13, authors have also calculated the AD values which is 18.5 for Weibull, 23.3 for lognormal, 127 for exponential and 22.6 for normal distribution function using ML estimates.

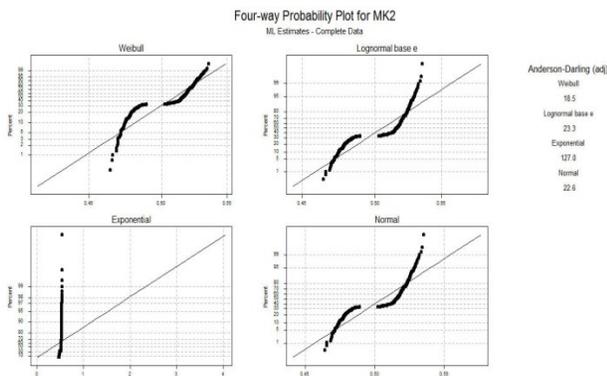


Fig. 13. Different plots for ML method using various distribution functions.

The correlation coefficients values for LS estimate are 0.922 for Weibull, 0.908 for Lognormal, and 0.911 for Normal distribution function is calculated using Fig 14. The AD values should be minimum and correlation values should be maximum, based on this author can say the best model is obtained using Weibull distribution function.

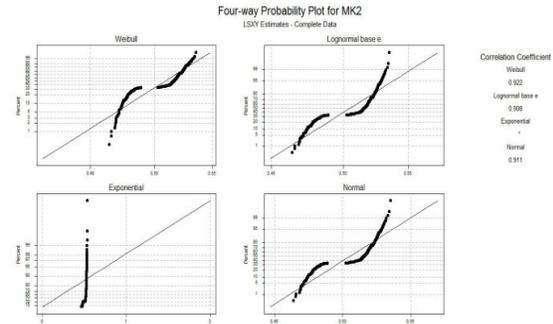


Fig. 14. Different plots for LS method using various distribution functions.

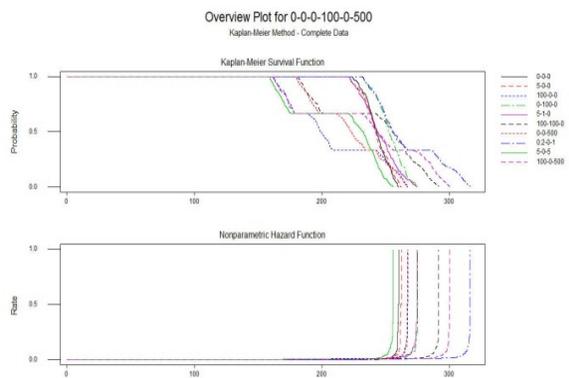


Fig. 15. Non parametric survival and hazard function.

Nonparametric plots: The nonparametric survival and hazard curves are step function because the empirical hazard function and Kalpan Meier survival estimates change values at exact failure times. Fig 15 shows the Kaplan Meier nonparametric plot of survival and hazard for HOG protein.

B. Mathematical Model

There are various methods for analyzing the relationship of predictor variables with survival time consisting of parametric, semiparametric and nonparametric. For estimating conditional survival functions, non-parametric estimators are preferred over the other two estimators due to robust estimation. Parametric and semi-parametric estimators, possess better operational characteristics than non-parametric estimators for small size data. Calculation of AD values using Normal, Kalpan Meier (KM) and Herd Johnson (HJ) methods for ML and LS approach for various distribution functions has been done. Fig. 16 to Fig. 20 shows the AD for the normal, KM and HJ method values for the ML and LS approach for 10 different values of three input proteins. Fig. 16 shows the AD values for Normal distribution, Fig 17 explains for Weibull distribution, Fig. 18 explains for the Exponential distribution, Fig. 19 explains for the Lognormal distribution, and Fig. 20 explains for Logistic distribution.

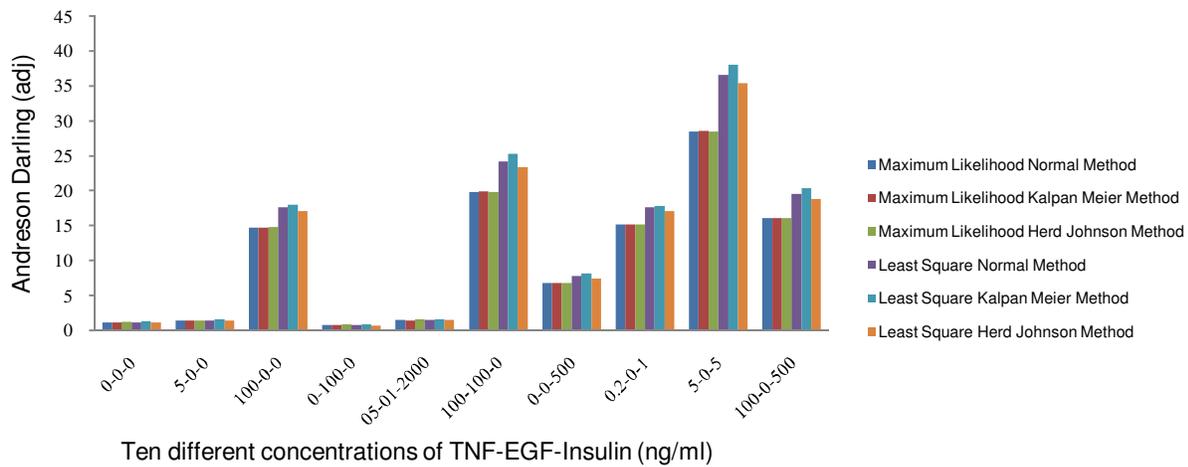


Fig. 16. AD values for ML and LS estimates using normal, KM and HJ method values for Normal Distribution.

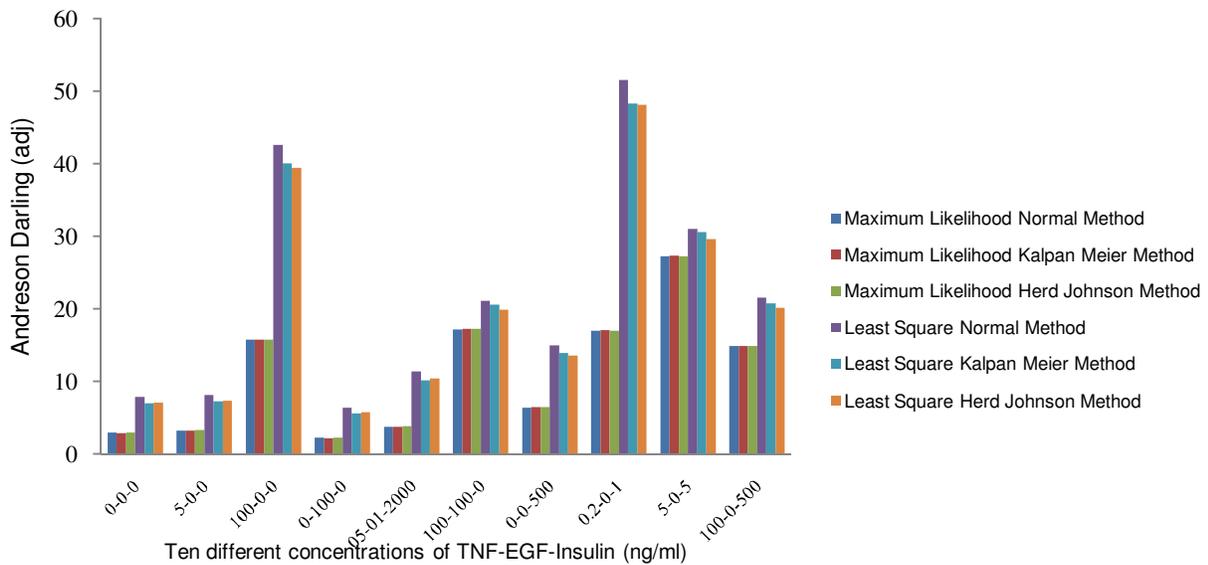


Fig. 17. AD values for ML and LS estimates using normal, KM and HJ method values for Weibull Distribution.

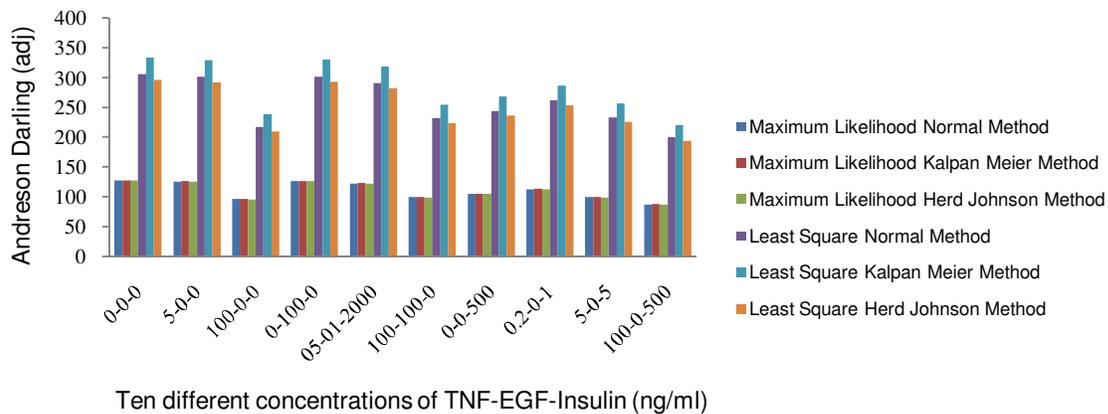


Fig. 18. AD values for ML and LS estimates using normal, KM and HJ method values for Exponential Distribution.

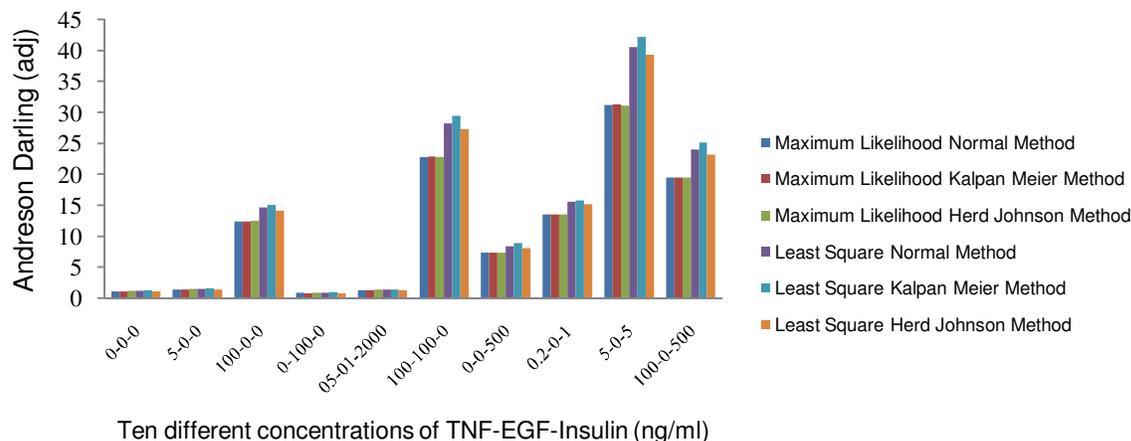


Fig. 19. AD values for ML and LS estimates using normal, KM and HJ method values for Lognormal Distribution.

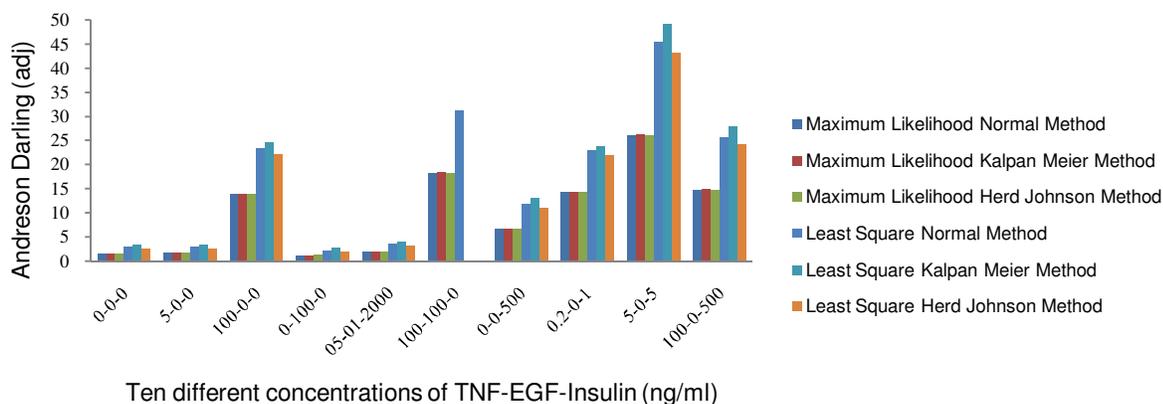


Fig. 20. AD values for ML and LS estimates using normal, KM and HJ method values for Logistic Distribution.

For Normal, Weibull, Lognormal and Logistic distributions, the best AD statistics is for 0 ng/ml of TNF, 100 ng/ml of EGF and 0 ng/ml of insulin concentration for ML and LS method, while for exponential distribution the best AD statistics is for 100 ng/ml of TNF, 0 ng/ml of EGF and 0 ng/ml of insulin concentration.

Table 6 and Table 7 shows that the comparison of Survival/Hazard model and Mathematical model respectively. From the tables author can interpret that for different marker proteins the concentration of TNF-EGF-Insulin are different. Also the distribution functions are different for different marker proteins.

Table 6: Comparison with other state of art technique for Survival/Hazard Model.

	Protein	AD values	Best Distribution Function
Proposed Model	p38/MK2/ HOG	18.5	Weibull
[21]	AkT	1.6	Normal

Table 7: Comparison with other state of art technique for Mathematical Model.

	Protein	Combination TNF-EGF-Insulin (ng/ml)	AD values	Best Distribution Function
Proposed Model	p38/MK2/ HOG	0-100-0	2.14	Weibull
		0-100-0	0.78	Normal
[21]	AkT protein	5-0-0	1.57	Lognormal
		5-0-0	1.68	Normal

AD values should be minimum, so for Mathematical model it can interpret that for TNF-EGF-Insulin combination of 0-100-0 ng/ml yields the best result using Normal distribution.

IV. CONCLUSION

In this paper we have proposed Survival/Hazard model and mathematical model to make a best linear model using ten concentrations combination of different pro-survival and pro- death protein for HOG. Different plots are plotted using maximum likelihood (ML) and least square (LS) estimates for parametric and non-parametric approaches. We have calculated the Anderson darling statistics for normal, Kalpan Meier and Herd Johnson method for LS and ML approaches for different distribution functions. The best results for Survival/Hazard model are obtained for Weibull distribution function due to its less AD values. For mathematical model; 0 ng/ml of TNF, 100 ng/ml of EGF and 0 ng/ml of insulin concentration give the best result of AD for Normal distribution function. In future other marker proteins were taken into consideration.

Conflict of interest declaration: The authors declare that there is no conflict of interest of any sort on this research.

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