# Parametric and non parametric distribution analysis of AkT for cell survival/death

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**Abstract:** AkT (protein kinase B) is a central signalling molecule in the phosphatidylinositol 3-kinase (PI3K) pathway that is frequently activated in human cancer. AkT promotes cell survival/death by activating or deactivating different proteins. In this paper a model was designed using parametric or non parametric distribution analysis. Anderson Darling adjustment values was calculated using maximum likelihood and least square estimators as parametric function in which normal, Kaplan Meier and Herd Johnson tests were done for different distribution functions for ten cominations of TNF/EGF and insulin. For non-parametric analysis: survival and hazard plots were plotted using Kaplan Meier estimator.

**Keywords:** protein kinase B; AkT; distribution functions; Kaplan Meier; Herd Johnson.

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**Biographical notes:** Shruti Jain received her PhD (Jaypee University of Information Technology, 2012); Mtech (Rajasthan Vidyapeeth University, 2007) and B-Tech (Kurukshetra University, 2004). She has published more than 25 papers in journals and 20 papers in conferences. She is a Senior Member of IEEE and IAENG. Her area of interest is bio-electronics and VLSI. She completed one externally funded project. She guided one PhD student, and member of many committees.

## 1 Introduction

The serine/threonine kinase Akt/PKB/Rac was first identified as an oncogene and as a kinase (Cohen, 2002; Jain, 2012; Jain et al., 2011a, 2011b; Jain and Naik, 2012; Jain et al., 2010) with properties resembling both PKA and PKC (hence PKB) (Coffer et al., 1998; Hemmings, 1997; Brunet et al., 1999; Jain and Chauhan, 2015; Jain et al., 2012; Gaudet et al., 2005). Translocation of AkT to the plasma membrane through its pleckstrin homology domain is likely required for its activity (Janes et al., 2005; Zhou, 2006), and constitutive targeting of Akt to the plasma membrane is sufficient to promote its activation. Both the upstream activating kinases and the recruitment of Akt to the plasma membrane are dependent upon the products of PI3K. Akt is important for mediating the

effects of these growth factors on the control of mammalian cell cycle progression and cell survival, as well as on the regulation of processes that influence growth, including protein synthesis and glucose metabolism. Akt plays a key role in the coordinated regulation of growth, apoptosis and metabolism by the TNF, EGF and insulin/ IGF-signalling pathway (Jain et al., 2011a, 2011b; Jain and Naik, 2012). Examples of such early signals include phosphatidylserine exposure, membrane permeability, nuclear fragmentation and caspase substrate cleavage (Bonni et al., 1999; Jain and Naik, 2012; Jain, 2015; Jain and Chauhan, 2015b; Jain, 2016a, 2016b).

In this paper a computational model and linear model was designed using different distribution functions. Initially parametric statics was done using maximum likelihood and least square analysis. For both analyses Anderson Darling values using normal method, Kaplan Meier method (KM) and Herd Johnson method (HJ) were calculated for different distribution functions (normal, Weibull, exponential, log-normal, and logistic).

To explore systematically relationships between cytokine-receptor interaction, activation of intracellular signalling cascades, and apoptosis-survival cell-fate decisions, cells were exposed to a set of ten cytokine treatments shown in Table 1 and monitored over a 48-hr period (Jain, 2012). Each treatment consisted of a combination of TNF and either EGF or insulin (Jain, 2012). Cells respond to TNF, EGF, and insulin in a dose-dependent manner and all three cytokines were therefore examined at sub saturating concentrations, designed to mimic physiological conditions, and at saturating concentrations, at which essentially all receptors were ligand-bound. At 13 time points after cytokine addition, three replicate dishes of cells (six for the zero time point) were harvested to measure kinase activities, changes in protein phosphorylation, caspase cleavage, and changes in protein abundance. All together, AkT signals were examined.

**Table 1** Ten cytokine treatments

| | *(a)* | *(b)* | *(c)* | *(d)* | *(e)* | *(f)* | *(g)* | *(h)* | *(i)* | *(j)* |
|---|---|---|---|---|---|---|---|---|---|---|
| TNF(ng/ml) | - | 5 | 100 | - | 5 | 100 | - | 0.2 | 5 | 100 |
| EGF(ng/ml) | - | - | - | 100 | 1 | 100 | - | - | - | - |
| Insulin(ng/ml) | - | - | - | - | - | - | 500 | 1 | 5 | 500 |

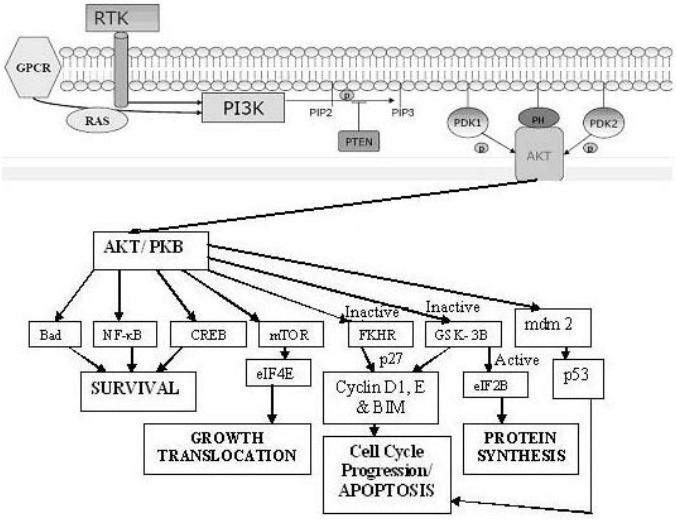
## 2 Computational model

The prediction model for cell survival/death heading by AkT has been implemented (Jain, 2012; Jain and Chauhan, 2015; Jain et al., 2012). The block diagram of the signalling system that was modelled is shown in Figure 1. TNF, EGF and insulin activate the PI3-Akt signalling cascade through corresponding receptor tyrosine kinases such as the high affinity neurotrophin receptors (Trk's). After receptor dimerisation, PI3K is recruited to the plasma membrane where its catalytic subunit generates lipid second messengers, phosphoinositide phosphates (PIP2, PIP3), at the inner surface of the plasma membrane. Phosphoinositide-dependent protein kinase-1 (PDK1) then acts in concert with PIP2 and PIP3 to phosphorylate and activate Akt. Dominant-negative and constitutively active forms of Ras, PI3K, and Akt have been used to study signalling through the PI3K-Akt pathway. These and other studies have demonstrated downstream

signalling effects that regulate cellular survival, proliferation, and metabolism. For example, Akt phosphorylates and inactivates FKHR1, a member of the family of Forkhead transcriptional regulators. Inactivated FKHR1 is unable to induce the expression of death genes. Akt activates the cAMP-responsive element binding protein (CREB) and nuclear factor-κB (NF-κB), additional transcriptional regulators that may promote neuronal survival. In addition, Akt can directly inhibit the apoptotic machinery by phosphorylation at sites both upstream (BAD) and downstream (Caspase-9) of mitochondrial cytochrome c release. Finally, there is evidence to support the role of Akt in promoting neuronal survival through metabolic effects, by regulating glucose metabolism in neurons.

Akt promotes cell survival by inhibiting apoptosis by phosphorylating and inactivating several targets, including Bad, forkhead transcription factors, c-Raf and caspase-9. Phosphatase and tensin homolog (PTEN) phosphatase is a major negative regulator of the PI3 kinase/Akt signalling pathway. In addition to its role in survival and glycogen synthesis, Akt is involved in cell cycle regulation by preventing GSK-3$\beta$ mediated phosphorylation and degradation of cyclin D1 and by negatively regulating the cyclin dependent kinase inhibitors p27 Kip and p21 Waf1/CIP1. Akt also plays a critical role in cell growth by directly phosphorylating mTOR in a rapamycin-sensitive complex containing raptor. More importantly, Akt phosphorylates and inactivates tuberin (TSC2), an inhibitor of mTOR within the mTOR-raptor complex. Inhibition of mTOR stops the protein synthesis machinery due to inactivation of its effector, p70 S6 kinase and activation of the eukaryotic initiation factor 4E binding protein 1 (4E-BP1), an inhibitor of translation. AKT promotes cell survival through the transcription of anti-apoptotic proteins. Intermediate transcription factors involved in this process are NF-κB and CREB.

**Figure 1** Block diagram of cell signalling regulated by AkT

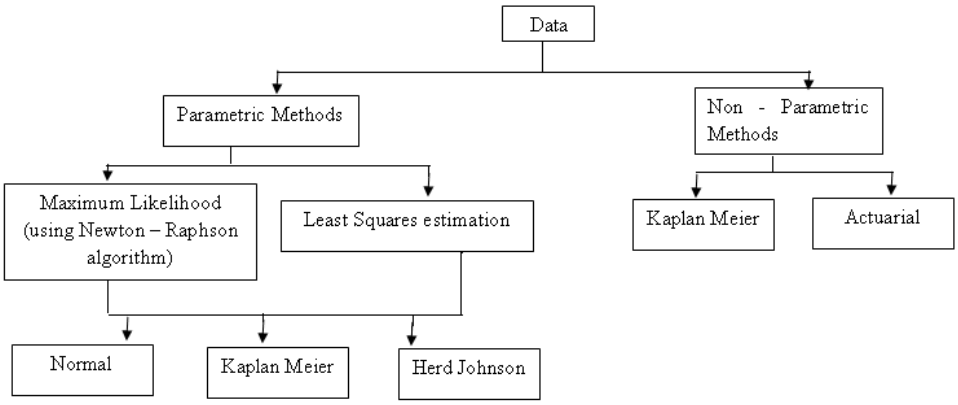



*Source:* Jain (2012)

## 3 Parametric and non-parametric analysis using different distribution functions

In this paper we are using parametric and non parametric distribution analysis. The parametric distribution analysis was done when we can assume our data follows a parametric distribution while in the nonparametric distribution analysis we cannot assume a parametric distribution. For parametric distribution analysis further two methods were used: maximum likelihood estimates (MLE), and least squares estimates (LSXY) shown in Fig 2. MLE are calculated by maximising the likelihood function. The likelihood function describes, for each set of distribution parameters, the chance that the true distribution has the parameters based on the sample. LSXY are calculated by fitting a regression line to the points in a probability plot. The line is formed by regressing time (X) to failure (Y) or log (time to failure) on the transformed percent.

**Figure 2** Parametric and non parametric analysis used for AkT




For each MLE and LSXY method Kaplan Meier (KM), herd Johnson (HJ) 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. Let $i$ be the $i^{\text{th}}$ failure with reverse rank $r_i = n - i + 1$ then the reliability is recursively calculated in both. The Herd Johson (HJ estimator) is

$$\hat{R}_i^* = \frac{r_i}{r_i + 1}\hat{R}_{i-1}^*, \quad \hat{R}_0^* = 1 \tag{1}$$

and Kaplan Meier (KM estimator) is

$$\hat{R}_i^+ = \frac{r_i - 1}{r_i}\hat{R}_{i-1}^+, \quad \hat{R}_0^+ = 1 \tag{2}$$

Corresponding failure probabilities are

$$\hat{F}_i^* = 1 - \hat{R}_i^* \text{ (for HJ)}; \quad \hat{F}_i^+ = 1 - \hat{R}_i^+ \text{ (for KM)}. \tag{3}$$

When the sample is complete HJ estimator results in $\hat{F}_i = \frac{1}{n+1}$ while KM estimator results in $\hat{F}_i = \frac{1}{n}$.

### *3.1 Parametric distribution analysis*

There are different distribution functions like normal, Weibull, lognormal base e, lognormal base 10, exponential, and logistic.

#### *3.1.1 A normal distribution is expressed as*

$$f(x, \mu, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} e^{\frac{-(x-\mu)^2}{2\sigma^2}} \tag{4}$$

where $\mu$ defines the mean or expectation (median and mode) of the distance; $\sigma$ is standard deviation. If $\mu = 0$ and $\sigma = 1$ the distance is called standard/unit normal distance. We have calculated the Anderson darling adjustment values shown in Table 2.

**Table 2** Normal, Kaplan Meier and Herd Johnson methods using maximum likelihood and least square for normal distribution function

| | *Maximum likelihood* | | | *Least square* | | |
|---|---|---|---|---|---|---|
| | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* |
| 0-0-0 | 7.66 | 7.65 | 7.73 | 8.53<br>0.964 | 8.65<br>0.963 | 8.23<br>0.966 |
| 5-0-0 | 1.71 | 1.68 | 1.77 | 1.78<br>0.989 | 1.90<br>0.986 | 1.69<br>0.990 |
| 100-0-0 | 36.93 | 37.03 | 36.93 | 49.65<br>0.861 | 50.18<br>0.861 | 48.27<br>0.864 |
| 0-100-0 | 3.75 | 3.72 | 3.82 | 4.02<br>0.981 | 4.10<br>0.979 | 3.85<br>0.982 |
| 5-1-0 | 31.41 | 31.50 | 31.36 | 41.06<br>0.880 | 42.68<br>0.876 | 39.81<br>0.882 |
| 100-100-0 | 1.78 | 1.76 | 1.84 | 1.85<br>0.988 | 2.02<br>0.985 | 1.77<br>0.989 |
| 0-0-500 | 9.31 | 9.32 | 9.38 | 10.76<br>0.955 | 11.06<br>0.953 | 10.34<br>0.957 |
| 0.2-0-1 | 14.12 | 14.15 | 14.14 | 16.44<br>0.942 | 17.23<br>0.939 | 15.88<br>0.944 |
| 5-0-5 | 42.12 | 42.25 | 42.13 | 59.50<br>0.839 | 60.24<br>0.839 | 57.81<br>0.841 |
| 100-0-500 | 19.27 | 19.32 | 19.29 | 24.12<br>0.915 | 25.07<br>0.912 | 23.29<br>0.917 |

When we use parametric distribution we get four different curves with the Anderson Darling values shown in Figure 3.

1 A probability plot, which displays estimates of the cumulative distribution function $F(y)$ vs. failure time.

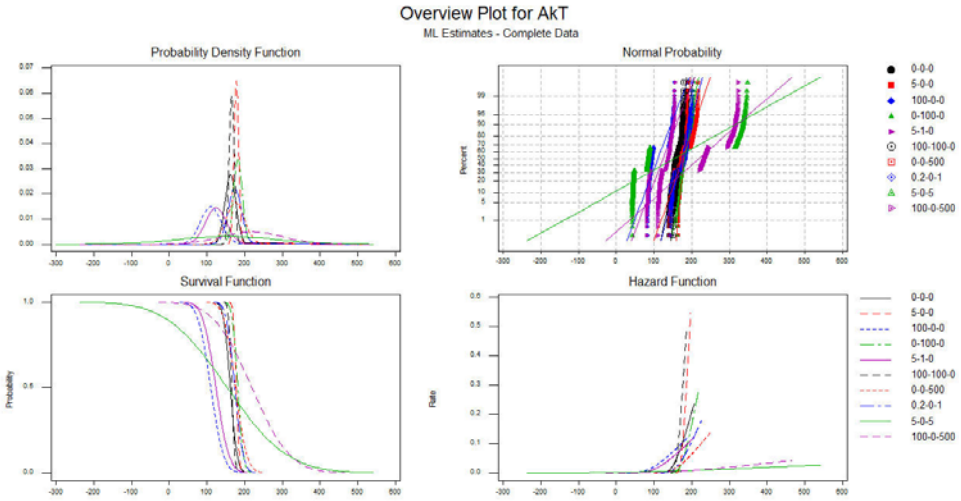
2 A parametric survival (or reliability) plot, which displays the survival (or reliability) function $1 - F(y)$ vs. failure time.

3 A probability density function, which displays the curve that describes the distribution of our data, or $f(y)$.

4 A parametric hazard plot, which displays the hazard function or instantaneous failure rate, $f(y)/(1 - F(y))$ vs. failure time.

These four plots describe the survival/failure rate of AkT at ten different Combinations of TNF/ EGF/Insulin. With these plots, we can determine how much more likely it is that the AkT will survive/fail when used in any of the ten combinations using normal distribution function using ML estimator for normal method. Similarly we can plot for MLE and LSXY for normal, Kaplan Meier and Herd Johnson method using different distribution functions.

**Figure 3** Different plots of AkT using ML estimator for normal distribution function (see online version for colours)




### 3.1.2 *A Weibull distribution function: the probability density function of a Weibull function is expressed as*

$$f(x;\lambda,k)=\begin{cases}\dfrac{k}{\lambda}\left(\dfrac{x}{\lambda}\right)^{k-1}e^{-\left(x/\lambda\right)^{k}} & x\geq 0\\ 0 & x<0\end{cases} \tag{5}$$

where $k > 0$ is the shape parameter and $\lambda > 0$ is the scale parameter of the distribution. If $k = 2$ and $\lambda = \sqrt{2}\lambda$, than Weibull function equals to Rayleigh distribution. We have calculated the Anderson darling adjustment values shown in Table 3.

**Table 3** Normal, Kaplan Meier and Herd Johnson methods using maximum likelihood and least square for Weibull distribution function

| | *Maximum likelihood* | | | *Least square* | | |
|---|---|---|---|---|---|---|
| | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* |
| 0-0-0 | 9.95 | 9.98 | 10 | 28.9<br>0.915 | 26.8<br>0.920 | 26.7<br>0.919 |
| 5-0-0 | 4.03 | 4.01 | 4.07 | 10.6<br>0.961 | 9.6<br>0.965 | 9.7<br>0.965 |
| 100-0-0 | 34.59 | 34.71 | 34.58 | 118.6<br>0.796 | 112.3<br>0.802 | 111.1<br>0.801 |
| 0-100-0 | 5.98 | 5.99 | 6.04 | 17.5<br>0.937 | 16.0<br>0.942 | 16.1<br>0.941 |
| 5-1-0 | 31.77 | 31.88 | 31.77 | 36.6<br>0.873 | 36.0<br>0.876 | 34.9<br>0.878 |
| 100-100-0 | 3.36 | 3.34 | 3.41 | 7.7<br>0.971 | 7.0<br>0.975 | 6.9<br>0.975 |
| 0-0-500 | 10.35 | 10.38 | 10.4 | 27.2<br>0.914 | 25.4<br>0.919 | 25.0<br>0.919 |
| 0.2-0-1 | 10.5 | 10.55 | 10.57 | 13.8<br>0.928 | 13.3<br>0.932 | 12.9<br>0.932 |
| 5-0-5 | 30.31 | 30.41 | 30.32 | 92.4<br>0.826 | 87.6<br>0.832 | 86.1<br>0.832 |
| 100-0-500 | 20.89 | 20.96 | 20.93 | 29.4<br>0.881 | 28.5<br>0.885 | 27.6<br>0.886 |

### *3.1.3 An exponential distribution function*

The exponential distribution is not the same as the class of exponential families of distributions, which is a large class of probability distributions that includes the exponential distribution as one of its members, but also includes the normal distribution, binomial distribution, gamma distribution, poission distribution and many others. The probability density function of an exponential distribution is expressed as

$$f(x;\lambda) = \begin{cases} \lambda e^{-\lambda x} & x \geq 0, \\ 0 & x < 0. \end{cases} \tag{6}$$

Here $\lambda > 0$ is the parameter of the distribution, often called the rate parameter. The distribution is supported on the interval $[0, \infty]$. In equation (5) if $k = 1$ than Weibull distribution equals to exponential distribution. We have calculated the Anderson Darling adjustment values shown in Table 4.

**Table 4** Normal, Kaplan Meier and Herd Johnson methods using maximum likelihood and least square for exponential distribution function.

| | *Maximum likelihood* | | | *Least square* | | |
|---|---|---|---|---|---|---|
| | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* |
| 0-0-0 | 114.6 | 114.9 | 114.3 | 268.3 | 294.0 | 260.0 |
| 5-0-0 | 127.9 | 128.3 | 127.6 | 307.9 | 336.6 | 298.7 |
| 100-0-0 | 86.4 | 86.7 | 86.2 | 186.1 | 205.3 | 180.0 |
| 0-100-0 | 120.1 | 120.5 | 119.8 | 284.5 | 0311.4 | 275.9 |
| 5-1-0 | 86.9 | 87.1 | 86.7 | 202.7 | 223.8 | 195.8 |
| 100-100-0 | 126.3 | 126.7 | 126.0 | 303.6 | 331.9 | 294.4 |
| 0-0-500 | 102.6 | 102.9 | 102.4 | 236.3 | 259.6 | 228.8 |
| 0.2-0-1 | 111.2 | 111.5 | 110.9 | 262.9 | 288.3 | 254.6 |
| 5-0-5 | 25.1 | 25.1 | 25.1 | 33.0 | 37.2 | 31.8 |
| 100-0-500 | 57.3 | 57.4 | 57.1 | 128.5 | 143.9 | 123.5 |

### *3.1.4 A lognormal distribution function*

In probability theory, a log-normal (or lognormal) distribution is a continuous probability distribution of a random variable whose logarithm is normally distributed. Thus, if the random variable $X$ is log-normally distributed, then $Y = \log(X)$ has a normal distribution. Likewise, if $Y$ has a normal distribution, then $X = \exp(Y)$ has a log-normal distribution. A random variable which is log-normally distributed takes only positive real values. A log-normally distributed random variable $X$ and two parameters $\mu$ and $\sigma$ that are, respectively, the mean and standard deviation of the variable's natural logarithm (by definition, the variable's logarithm is normally distributed), we can write $X$ as

$$X = e^{(\mu+\sigma Z)}$$

with $Z$ a standard normal variable. On a logarithmic scale, $\mu$ and $\sigma$ can be called the location parameter and the scale parameter, respectively. In contrast, the mean ($m$), standard deviation ($sd$), and variance ($v$) of the non-logarithmised sample values are:

$$\mu = \ln\left(\frac{m}{\sqrt{1+\frac{v}{m^2}}}\right), \sigma = \sqrt{\ln\left(1+\frac{v}{m^2}\right)} \tag{7}$$

We have calculated the Anderson Darling adjustment values shown in Table 5 and Table 6 respectively.

**Table 5** Normal, Kaplan Meier and Herd Johnson methods using maximum likelihood and least square for lognormal e

| | *Maximum likelihood* | | | *Least square* | | |
|---|---|---|---|---|---|---|
| | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* |
| 0-0-0 | 6.56 | 6.54 | 6.62 | 7.27<br>0.969 | 7.42<br>0.967 | 6.98<br>0.970 |
| 5-0-0 | 1.60 | 1.57 | 1.66 | 1.67<br>0.989 | 1.80<br>0.986 | 1.58<br>0.990 |
| 100-0-0 | 33.41 | 33.49 | 33.42 | 44.15<br>0.873 | 44.71<br>0.872 | 42.88<br>0.875 |
| 0-100-0 | 3.27 | 3.24 | 3.33 | 3.49<br>0.983 | 3.61<br>0.981 | 3.32<br>0.984 |
| 5-1-0 | 35.23 | 35.31 | 35.15 | 46.97<br>0.867 | 48.84<br>0.862 | 45.57<br>0.869 |
| 100-100-0 | 1.81 | 1.79 | 1.86 | 1.88<br>0.987 | 2.08<br>0.984 | 1.81<br>0.989 |
| 0-0-500 | 8.27 | 8.27 | 8.33 | 9.53<br>0.959 | 9.89<br>0.956 | 9.13<br>0.961 |
| 0.2-0-1 | 15.85 | 15.88 | 15.86 | 18.61<br>0.936 | 19.51<br>0.932 | 17.99<br>0.938 |
| 5-0-5 | 26.85 | 26.91 | 26.88 | 35.14<br>0.888 | 35.87<br>0.886 | 34.03<br>0.890 |
| 100-0-500 | 25.66 | 25.73 | 25.65 | 33.10<br>0.894 | 34.45<br>0.890 | 32.01<br>0.896 |

**Table 6** Normal, Kaplan Meier and Herd Johnson methods using maximum likelihood and least square for Lognormal 10

| | *Maximum likelihood* | | | *Least square* | | |
|---|---|---|---|---|---|---|
| | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* |
| 0-0-0 | 6.56 | 6.54 | 6.62 | 7.27<br>0.969 | 7.42<br>0.967 | 6.98<br>0.970 |
| 5-0-0 | 1.60 | 1.57 | 1.66 | 1.67<br>0.989 | 1.80<br>0.986 | 1.58<br>0.990 |
| 100-0-0 | 33.41 | 33.49 | 33.42 | 44.15<br>0.873 | 44.71<br>0.872 | 42.88<br>0.875 |
| 0-100-0 | 3.27 | 3.24 | 3.33 | 3.49<br>0.983 | 3.61<br>0.981 | 3.32<br>0.984 |
| 5-1-0 | 35.23 | 35.31 | 35.15 | 46.97<br>0.867 | 48.84<br>0.862 | 45.57<br>0.869 |

**Table 6** Normal, Kaplan Meier and Herd Johnson methods using maximum likelihood and least square for Lognormal 10 (continued)

| | *Maximum likelihood* | | | *Least square* | | |
|---|---|---|---|---|---|---|
| | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* |
| 100-100-0 | 1.81 | 1.79 | 1.86 | 1.88<br>0.987 | 2.08<br>0.984 | 1.81<br>0.989 |
| 0-0-500 | 8.27 | 8.27 | 8.33 | 9.53<br>0.959 | 9.89<br>0.956 | 9.13<br>0.961 |
| 0.2-0-1 | 15.85 | 15.88 | 15.86 | 18.61<br>0.936 | 19.51<br>0.932 | 17.99<br>0.938 |
| 5-0-5 | 26.85 | 26.91 | 26.88 | 35.14<br>0.888 | 35.87<br>0.886 | 34.03<br>0.890 |
| 100-0-500 | 25.66 | 25.73 | 25.65 | 33.10<br>0.894 | 34.45<br>0.890 | 32.01<br>0.896 |

### *3.1.5 A logistic distribution function*

The pdf of the logistic distribution is given by:

$$f\left(x;\mu,s\right)=\frac{e^{-\frac{x-\mu}{s}}}{s\left(1+e^{-\frac{x-\mu}{s}}\right)}=\frac{1}{4s}\sec h^2\left(\frac{x-\mu}{2s}\right) \tag{8}$$

Because the pdf can be expressed in terms of the square of the hyperbolic secant function 'sech', it is sometimes referred to as the *sech-square(d) distribution*. We have calculated the Anderson Darling adjustment values shown in Table 7.

**Table 7** Normal, Kaplan Meier and Herd Johnson methods using maximum likelihood and least square for logistic distribution function

| | *Maximum likelihood* | | | *Least square* | | |
|---|---|---|---|---|---|---|
| | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* |
| 0-0-0 | 7.47 | 7.40 | 7.53 | 12.40<br>0.946 | 13.03<br>0.941 | 11.59<br>0.950 |
| 5-0-0 | 2.11 | 2.08 | 2.15 | 3.67<br>0.975 | 4.22<br>0.968 | 3.28<br>0.979 |
| 100-0-0 | 34.30 | 34.26 | 34.32 | 60.05<br>0.839 | 61.69<br>0.836 | 57.40<br>0.844 |
| 0-100-0 | 4.03 | 3.98 | 4.08 | 6.96<br>0.965 | 7.50<br>0.960 | 6.38<br>0.968 |
| 5-1-0 | 28.62 | 28.86 | 28.55 | 50.30<br>0.857 | 54.21<br>0.848 | 47.93<br>0.861 |

**Table 7** Normal, Kaplan Meier and Herd Johnson methods using maximum likelihood and least square for logistic distribution function (continued)

| | *Maximum likelihood* | | | *Least square* | | |
|---|---|---|---|---|---|---|
| | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* | *Normal method* | *Kaplan Meier method* | *Herd Johnson method* |
| 100-100-0 | 2.04 | 2.04 | 2.09 | 3.34<br>0.976 | 3.93<br>0.968 | 3.01<br>0.979 |
| 0-0-500 | 8.93 | 8.91 | 8.98 | 15.39<br>0.933 | 16.39<br>0.928 | 14.37<br>0.938 |
| 0.2-0-1 | 13.20 | 13.35 | 13.20 | 22.08<br>0.922 | 24.23<br>0.914 | 20.83<br>0.926 |
| 5-0-5 | 38.85 | 38.85 | 38.88 | 70.77<br>0.815 | 72.81<br>0.812 | 67.67<br>0.819 |
| 100-0-500 | 17.53 | 17.66 | 17.53 | 30.24<br>0.889 | 32.64<br>0.881 | 28.60<br>0.894 |

## *3.2 Non parametric distribution analysis*

A non parametric survival and hazard function has been plotted using Kaplan Meier method shown in Figure 4 and Figure 5 respectively. The Kaplan-Meier estimate is the simplest way of computing the survival over time in spite of all these difficulties associated with subjects or situations. The survival curve can be drawn assuming various situations. It involves computing of probabilities of occurrence of event at a certain point of time and multiplying these successive probabilities by any earlier computed probabilities to get the final estimate.

**Figure 4** Non parametric survival plot for AkT (see online version for colours)

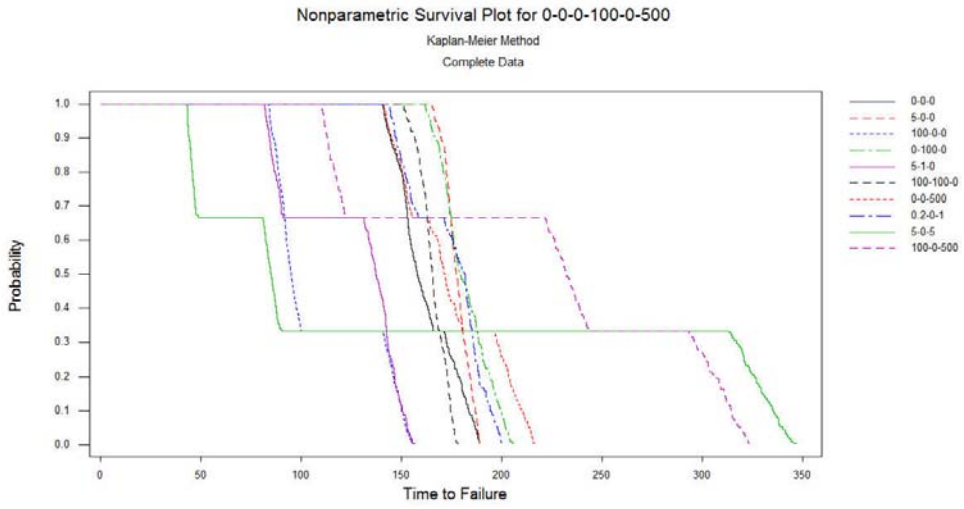
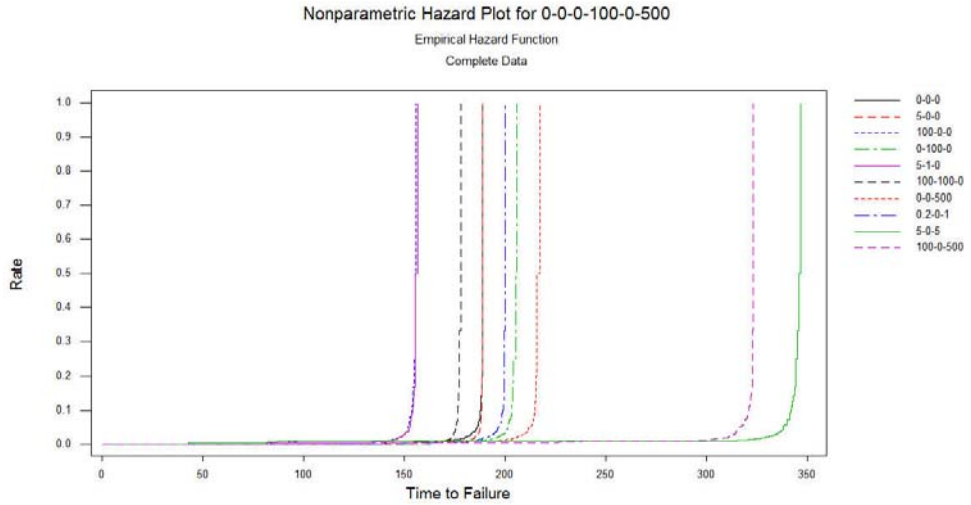


**Figure 5** Non parametric hazard plot for AkT (see online version for colours)




The Kaplan-Meier survival estimates and empirical hazard function change values only at exact failure times, so the nonparametric survival and hazard curves are step functions. Parametric survival and hazard estimates are based on a fitted distribution and the curve will therefore be smooth.

## 4 Conclusions

We have made a best fit model using parametric and non-parametric analysis. For different distribution function like normal, Weibull, lognormal base e, lognormal base 10, exponential, and logistic distribution we have calculated the Anderson Darling adjustment values using normal, Kaplan Meier and Herd Johnson test for maximum likelihood and least square method. Survival and hazard plots were also plotted using Kaplan Meier approach. In future we will calculate Kolmogorov Smirnov, an Anderson Darling and chi square test using different distribution functions.

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