Estimate the median lethal dose using the exponential model

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Abstract: In this research, biological assays for testing toxins in the disinfection jungles Roanstar are studied on a group of fish. The dose-response relationship was estimated using an exponential model, applied the MLE method to estimate the parameters of the exponential distribution. The Fisher’s information was used and the cumulative distribution function to estimate the median lethal dose \( LD_{50} \) which extracted confidence limits for it at specific time intervals.

Keyword: response, exponential model, fisher information, median lethal dose.

1. Introduction:

Bioassays are the experiment to estimate the composition specify of the activity of a given substance by the reaction resulting from its application to living organisms. Biological testing contains the catalyst (e.g. vitamin, drug, fungal), applies to the person concerned (e.g. animal, plant, a piece of animal fabric), can measure the effect of the catalyst (the dose) on the person concerned through the response property. The dose-response relationship can be expressed graphically or as an algebraic equation, but the response is subject to random error. Tests rarely present major statistical problems. For statisticians, methods make it possible to achieve the best results from available data. A good study of the principles method was found (1978). Finney used many methods to find the testing in Bioassays [2]. David and James (1996) determine the modeling of the dose-response relationship using generalized linear models [5]. Chen (2007) for pharmacological trials, an experiment on a spinal assays that records a response such as death in a group of animals over time points under different dose levels was designed in which a linear, polynomial and generalized cumulative model that integrates time with other experimental conditions was proposed [1]. Christian (2010) wrote about dose-response models used in ecotoxicology, used Logistic and Weibull models, and provided an outline for the implementation of the proposed framework in statistical software systems [8]. Neelu, Rajbala, and Inderpal (2015), they wrote a study on determining the median lethal dose \( LD_{50} \) for the synthetic pyrethroid pesticide in male and female swiss albino rate. Estimating this dose is an initial step in assessing the toxicity of a chemical. Based on body weight, a dose of the pesticide is given through oral dissolving in maize oil to a group of male and female rate component of 10 animals [7]. Hayes, Matava, Pehora, El-Beheiry, Jarvis, and Finkelstein (2018), have written about the use of propofol to promote general anesthesia of procedures in children and the addition of adjuvants such as ketamine. The conducted a trial to determine the effective dose of propofol in combination with ketamine that induced an adequate depth of anaesthesia in 50% of children receiving duodenoscopy. The sample was randomized to one of four groups of ketamine followed by a dose of propofol according to Dixon’s up-and-down methodology. It was concluded that a concentration
of (0.5-1) mg ketamine reduces the dose of propofol to provide a general determination of gastric
deconstruction in children and reduces the incidence of propofol related changes in hemodynamics [4].
Caroline, Anne, and Sebastien at (2019), have written about testing the efficacy of a chemical compound
through dose-response experiments, through which measures of efficacy such as ISSO are derived, and
non-linear regression has been used to estimate these measures. He proposed a Bayesian inference
methodology to analyze and compare dose-response experiments. A simple grid interface was
implemented that allowed users to analyze a single dataset for dose-response, and to compare
measurements statistically for two datasets [6]. The aim of this research is to study the concept of
biological assay to estimate the median lethal dose of the poison for disinfectant jungles is called
Roanstar on the fish. The goal is for fish to survive. This paper is organized as follows. In section 2,
showing a theoretical aspect. In section 3, showing an application aspect. In section 4, conclusions are
given.

2. Theoretical Aspect:
In this section, focusing to the theoretical aspect in the following paragraph, but there is linear relation
between $\ln \lambda(x_i)$ and $\ln d_i$ as follows:
\[ \ln \lambda(x_i) = \alpha + \beta \ln d_i \quad \text{where} \quad \beta \neq 0 \text{ and } -\infty < \alpha < \infty \]

2.1. The Exponential Model:
The probability density function of an exponential model is:
\[ f(t; \lambda) = \begin{cases} \lambda e^{-\lambda t} , & t > 0 \\ 0 , & o/w \end{cases} \]  \hspace{1cm} (1)
Where, $\lambda = e^{(\alpha+\beta \ln d_i)}$. Therefore:
\[ f(t_j; \alpha, \beta) = e^{(\alpha+\beta \ln d_i)} e^{(-e^{(\alpha+\beta \ln d_i)}t_j)} \]  \hspace{1cm} (2)
The likelihood function for two-parameters is:
\[ L(\alpha, \beta; t_1, \cdots, t_n) = e^{\sum_{j=1}^{n}(\alpha+\beta \ln d_i)} e^{-\sum_{j=1}^{n}e^{(\alpha+\beta \ln d_i)}t_j} \]  \hspace{1cm} (3)
Taking the logarithm for the likelihood function, so as follows:
\[ \ln L = n\alpha + \beta \sum_{j=1}^{n} \ln d_i - \sum_{j=1}^{n} t_j e^{(\alpha+\beta \ln d_i)} \]  \hspace{1cm} (4)
The partial derivatives for the log-likelihood function for unknown parameters $\alpha$ and $\beta$ are:
\[ \frac{\partial \ln L}{\partial \alpha} = n - \sum_{j=1}^{n} t_j e^{(\alpha+\beta \ln d_i)} \]  \hspace{1cm} (5)
\[ \frac{\partial \ln L}{\partial \beta} = \sum_{j=1}^{n} \ln d_i - \sum_{j=1}^{n} t_j \ln d_i e^{(\alpha+\beta \ln d_i)} \]  \hspace{1cm} (6)
The partial derivatives are replaced to the log-likelihood with respect to $\alpha$ and $\beta$ to zero, as
follows:
\[
\sum_{j=1}^{n} t_j e^{(\alpha^* \beta^* \ln d_i)} = 0 
\]

(7)

\[
\sum_{j=1}^{n} l \ln d_i - \sum_{j=1}^{n} t_j l \ln d_i e^{(\alpha^* \beta^* \ln d_i)} = 0 
\]

(8)

Observing that the two equations (7, 8) are difficult and complicated to solve, then it is impossible to find MLE for \(\alpha^* and \beta^*\) directly. The numerical-analysis is used to obtain and estimate \(\alpha^* and \beta^*\) by maximize the likelihood function. One of these methods is Newton-Raphson method.

\[
g_1(\alpha) = n - \sum_{j=1}^{n} t_j e^{(\alpha + \beta \ln d_i)} 
\]

(9)

\[
g_2(\beta) = \sum_{j=1}^{n} l \ln d_i - \sum_{j=1}^{n} t_j l \ln d_i e^{(\alpha + \beta \ln d_i)} 
\]

(10)

The partial derivatives of equation (9) for the two unknown parameters \(\alpha \text{ and } \beta\) are:

\[
\frac{\partial g_1(\alpha)}{\partial \alpha} = -\sum_{j=1}^{n} t_j e^{(\alpha + \beta \ln d_i)} 
\]

(11)

\[
\frac{\partial g_1(\beta)}{\partial \beta} = -\sum_{j=1}^{n} t_j l \ln d_i e^{(\alpha + \beta \ln d_i)} 
\]

(12)

The partial derivatives of equation (10) for the two unknown parameters \(\alpha \text{ and } \beta\) are:

\[
\frac{\partial g_2(\alpha)}{\partial \alpha} = -\sum_{j=1}^{n} t_j l \ln d_i e^{(\alpha + \beta \ln d_i)} 
\]

(13)

\[
\frac{\partial g_2(\beta)}{\partial \beta} = -\sum_{j=1}^{n} t_j (l \ln d_i)^2 e^{(\alpha + \beta \ln d_i)} 
\]

(14)

\[
J_k = \begin{bmatrix}
\frac{\partial g_1(\alpha)}{\partial \alpha} & \frac{\partial g_1(\alpha)}{\partial \beta} \\
\frac{\partial g_2(\beta)}{\partial \alpha} & \frac{\partial g_2(\beta)}{\partial \beta}
\end{bmatrix}
\]

(15)

The Jacobin matrix must be a non-singular symmetric matrix, so its inverse can be found.

\[
\begin{bmatrix}
\alpha_{k+1} \\
\beta_{k+1}
\end{bmatrix} = \begin{bmatrix}
\alpha_k \\
\beta_k
\end{bmatrix} - (J_k)^{-1} \begin{bmatrix}
g_1(\alpha) \\
g_2(\beta)
\end{bmatrix}
\]

(16)

If \(k = 0\), then \(\alpha_o \text{ and } \beta_o\) are the initial values which are assumed.

The absolute value for the difference between the new values \(\alpha \text{ and } \beta\) with previous value \(\alpha \text{ and } \beta\), in last iterative represent the error term. Its symbol is \(\varepsilon\), which is a very small and assumed value. Then, the formula for error term is:
The matrix of Fisher's information, as follows:
\[
\begin{bmatrix}
  e_{k+1}(\alpha) \\
  e_{k+1}(\beta)
\end{bmatrix}
= \begin{bmatrix}
  \alpha_{k+1} - \beta_{k+1} - \beta_k
\end{bmatrix}
\]  
(17)

2.2. The Initial Value for Exponential Model:
The cumulative model function is given by:
\[
F(t_j; \lambda) = 1 - e^{-\lambda t_j}, \text{where } \lambda = e^{(\alpha + \beta \ln d_i)}
\]  
(18)
\[
F(t_j; \alpha, \beta) = 1 - e^{-e^{(\alpha + \beta \ln d_i) t_j}}
\]  
(19)
\[
e^{-e^{(\alpha + \beta \ln d_i) t_j}} = 1 - F(t_j) \quad \text{ (take ln)}
\]
\[
-e^{(\alpha + \beta \ln d_i) t_j} = \ln[1 - F(t_j)]
\]  
\[
e^{(\alpha + \beta \ln d_i) t_j} = -\ln[1 - F(t_j)] \quad \text{ (take ln)}
\]
\[
\alpha + \beta \ln d_i + \ln t_j = \ln[-\ln[1 - F(t_j)]]
\]
\[
\ln t_j - \ln[-\ln[1 - F(t_j)]] = -\alpha - \beta \ln d_i
\]  
(20)

Compare an equation (20) with the simple linear model: 
\[Y_i = \alpha_0 + \beta_0 X_i\]

Where:  \[Y_i = \ln t_j - \ln[-\ln[1 - F(t_j)]] , X_i = \ln d_i, \alpha_0 = -\alpha, \beta_0 = -\beta\]

Then \(F(t_j)\) is cumulative distribution function which formula as: \(F(t_j) = \frac{t-0.5}{n}\)

2.3. The Cumulative of Exponential Model:
Consider getting sample units estimating the cumulative number estimator which is called influence \(C^\lambda_{ijl}\) when the dose \(i\) in time \(j\) and replicate \(l\), accordance with the following formulas:

**The first model**
\[C^\lambda_{ijl} = n_{il} \left[1 - e^{-e^{(\alpha l + \beta l \ln d_i) t_j}}\right]\]  
(21)

**The second model**
\[C^\lambda_{ijl} = n_{il} \left[1 - e^{-e^{(\alpha l + \beta l \ln d_i) t_j}}\right]\]  
(22)

**The third model**
\[C^\lambda_{ijl} = n_{il} \left[1 - e^{-e^{(\alpha l + \beta l \ln d_i) t_j}}\right]\]  
(23)

**The fourth model**
\[C^\lambda_{ijl} = n_{il} \left[1 - e^{-e^{(\alpha l + \beta l \ln d_i) t_j}}\right]\]  
(24)

Where \(n_{il}\) represent the number of sample units in dose \(i\) and replicate \(l\).

2.4. The Fisher's Information of Exponential Model:
The matrix of Fisher's information, as follows:
\[
I(\alpha, \beta) = \begin{bmatrix}
-nE \left[\frac{\partial^2}{\partial \alpha^2} \ln f(t_j; \alpha, \beta)\right] & -nE \left[\frac{\partial^2}{\partial \alpha \partial \beta} \ln f(t_j; \alpha, \beta)\right] \\
-nE \left[\frac{\partial^2}{\partial \beta^2} \ln f(t_j; \alpha, \beta)\right] & -nE \left[\frac{\partial^2}{\partial \beta^2} \ln f(t_j; \alpha, \beta)\right]
\end{bmatrix}
\]  
(25)

Based on function (1), to find its natural-logarithm:
\[ \ln f(t; \alpha, \beta) = -(\alpha + \beta lnd_i) t_j e^{(\alpha + \beta lnd_i)} \]  

(26)

To find the second partial derivatives for parameters \( \alpha \) and \( \beta \):

\[ \frac{\partial^2 \ln f}{\partial \alpha^2} = -t_j e^{(\alpha + \beta lnd_i)} (\alpha + \beta lnd_i + 2), \quad \frac{\partial^2 \ln f}{\partial \beta^2} = -t_j (lnd_i)^2 e^{(\alpha + \beta lnd_i)} (\alpha + \beta lnd_i + 2) \]

\[ \frac{\partial^2 \ln f}{\partial \alpha \partial \beta} = -t_j (lnd_i) e^{(\alpha + \beta lnd_i)} (\alpha + \beta lnd_i + 2), \quad \frac{\partial^2 \ln f}{\partial \beta \partial \alpha} = -t_j (lnd_i) e^{(\alpha + \beta lnd_i)} (\alpha + \beta lnd_i + 2) \]

Now, to take the expected for these derivatives:

\[ E \left[ \frac{\partial^2 \ln f}{\partial \alpha^2} \right] = -(\alpha + \beta lnd_i + 2), \quad E \left[ \frac{\partial^2 \ln f}{\partial \beta^2} \right] = -(lnd_i)^2 (\alpha + \beta lnd_i + 2) \]

\[ E \left[ \frac{\partial^2 \ln f}{\partial \alpha \partial \beta} \right] = -(lnd_i) (\alpha + \beta lnd_i + 2), \quad E \left[ \frac{\partial^2 \ln f}{\partial \beta \partial \alpha} \right] = -(lnd_i) (\alpha + \beta lnd_i + 2) \]

Then, the fisher’s information matrix is:

\[ I(\alpha, \beta) = \begin{bmatrix} n(\alpha + \beta lnd_i + 2) & n(lnd_i) (\alpha + \beta lnd_i + 2) \\ n(lnd_i) (\alpha + \beta lnd_i + 2) & n(lnd_i)^2 (\alpha + \beta lnd_i + 2) \end{bmatrix} \]

Where \( \text{var}(\alpha^*) = n(\alpha + \beta lnd_i + 2), \text{var}(\beta^*) = n(lnd_i)^2 (\alpha + \beta lnd_i + 2) \).

(27) and \( \text{cov}(\alpha^*, \beta^*) = n(lnd_i) (\alpha + \beta lnd_i + 2) \).

2.5. To estimate the median lethal dose \( LD_{50} \), and find the confidence intervals:

The \( LD_{50} \) can be estimate by making the function (19) equal to 0.50, and as follows:

\[ 1 - e^{(-e^{(\alpha^* + \beta^* lnd_i) t_j})} = 0.50 \]

\[ e^{(-e^{(\alpha^* + \beta^* lnd_i) t_j})} = 0.5 \]  \hspace{1cm} \text{(take ln)}

\[ -e^{(\alpha^* + \beta^* lnd_i) t_j} = -0.693147 \]

\[ e^{(\alpha^* + \beta^* lnd_i) t_j} = 0.693147 \]  \hspace{1cm} \text{(take ln)}

\[ lnt_j + (\alpha^* + \beta^* lnd_i) = -0.36651 \]

\[ lnd_i = \frac{-0.36651 - \alpha^* - lnt_j}{\beta^*} \]  \hspace{1cm} \text{(28)}

Assuming that \( x_i = lnd_i \), to take the exponential for both parties. Then \( LD_{50} = d_i = e^{x_i} \). \hspace{1cm} \text{(29)}

To derive confidence intervals depend on the Fiehler theorem [2] in the following research to find \( \text{var}(lnd_i) \), this theorem states by taking the variance to estimate the \( LD_{50} \) and the common variance of the \( LD_{50} \) parameters, to catch the variance for the following equation:

\[ x_i \beta^* + 0.36651 + \alpha^* + lnt_j = 0 \]

Therefore, \( (x_i \beta^* + 0.36651 + \alpha^* + lnt_j) = S^2 \left[ x_i \beta^* + 2(x_i \beta^*, 0.36651 + \alpha^* + lnt_j) \right] \)

\[ (x_i \beta^* + 0.36651 + \alpha^* + lnt_j) = t^2 \left[ \text{var}(x_i \beta^*) + 2 \text{cov}(x_i \beta^*, 0.36651 + \alpha^* + lnt_j) \right] \]
\[ \text{var}(\ln d_i) = \left(x_i^2 + 2(\ln t_j)^2\right)\text{var}(\beta^\ast) + 2x_i\text{cov}(\beta^\ast, \alpha^\ast) + \text{var}(\alpha^\ast) \]  

(30)

Calculate the confidence intervals for \( LD_{50} \) at each time point \( j \), by:

\[ C.I. = \ln d_i \pm t_{(n-p,1-\alpha)}\sqrt{\text{var}(\ln d_i)} \]  

(31)

3. Application Aspect:

3.1. Description of Data:

This study depends upon biological real data which is runout to test the poison for disinfectant jungles called Roanstar at the fishes, where the disinfectant jungles have side effects on the fishes, which means the disinfectant jungles lead to killing the fishes while utilized for a certain long time. The aim of using the disinfectant is to annihilate the jungles. The data of this experiment represented the number of units which are effected by the doses at sample units where sample units represent the number of killing the fish in four days censoring. The data is called multivariate quantal response, noting that the response variables are function to dose and time. The experiment designed by (4) aquariums glass which represent the experimental units with equal dimension(40 * 40 * 40) cm. Every aquarium contains (10) fish which represent the sample units, the weight mean of one fish is (2g) and the length mean of fish is (3cm). The doses may be in this experiment are \((7, 7.5, 8, 9)\) \(mg/l\), the experiment replicates (3) times in the same and homogenous circumstance and regard the number killing of fish in (4) day [8].

Table (1) the number of observing and cumulating death from fishes.

| Replicate | Time | Concentration (mg/l) | Death | Cumulative |
|-----------|------|----------------------|-------|------------|
|           |      | 7        | 7.5    | 8         | 9         |
| 1         | 1    | Observe   | 1      | 1         | 1         |
|           |      | Cumulative| 1      | 1         | 1         |
| 2         | 2    | Observe   | 1      | 2         | 4         |
|           |      | Cumulative| 2      | 2         | 4         |
| 3         | 3    | Observe   | 1      | 2         | 5         |
|           |      | Cumulative| 3      | 4         | 9         |
| 4         | 4    | Observe   | 2      | 3         | 9         |
|           |      | Cumulative| 5      | 7         | 11        |

3.2. Numerical Results:
In this section, the least squares method is applied to data by using statistical program (spss) to find the initial values \( \alpha_0, \beta_0 \) for all the replicate, then using the observation experiment in table (1) to find the estimate values \( \hat{\alpha}, \hat{\beta} \) by utilizing matlab program. So, put an end to the error term in this program. As shown in the table below:

| Replicate | Initial Value | Estimate Value | Error |
|-----------|---------------|----------------|-------|
| 1         | \( \alpha_0 = 0.935, \beta_0 = -1.112 \) | \( \hat{\alpha} = 5.4379, \hat{\beta} = -2.9275 \) | \( 7.6923e^{-009} \) |
| 2         | \( \alpha_0 = 0.231, \beta_0 = -0.801 \) | \( \hat{\alpha} = 4.4824, \hat{\beta} = -2.5142 \) | \( 1.2746e^{-009} \) |
| 3         | \( \alpha_0 = 0.827, \beta_0 = -1.089 \) | \( \hat{\alpha} = 3.9980, \hat{\beta} = -2.2966 \) | \( 4.3810e^{-011} \) |
| All experiment | \( \alpha_0 = -2.033, \beta_0 = 0.265 \) | \( \hat{\alpha} = 4.6150, \hat{\beta} = -2.5686 \) | \( 5.8977e^{-007} \) |

Now, apply the equations (21, 22, 23, 24) to compute the cumulative model and the results put in table (3).

| Models | \( \hat{\alpha} \) | \( \hat{\beta} \) |
|--------|----------------|----------------|
| First  | 5.4379         | -2.9275        |
| Second | 4.4824         | -2.5686        |
| Third  | 4.6150         | -2.2966        |
| Fourth | 4.6150         | -2.5686        |

The \( C_{ijl} \) values for all models are calculated with decimal values, given the sample is a group of fish, where the results approximate to integer. In the following tables, the estimated cumulative number of deaths and the estimated observed number of deaths are presented.

| Replicate | Time | Death         | Concentration (mg/l) |
|-----------|------|---------------|----------------------|
|           |      | Cumulative Observe | 7 | 7.5 | 8 | 9 |
| 1         | 1    | Cumulative Observe | 2 | 2 | 2 | 1 |
|           | 2    | Cumulative Observe | 3 | 3 | 4 | 4 |
|           | 3    | Cumulative Observe | 4 | 4 | 4 | 4 |
|           | 4    | Cumulative Observe | 4 | 4 | 4 | 4 |
| 2         | 1    | Cumulative Observe | 4 | 4 | 5 | 3 |
|           | 2    | Cumulative Observe | 6 | 7 | 7 | 7 |
|           | 3    | Cumulative Observe | 2 | 3 | 2 | 4 |
Cumulative Observe

### Table (5) the number of cumulating and observing estimated for the second model.

| Replicate | Time | Death | Concentration (mg/l) |
|------------|------|-------|----------------------|
| 1          | 1    | Cumulative Observe | 8 | 8 | 8 | 8 |
| 2          | 2    | Cumulative Observe | 6 | 6 | 8 | 6 |
| 3          | 3    | Cumulative Observe | 9 | 9 | 11 | 10 |
| 4          | 4    | Cumulative Observe | 12 | 12 | 12 | 12 |

### Table (6) the number of cumulating and observing estimated for the third model.

| Replicate | Time | Death | Concentration (mg/l) |
|------------|------|-------|----------------------|
| 1          | 1    | Cumulative Observe | 8 | 7 | 7 | 7 |
| 2          | 2    | Cumulative Observe | 6 | 6 | 7 | 7 |
| 3          | 3    | Cumulative Observe | 10 | 11 | 12 | 12 |
| 4          | 4    | Cumulative Observe | 12 | 12 | 12 | 12 |
To find the best models by using the mean square error (MSE), from this formula:

$$MSE = \sum_{i,j,d} \frac{(t_{ij} - t_{ij}^*)^2}{n - p}$$
Where n represent the sample size and p represent the number of parameters. Accordingly:

Table (8): MSE for the models.

| Models | MSE   |
|--------|-------|
| First  | 17.3  |
| Second | 13.4  |
| Third  | 31.7  |
| Fourth | 5     |

By comparing the results, when applying the MSE for a select model. The fourth model is noted to have less value. This is done selecting this model. Lastly, the values of variance and covariance are found of $\alpha^\wedge$, $\beta^\wedge$ based on equation (27). After computing the $LD_{50}$ by equation (29), then finding the confidence intervals for $LD_{50}$ by utilizing the equation (31) and the results are put in table (9) as follows:

Table (9): $LD_{50}$ and confidence intervals for the best model.

| $t_j$ | $ln t_j$ | $x_i$ | $LD_{50}$ | Confidence Intervals |
|-------|----------|-------|-----------|----------------------|
| 1     | 0        | 1.94  | 6.96      | -18.48               |
| 2     | 0.69     | 2.21  | 9.12      | -18.16               |
| 3     | 1.10     | 2.37  | 10.70     | -16.09               |
| 4     | 1.39     | 2.48  | 11.94     | -11.88               |

The results of $LD_{50}$ are noted the results of confidence intervals.

Finally, to prove that the relationship between $ln d_i$ and $ln \lambda^\wedge_i(x_i)$ is linear, like this:

$ln \lambda^\wedge_i(x_i) = \alpha^\wedge_i + \beta^\wedge_i ln d_i$, where $x_i$ represent the logit dose $i$.

As shown in the following charts:
4. Conclusion:

1. Noting from table (9) it seems that the insecticide of Roanstar be expect to lead the lethal effect to fishes with 50% percentage at the first day when the concentration reach in the water (7 mg/l) and so on it continuous poison effect to this insecticide of Roanstar units decreasing the concentration of this insecticide over time, that means if the expected happen less effect lethal with 50% percentage in four days when the concentration in water become (9 mg/l).

2. Noting from the same table, the effect of poison insecticide based on confidence limits happen through one day and lead to lethal effect for the fish with 50% percentage, after that the poison decreases after four days.

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