Mathematical Model to find the effect of spirometry and exercise in Asthmatic children

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Abstract: Estimation of system reliability requires understanding of the association between the lifetimes of components in the system. When the association between component lifetimes in the two-component parallel system is known, one might be able to estimate the lifetime of a more complicated system by assuming that this association is applicable to several of its components. When two-component parallel systems are tested, the data $X_{(i)}, i=1,2,...,n,$ form one component, and their concomitants $Y_{[i]}$ randomly censored at $X_{(r)}$, the stopping time of the experiment. In this article we use bivariate exponential distribution to illustrate our statistical inference procedures. Twenty-four asthmatic children (mean age 12.8 years) were enrolled. FE_{NO} was measured with a chemiluminescence analyzer. Measurements of FE_{NO} were performed before and 5, 15, 30, 45 and 60 minutes after spirometry or a 6-min walk test, on two separate days in random order. Geometric mean FE_{NO} at baseline was 25.6 parts per billion (ppb) before spirometry and 23.5 ppb before exercise. A small drop of FE_{NO} to 24.2 and 23.7 ppb was found 5 and 15 min after spirometry (both p = 0.04). After exercise, FE_{NO} values showed a larger drop to 18.5 ppb after 5 min and 20.7 ppb after 15 min (p < 0.001; p = 0.004 resp.). Changes in FE_{NO} occurred after exercise irrespective of baseline FE_{NO} and returned to baseline within 30 minutes.
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1. Introduction

Parameter estimation for bivariate shock models

The survival function (SF) of Bivariate Exponential (BVE) distribution [13] is as follows.

$$\bar{F}(x,y)=\Pr(X>x,Y>y)$$
$$=\exp(-\lambda_1 x-\lambda_2 y-\lambda_3 \max(x,y)) \quad (x>0,y>0), \qquad \ldots (1.1)$$

and the parameter space is $\Omega=\{(\lambda_1,\lambda_2,\lambda_3):\lambda_1>0,\lambda_2>0,\lambda_3\geq 0\}$. The probability of $X=Y$ is not equal to zero, so the typical two-dimensional Lebesgue measure cannot be used as the dominating measure to derive the probability density function (pdf).

We first estimate the mean parameters $\gamma_1=\lambda_1+\lambda_3$ and $\gamma_2=\lambda_2+\lambda_3$ of the marginal distributions for X and Y, respectively. We denote these estimates as $\bar{\gamma}_i, i=1,2$. Then, we use the one-parameter 'full' likelihood to estimate the parameter λ_3, where $\lambda_i, i=1,2$, are treated as functions of $\tilde{\gamma}_i$ and λ_3. This simple estimation method makes it easy to calculate their closed-form expressions, and is shown to perform well compared to the maximum likelihood extimator (MLE).

The plan proposed by Lu (1997) stops the life-testing experiment after observing the first r failure times of $A: x_{(1)}\leq x_{(2)}\leq ..\leq x_{(r)}$ [11]. The lifetimes of component B are thus all censored at $X_{(r)}=x_{(r)}$. The available observations are

$$\begin{bmatrix} x_{(1)} \\ y_{[1]} \end{bmatrix}, \begin{bmatrix} x_{(2)} \\ y_{[2]} \end{bmatrix}, \ldots, \begin{bmatrix} x_{(r)} \\ y_{[r]} \end{bmatrix}, \begin{bmatrix} x^*_{(r+1)} \\ y_{[r+1]} \end{bmatrix}, \ldots, \begin{bmatrix} x^*_{(n)} \\ y_{[n]} \end{bmatrix} \ldots (1.2)$$

where $y_{[i]}$ is the concomitant order statistic of $x_{(i)}$, and data with superscript '*' are censored at $X_{(r)}=x_{(r)}$. That is, the observation times $x^*_{(r+1)},\ldots,x^*_{(n)}$ of unfailed components are all equal to $x_{(r)}$ and $y^*_{[i]}=y_{[i]}$ if $y_{[i]}\leq x_{(r)}$; otherwise $y^*_{[i]}=x_{(r)}$.

2. The Likelihood function

In the complete sample case, Bemis, Bain and Higgins (1972), Bhattacharyya and Johnson (1973) and Proschan and Sullo (1976) [4, 6, 17] provided several classical inference procedures for the BVE model parameters. Pena and Gupta (1990) gave Bayesian estimation results [14]. In the censored data case, Lu (1992a) developed Bayesian inference procedures with information from both component and system testings [10]. Lu (1997) derived the following general likelihood function [11] for the data in (1.2):

$$\ell=\frac{n!}{(n-r)!}\prod_{i=1}^{r} f_X(x_{(i)}\prod_{i=1}^{r} f_Y(y_{(i)}|X=x_{(i)})^{\delta_i}\bar{F}_Y(x_{(r)}|X=x_{(i)})^{1-\delta_i})$$

$$\times(\bar{F}_X(x_{(r)}))^{n-r}\prod_{i=r+1}^{n} f_Y(y_{(i)}|X>x_{(r)})^{\delta_i}\bar{F}_Y(x_{(r)}|X>x_{(r)})^{1-\delta_i}), \quad \ldots (2.1)$$

where $\bar{F}=1-F$ denotes the survival function (*SF*), F_X is cdf of X, $\bar{F}_Y(y|Q)$ is the conditional *SF* of Y given the condition Q and $\delta_i=I\{Y_{[i]}<X_{(r)}\}$.

For the BVE distribution, examples of the marginal and conditional pdfs of SFs are given as follows. The marginal SFs for X and Y are, respectively,

$\bar{F}_X(x)=\exp\{-(\lambda_1+\lambda_3)x\}$ and $\bar{F}_Y(y)=\exp\{-(\lambda_2+\lambda_3)y\}$.

A mixture of one-dimensional *(v)* and two-dimensional (μ_2) Lebesgue measures [6], $\mu=v+\mu_2$, is employed for deriving the pdf of (1.1):

$$f(x,y)=\sum_{j=1}^{3} f_j(x,y)R_j(x,y), \quad \ldots (2.2)$$

where $f_1(x,y)=\lambda_1\gamma_2\exp(-\lambda_1 x-\gamma_2 y)$,

$f_2(x,y)=\lambda_2\gamma_1\exp(-\gamma_1 x-\lambda_2 y)$,

$f_3(x,y)=\lambda_3\exp^{-\lambda x}$, $\lambda=\lambda_1+\lambda_2+\lambda_3$ and R_j is an indicator for different domains of (x,y) with $R_1(x,y)=I\{0\le x<y<\infty\}$,

$R_2(x,y)=I\{0\le y<x<\infty\}$, and $R_3(x,y)=I\{0<x=y<\infty\}$.

The estimation and inference procedures do not depend on the measure μ defined above as long as the non-zero probability measure of $\Pr(X=Y)$ is included. For example, if one uses $\mu^*=7v+\mu_2$ instead of the measure $\mu=v+\mu_2$ given above, the likelihood is adjusted by a constant (1/7) in the $(X=Y)$ case. The estimation and inference results are unchanged. However, if the one-dimensional Lebesgue measure *(v)* is not included in the dominating measure, the likelihood and the resulting inference results are different.

Using the ratio $f(x,y)/f_X(x)$, we can derive the conditional cdf of Y given $X=x$:

$$F_{Y|X=x}(y)=\begin{cases}1-\exp(-\lambda_2 y) & \text{for } y<x,\\ 1-\lambda_1\gamma_1^{-1}\exp(-\lambda_2 x) & \text{for } y=x,\\ 1-\lambda_1\gamma_1^{-1}\exp(-\gamma_2 y-\lambda_3 x) & \text{for } y>x.\end{cases}$$

Let $\beta=\beta_1\cup\beta_2$ denote the boundary of the parameter space Ω of the BVE distribution where $\beta_1=\{\lambda_1>0,\lambda_2>0,\lambda_3=0\}$ and $\beta_2=\{\lambda_1=0\}\cup\{\lambda_2=0\}$. Let

$$N_{11}=\sum_{i=1}^{r} I\{X_{(r)}<Y_{[i]}\},$$

$$N_{12}=\sum_{i=1}^{r} I\{X_{(i)}<Y_{[i]}<X_{(r)}\},$$

$$N_{21}=\sum_{i=1}^{r} I\{Y_{[i]}<X_{(i)}<X_{(r)}\},$$

$$N_{22}=\sum_{i=r+1}^{n} I\{Y_{[i]}<X_{(r)}\},$$

$$N_3=\sum_{i=1}^{r} I\{X_{(i)}=Y_{[i]}\},\quad N_1=N_{11}+N_{12},\quad N_2=N_{21}+N_{22},$$

$$W_1=\sum_{i=1}^{r} X_{(i)}+(n-r)X_{(r)},\quad W_2=\sum_{i=1}^{n} Y^*_{[i]},$$

$$W_3=\sum_{i=1}^{r}\max(X_{(i)},Y^*_{[i]})+(n-r)X_{(n)}.$$

After some algebraic manipulations, the likelihood function (2.1) for the BVE model is

$$\ell(\lambda_1,\lambda_2,\lambda_3)=\frac{n!}{(n-r)!}\lambda_1^{n_1}\lambda_2^{n_2}\lambda_3^{n_3}\gamma_1^{n_{21}}\gamma_2^{n_{12}}\exp(-\lambda_1 w_1-\lambda_2 w_2-\lambda_2 w_3)\ \text{on}\ \Omega-\beta_1,$$

From the Factorization theorem, it follows that $\{N_{11},N_{12},N_{21},N_{22},N_3,W_1,W_2,W_3\}$ is a set of sufficient statistics. On β_1, X and Y are independent exponential random variables, and hence $\Pr(X=Y)=0$, i.e. $\Pr(N_3=0)=1$. Therefore, when $N_3>0$ is observed, we must have $\lambda_3>0$. When $N_3=0$ is observed, then either $\lambda_3>0$ or $\lambda_3=0$. The likelihood function in this case is then

$$\ell(\lambda_1,\lambda_2\lambda_3)=\begin{cases}\frac{n!}{(n-r)!}\lambda_1^{n_1}\lambda_2^{n_2}\gamma_1^{n_{21}}\gamma_2^{n_{12}}\exp(-\lambda_1 w_1-\lambda_2 w_2-\lambda_3 w_3) & \text{on}\ \Omega-\beta_1,\\ \frac{n!}{(n-r)!}\lambda_1^{n_1+n_{21}}\lambda_2^{n_2+n_{12}}\exp(-\lambda_1 w_1-\lambda_2 w_2) & \text{on}\ \beta_1.\end{cases}$$

3. Maximum likelihood estimation

Equating the first partial derivatives of $\log l(\lambda_1,\lambda_2,\lambda_3)$ on $\Omega-\beta_1$ to zero, we have the following likelihood equations.

$$w_1=\frac{n_1}{\lambda_1}+\frac{n_{21}}{\gamma_1},\ w_2=\frac{n_2}{\lambda_2}+\frac{n_{12}}{\gamma_2},\ w_3=\frac{n_{21}}{\gamma_1}+\frac{n_{12}}{\gamma_2}+\frac{n_3}{\lambda_3}. \quad \ldots (3.1)$$

The second partial derivatives of $\log\ell(\lambda_1,\lambda_2,\lambda_3)$ are given as

$$\left[\frac{\partial^2\log\ell(\lambda_1,\lambda_2,\lambda_3)}{\partial\lambda_i\partial\lambda_j}\right]=[a_{iij}]\quad (i,j=1,2,3),$$

where $a_{11}=n_1\lambda_1^{-2}+n_{21}\gamma_1^{-2}$, $a_{12}=a_{21}=0$, $a_{13}=a_{31}=n_{21}\gamma_1^{-2}$,

$a_{22}=n_2\lambda_2^{-2}+n_{12}\gamma_2^{-2}$, $a_{23}=a_{32}=n_{12}\gamma_2^{-2}$ and $a_{33}=n_1\gamma_1^{-2}+n_{12}\gamma_2^{-2}+n_3\lambda_3^{-2}]$

4. Application

Fractional exhaled nitric oxide (FE_{NO}) is an easy, repeatable, safe and noninvasive marker of bronchial inflammation in allergic asthma [1, 5]. Exercise may reduce FE_{NO} values as well and guidelines recommend to retain from strenuous exercise for 1 hour before the FE_{NO} test [2, 3, 7-9, 12, 15-16, 18-19]. FE_{NO} is increasingly used next to spirometry, hence it seems of practical importance to understand whether forced expiratory maneuvers influence FE_{NO} values in children. The aim of the present study was to observe whether or not spirometry or exercise immediately preceding FE_{NO} measurements could influence FE_{NO} values in asthmatic children.

5. Methods

A diagnosis of asthma was based on a history of recurrent episodes of wheezing, coughing and shortness of breath, reversible bronchoconstriction and/or airway hyperresponsiveness to methacoline [8]. 24 asthmatic children were recruited with a range of FE_{NO} values [6.5 - 176.2 parts per billion (ppb)]]. None of the patients had a history of upper respiratory tract in infection or asthma exacerbation during 2 week before the study.

Study design

The study was performed on 2 days within 2 week. In random order, children performed spirometry (day A) or a 6 min walk –test (days B). On both days baseline FE_{NO} was measured twice during a resting period of 30 min, at $t=-30$ min and $t=-15$ min. Then either exercise or spirometry was performed (t=0), followed by measurements at t=5, 15, 30, 45 and 60 min.

Pulmonary function testing

Spirometry was performed with a dry rolling seal spirometer [7]. Three forced vital capacity (FVC) maneuvers were performed and the best value of FVC and forced expiratory volume in 1s (FEV_1) was recorded.

Exercise testing

A 6-min walk test was performed indoors along a long, flat, straight, enclosed corridor with a hard surface [2]. The test was modified and adapted to the study needs, children walked between two 8 m points for 6 min. Heart rate was recorded at the start and at the end of the exercise; the total number of rounds and the total meters covered were recorded.

FE_{NO} measurements

The FE_{NO} measurements were carried out with the NIOX NO - analyzer [2]. Children inspired NO-free air and exhaled for a minimum of 7s. Exhalation flow was kept constant at 50 ml/s through a visual feedback mechanism and dynamic flow restrictor. At each session three correctly executed exhalations were recorded. FE_{NO} value were expressed in ppb.

Baseline FE_{NO} before spirometry and exercise were not significantly different and the two baseline measurements were highly reproducible within children. Hence, the geometric mean of the two baseline values was calculated and used as the individual baseline for the analysis. Baseline geometric mean FE_{NO} values were 25.6 ppb (range 6.5-176.2 ppb) before spirometry and 23.5 ppb (range 7.0 - 105.3 ppb) before exercise.

Mean FEV_1 was 97% of predicted (range 75-116%) and mean FVC was 100% of predicted (range 68-126%). A small but significant drop of FE_{NO} at 24.2 ppb and to 23.7 ppb was found, respectively, 5 and 15 min after spsirometry (both P=0.04, Fig 1). Values of FEV_1, did not significantly correlate either with the baseline FE_{NO} or changes in FE_{NO}.

Children covered an average distance of 473m (range 272-848m), leading to a mean increase in heart rate of 87 beats per minute (range 31-133). Nineteen subjects (79%) showed the maximum drop in FE_{NO} values within 5 min after exercise. The mean changes in FE_{NO} from baseline at 5 min after spirometry and exercise were significantly larger after exercise than after spirometry ($P < 0.001$, paired t –test).

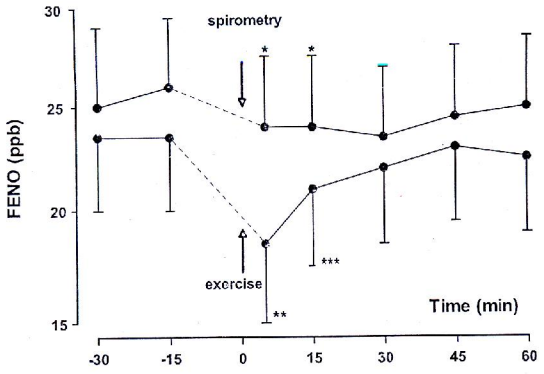

Fig 1. FE_{NO} before and after spirometry (upper curve and exercise (lower curve) in asthmatic children (n=24). FE_{NO} is shown as geometric means and SEM. The changes in log-transformed FE_{NO} values 5 and 15 min after spirometry and exercise, compared to baseline values, are significant (*p = 0.04, **p < 0.001, *** p = 0.004).

Result

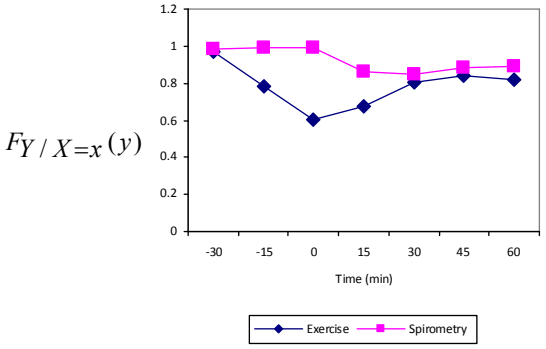

Fig.2. $F_{Y/X=x}(y)$ Vs Time (min)

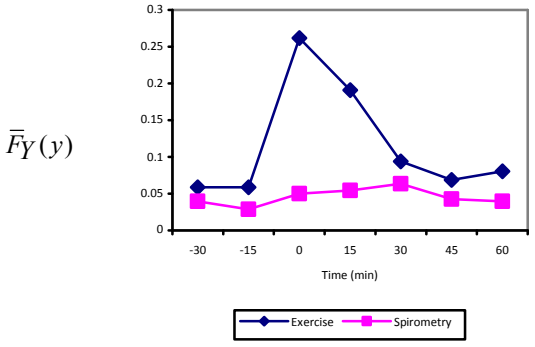

Fig.3. $\bar{F}_Y(y)$ Vs Time (min)

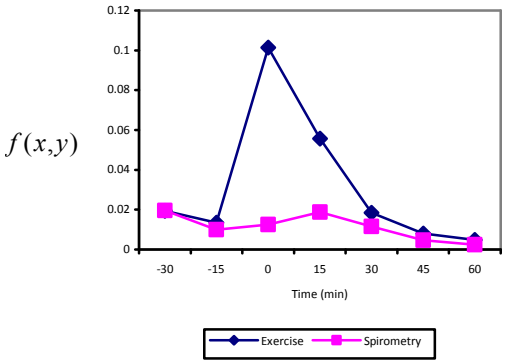

Fig.4. $f(x,y)$ Vs Time (min)

Conclusion

Estimation of system reliability requires understanding of the association between the lifetimes of components in the system. Testing of components connected in series is not efficient compared to testing of components in parallel systems. Lu (1997) proposed a plan for shortening the testing of parallel systems. Although the life-testing plan is motivated from the effectiveness of testing experiments, there are potential practical motivations. For example, here 24 asthmatic children were enrolled FE_{NO} was measured with a chemiluminescence analyser. After spirometry for a six month walk test on separate days in random order a bivariate exponential distribution is utilized. The corresponding values are obtained for both spirometry and exercise cases for conditional probability, $\bar{F}_Y(y)$ and density function.

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