Bayesian Concordance Correlation Coefficient with Application to Repeatedly Measured Data

Tekrarlı Ölçülmüş Verilere Uygulaması ile Bayesci Uyum Korelasyon Katsayısı

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ABSTRACT Objective: In medical research, Lin's classical concordance correlation coefficient (CCC) is frequently applied to evaluate the similarity of the measurements produced by different raters or methods on the same subjects. It is particularly useful for continuous data. The objective of this paper is to propose the Bayesian counterpart to compute CCC for continuous data. **Material and Methods:** A total of 33 patients of astrocytoma brain treated in the Department of Radiation Oncology at Malabar Cancer Centre is enrolled in this work. It is a continuous data of tumor volume and tumor size repeatedly measured during baseline pretreatment workup and post surgery follow-ups for all patients. The tumor volume and tumor size are measured separately by MRI and CT scan. The agreement of measurement between MRI and CT scan is calculated through CCC. The statistical inference is performed through Markov Chain Monte Carlo (MCMC) technique. **Results:** Bayesian CCC is found suitable to get prominent evidence for test statistics to explore the relation between concordance measurements. The posterior mean estimates and 95% credible interval of CCC on tumor size and tumor volume are observed with 0.96(0.87,0.99) and 0.98(0.95,0.99) respectively. **Conclusion:** The Bayesian inference is adopted for development of the computational algorithm. The approach illustrated in this work provides the researchers an opportunity to find out the most appropriate model for specific data and apply CCC to fulfill the desired hypothesis.

Key Words: Bayes factor; MCMC; repeatedly measured data; CCC; CT-MRI; tumor size

ÖZET Amaç: Tıbbi araştırmalarda, aynı denekler üzerinde farklı değerlendiriciler veya yöntemler tarafından elde edilen ölçümlerin yakınlığını değerlendirmek için Lin'in klasik uyum korelasyon katsayısı sıklıkla kullanılmaktadır. Bu, özellikle sürekli veriler için faydalıdır. Bu makalenin amacı sürekli veriler için uyum korelasyon katsayısının hesaplanacağı bayesci karşılığını sunmaktır. **Gereç ve Yöntemler:** Bu çalışmada, Malabar Kanser Merkezi Radyasyon Onkolojisi departmanındaki Toplam 33 Astrositoma beyin tümörü hastası kayıtlıdır. Bu, tüm hastalar için temel ön tedavi tetkiki ve ameliyat sonrası izlem süresince tümör volümü ve boyutunun tekrarlı olarak ölçüldüğü bir sürekli veridir. Tümör volümü ve tümör boyutu manyetik rezonans görüntüleme (MRG) ve bilgisayarlı tomografi (BT) taramalarıyla ayrı ayrı ölçülmüştür. MRG ve BT taraması arasındaki ölçüm uyumu da CCC aracılığıyla hesaplanmaktadır. İstatistiksel çıkarım Markov Zinciri Monte Carlo (MCMC) yöntemi ile yapılmaktadır. **Bulgular:** Bayesci CCC, uyum ölçümleri arasındaki ilişkiyi araştırmak için test istatistiklerine dair belirgin kanıt elde etmede uygun bulunmuştur. Tümör boyutu ve tümör volümündeki CCC için sonsal ortalama tahminleri ve %95 güven aralığı sırasıyla 0,96 (0,87, 0,99) ve 0,98 (0,95, 0,99)'dir. **Sonuç:** Bayesci çıkarım hesaplama algoritmasının geliştirilmesi için uygulanmıştır. Bu çalışmada gösterilen yaklaşım araştırmacılara, istenilen hipotezi yerine getirmek için CCC'yi uygulama ve belirli veriler için en uygun modeli bulma olanağı sağlar.

Anahtar Kelimeler: Bayes faktörü; MCMC; tekrarlı ölçüm verisi; CCC; BT-MRG; tümör büyüklüğü

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Diagnostic, therapeutic and prognostic tools are the basic requirements for evaluation of clinical practice in any health care service. It is obviously required to check the performance of newer ad-

vanced tool before it is being adopted for regular service. The concordance correlation coefficient (CCC) is useful to detect the performance of latest tool measured through continuous random variable.[1] However, t-test, Pearson correlation coefficient, coefficient of variation, intra-class correlation and least square analysis are very useful in this scenario and already widely adopted.[2] It is to be noted that the Intra-class correlation coefficient and coefficient of variation generally are considered, assuming that the readings between two observers are interchangeable. The t-test, least squares analysis usually fail to reject the null hypothesis in case of very large or small residual errors. The Pearson correlation is not able to measure the accuracy.[3] The CCC is found to be useful to measure the difference between the observations made. It evaluates the agreement between two readings through capturing the variation from 450 lines of the origin. Precision (by degree of variation) and accuracy (degree of location or scale-shift) are already being considered into CCC.[4]

The literature and available methods for discrete outcome to measure the performance of new diagnostic tool in comparison to existing is quite developed. The kappa statistics and weighted kappa[5] are widely used indices for measuring the agreement between two rater/ tool through discrete outcomes. The intra-class correlation to measure the reproducibility is found suitable.[6,7] The within-subject coefficient of variation to capture the reproducibility through random-effect modeling is also illustrated.[8] The Intra-class correlation coefficient obtained from ordinal data is equivalent to weighted kappa for integer scoring.[6,9-11] The application of CCC for repeated measured data were attempted through intra-class correlation coefficient.[12] The confidence interval of CCC (ρ_{ccc}) through Z-transformation Z_{ccc} is very complex to apply.[1,13] It is to be noted that the computation of Z-transformation is cumbersome. It has also been established that CCC tends to Pearson correlation coefficient in case of both rater having equal mean and variance of the measurement of interest.[1] The variance component to estimate CCC has also been illustrated.[14] It is defined that CCC is covariance-based index. The estimation procedure of this covariance -index is driven by the covariance adjusted method, particularly covariance related to subject effect. Separately, the stratified CCC[15] and the covariate adjustment in CCC through Generalized Estimating Equation has also been explored.[16]

Pre and post treatment tumor size is one of the important prognostic tool and indicator of therapeutic success or failure. Recently, several types of advanced imaging modalities are available for tumor size detection like magnetic resonance imaging (MRI) and computed tomography (CT). Ideally the same imaging modality should be applied to detect the tumor size before and after therapy to reduce the variation in different imaging. Simultaneously, same method of interpretation about tumor size needs to be performed. Broadly, two types of approaches are available for detection of tumor size, either through tumor volume or by maximum area covered by the tumor i.e tumor size. It is quite natural that maximum area covered by a tumor will be having maximum tumor volume; however it may not be true always. There is always a dilemma in health service providers whether to give priority to tumor volume or tumor size for assessment of T (tumor) stage of cancer patients. This paper illustrates the application of concordance correlation between tumor volume and maximum size covered by tumor imaged by different diagnostic tools. Moreover, the extension of the Bayesian approach of concordance correlation is considered to compute the CCC. Particularly, this paper proposes the Bayesian counterpart to compute CCC for repeatedly measured continuous data.

MATERIAL AND METHOD

This study considered the tumor size data of astrocytoma brain patients treated in the Department of Radiation Oncology at Malabar Cancer Centre between 2012 to 2014. Retrospective analyses of 33 patients were performed in this study. The data set is a tumor volume and tumor size measurements of those 33 individuals. The tumor volume and tumor size are measured separately by MRI and CT scan during baseline and post surgery visits of the patients.

The response vector is defined as $Y_i (i = 1,2,N, i \leq I)$ for I x 1 vector that contains the I readings. The term i=1 for CT & i=2 for MRI scanner are fixed for all Individuals i.e. N=33. The same individual's separate reading measured through different scanner are denoted as Y_i and Y_i respectively. The expected squared difference $E[(Y_i - Y_{i'})^2]$ is used to define the CCC as scaled between -1 to 1. The classical definition of CCC is recalled as

$$\rho_{ccc} = 1 - \frac{E[(Y_i - Y_{i'})^2]}{\sigma_i^2 + \sigma_{i'}^2 + (\mu_i - \mu_{i'})^2} = \frac{2\sigma_{ii'}}{\sigma_i^2 + \sigma_{i'}^2 + (\mu_i - \mu_{i'})^2} \quad (1)$$

where

$E(Y_i) = \mu_i, E(Y_{i'}) = \mu_{i'}$,

$\sigma_i^2 = var(Y_i), \sigma_{i'}^2 = var(Y_{i'}), \sigma_{ii'} = var(Y_{i'}), \sigma_{ii'} = cov(Y_i, Y_{i'}) = \sigma_i \sigma_{i'} \rho_{ii'}$. The terms $S_{ii'}$, S_i^2 $S_{i'}^2$, $\bar{Y}_i$ and $\bar{Y}_{i'}$ are assumed as unbiased estimates of $\sigma_{ij}, \sigma_i^2, \sigma_{i'}^2, \mu_i$ and $\mu_{i'}$ respectively are detailed below.

The expectation of these estimates is observed for k types of different methods/tools and here it is limited with $k=2$ for two scanners as

$$E\left(\frac{2}{k(k-1)} \sum_{i=1}^{k=1} \sum_{i'=i+1}^{k} S_{ii'}\right) = \frac{2}{k(k-1)} \sum_{i=1}^{k=1} \sum_{i'=i+1}^{k} \sigma_{ii'} \quad (2)$$

$$E\left(\frac{1}{k} \sum_{i=1}^{k} S_i^2\right) = \frac{1}{k} \sum_{i=1}^{k} \sigma_i^2 \quad (3)$$

$$E\left(\frac{1}{k(k-1)} \sum_{i=1}^{k-1} \sum_{i'=i+1}^{k} (\bar{Y}_i - \bar{Y}_{i'})^2\right) = \frac{1}{k(k-1)} \sum_{i=1}^{k-1} \sum_{i'=i+1}^{k} (\mu_i - \mu_{i'})^2 + \frac{\sigma_g^2}{n} \quad (4)$$

Now, $\sum_{i=1}^{k-1} \sum_{i'=i+1}^{k} (\bar{Y}_i - \bar{Y}_{i'})^2$ is a biased estimator of $\sum_{i=1}^{k=1} \sum_{i'=i+1}^{k} (\mu_i - \mu_{i'})^2$

and corresponding unbiased estimator is defined as

$$\sum_{i=1}^{k-1} \sum_{i'=i+1}^{k} (\bar{Y}_i - \bar{Y}_{i'})^2 - \frac{k(k-1)}{n} \sigma_g^2 = \sum_{i=1}^{k=1} \sum_{i'=i+1}^{k} (\bar{Y}_i - \bar{Y}_{i'})^2 - \frac{k(k-1)}{n} \sum_{i=1}^{k=1} \sum_{i'=i+1}^{k} (S_i^2 + S_{i'}^2 - 2S_{ii'})^2 \quad (5)$$

Finally, unbiased estimate of ρ_{ccc} is defined as $\bar{\rho}_{ccc}$.

$$\bar{\rho}_{ccc} = \frac{2 \sum_{i=1}^{k-1} \sum_{i'=i+1}^{k} S_{ii'}}{(k-1) \sum_{i=1}^{k} S_i^2 + \sum_{i=1}^{k-1} (\bar{Y}_i - \bar{Y}_{i'})^2 - \frac{k(k-1)}{n} \sum_{i=1}^{k-1} \sum_{i'=i+1}^{k} (S_i^2 + S_{i'}^2 - 2S_{ii'})} \quad (6)$$

MEASUREMENT THROUGH CCC

Let i and i' are two different reading for the j[th] patients and $k=2$ as representative of the number of methods/tools i.e. CT scanner and MRI scanner. The response of interest is Y_{ij} and $Y_{i'j}$ of the same patients 'j'. The simple linear model for two scanners is defined as

$$Y = \theta + \beta Y + \beta_i Y_i + \beta_{i'} Y_{i'} + \varepsilon_{ii'j} \quad (7)$$

Here, $Y_{ii'j}$ is a continuous response measured of the j[th] individual, i[th] observation by k[th] method, θ is the overall mean value of tumor size, Y is considered as fixed effect. The terms Y_i and $Y_{i'}$ are considered as random effects. It is assumed that the error term $\varepsilon_{ii'j} \sim N(0,\tau)$. The term $\varepsilon_{ii'j}$ is stands for precision for j[th] individual. In this work the prior assumption about the regression parameters of fixed effect is assumed to follow N(0.0.0001) and random effects as Gamma(0.0.0001).

The variance of fixed effect, random effect and error terms in equation (7) is defined as

$$\sigma_{fixed}^2 = \frac{2}{k(k-1)} \sum_{i+1}^{k-1} \sum_{i=i+1}^{k} \sigma_{ij} \quad (8)$$

$$\sigma_{random}^2 = \frac{1}{k(k-1)} \sum_{1}^{k-1} \sum_{i=i+1}^{k} (\mu_i - \mu_{i'})^2 \quad (9)$$

and

$$\sigma_{error} = \frac{2}{k(k-1)} \sum_{i=1}^{k-1} \sum_{i=i+1}^{k} \frac{1}{2} (\sigma_i^2 + \sigma_{i'}^2 - 2\sigma_{ii'})^2 = \frac{1}{k} \sum_{i=1}^{k} \sigma_i^2 - \frac{2}{k(k-1)} \sum_{i=1}^{k-1} \sum_{i=i+1}^{k} \sigma_{ii'} \quad (10)$$

The CCC is defined as

$$\rho_{ccc} = \frac{\sigma_{fixed}^2}{\sigma_{fixed}^2 + \sigma_{random}^2 + \sigma_{error}^2} \quad (11)$$

The term θ is constant.

$\sigma_{fixed}^2 = \frac{1}{\tau_f}$, $\sigma_{random}^2 = \frac{1}{\tau_r}$ and $\sigma_{error}^2 = \frac{1}{\tau_e}$.

To formulate the Bayesian analysis, we assign prior on the parameters, τ_f, τ_r, τ_e as follows:

$\theta \sim dnorm$ (0,0.001)

$\tau_f \sim dgamma$ (0.0001,0.0001)

$\tau_r \sim dnorm$ (0.0001,0.0001) and

$\tau_e \sim dgamma$ (0.0001,0.0001)

where dnorm stands for normal distribution, dgamma denotes the Gamma distribution. The parameters of the distribution considered as non-informative prior and fixed as 0 and 0.001 for normal distribution and 0.0001 and 0.0001 for Gamma distribution.

The Bayesian factor is applied through JZS for Concordance Correlation in regression line.[17] The regression coefficient β is permitted to the application of JZS prior. The CCC, Intercept (θ), regression coefficients and error term ($\varepsilon_{ii'j}$) are detailed in equation (7). Let the equation (7) further been separated into Model (M_1) and Model (M_0) by

$$M_1: Y = \theta + \beta X + \varepsilon_{ii'j} \quad (12)$$

$$M_0: Y = \theta + \varepsilon_{ii'j} \quad (13)$$

The model (M_1) states the presence of CCC and absence of it by Model (M_0). Now, the Bayes Factor through JZS is defined as,[17-19]

$$BF_{10} = \frac{(\frac{n}{2})^{\frac{1}{2}}}{\tau(\frac{1}{2})} \times \int_0^{\infty} (1+g)^{(n-2)/2} \times [1+(1-r^2)g]^{-\frac{(n-1)}{2}} \quad (14)$$

$$BF_{10} = \frac{p(Y(M_1))}{p(Y(M_0))} \quad (15)$$

If the value of BF_{10} becomes more than 1, it states about the presences of CCC otherwise not.

The statistical test can be performed with two Hypotheses: the Null Hypothesis, H_{0} as given in model (M_0) and the alternative Hypothesis H_1 or (M_1). The prior probability of Null Hypothesis is assigned as $p(M_0)$ and Alternative as $p(M_1)$. Therefore, Baye's theorem is applied to the observed data to compute the posterior probability of the Hypothesis. The appearance of the posterior probability of Alternative Hypothesis is computed as

$$p(M_1/Y) = \frac{p(Y|M_1)p(M_1)}{p(Y|M_1)p(M_1)+p(Y|M_0)p(M_0)} \quad (16)$$

The term $P(M_1 \mid Y)$ is the marginal likelihood of the data for alternative hypotheses. Further, the marginal likelihood is calculated as

$$p(Y|M_1) = \int_g^{\infty} p(Y|\theta, M_1)p(\theta|M_1)d\theta \quad (17)$$

Bayes Factor is used to compute the appearance of $P(M_1|Y)$ in comparison to $P(M_0|Y)$:[20]

$$\frac{p(M_1|Y)}{p(M_0|Y)} = BF_{10} \times \frac{p(M_1)}{p(M_0)} \quad (18)$$

RESULTS

The relations between Pre Surgery and Post Surgery Tumor Volume in Male and Female patients are graphically explored in Figure1 and Figure2 respectively. The relation of Tumor size explored through spaghetti plots for male and female given in Figure 3 and Figure 4 separately. Figure 5 and Figure 6 provide the scatter plots on pre-surgery (Tumor size and Tumor volume) and post-surgery (Tumor size and Tumor volume).

The descriptive statistics of the patient's tumor size on pre and post surgery are given in Table 1.

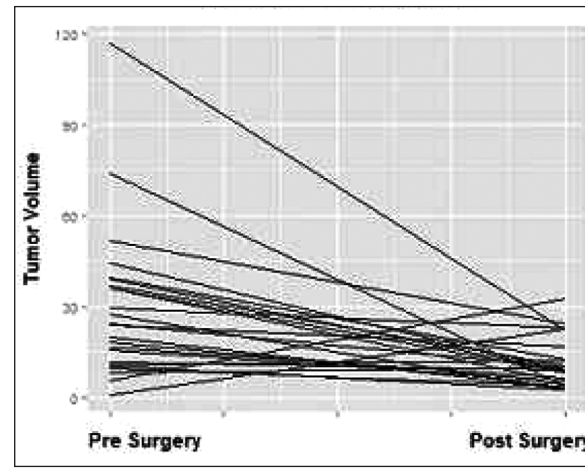

FIGURE 1: Pre surgery and post surgery tumor volume in male.

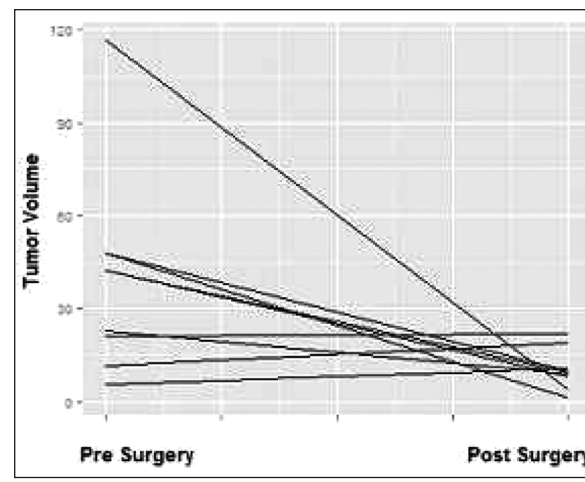

FIGURE 2: Pre surgery and post surgery tumor volume in female.

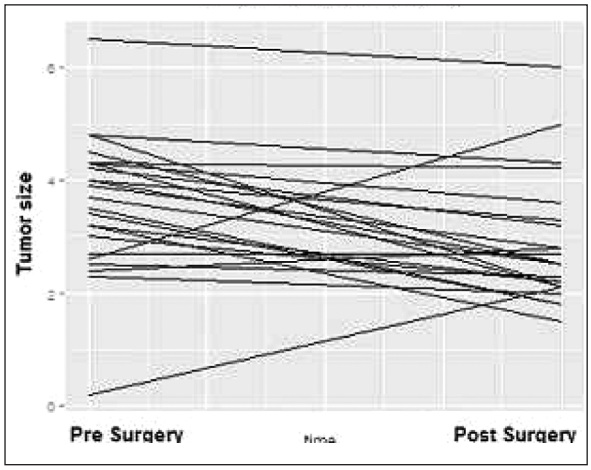

FIGURE 3: Pre surgery and post surgery tumor size in male.

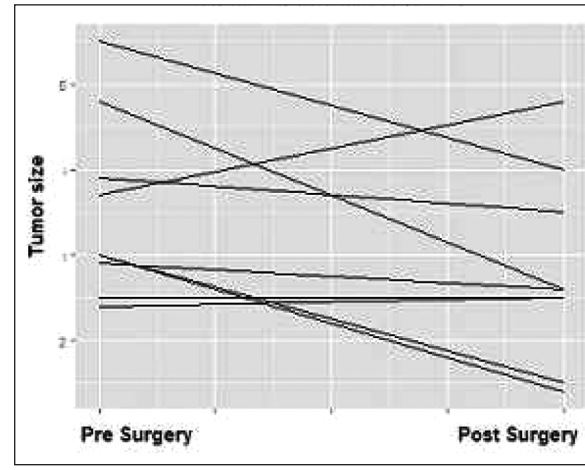

FIGURE 4: Pre surgery and post surgery tumor size in female.

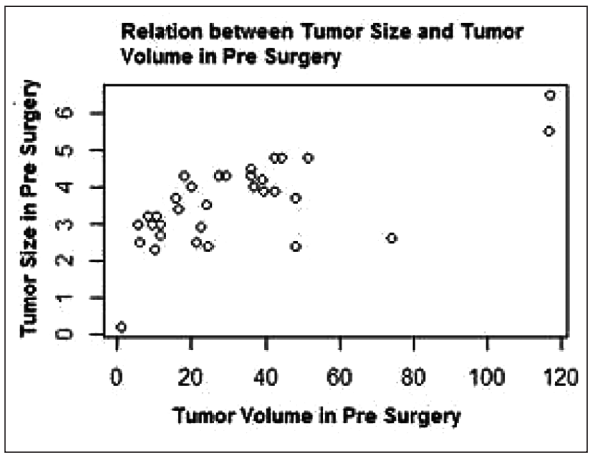

FIGURE 5: Relation between tumor size and tumor volume in pre surgery.

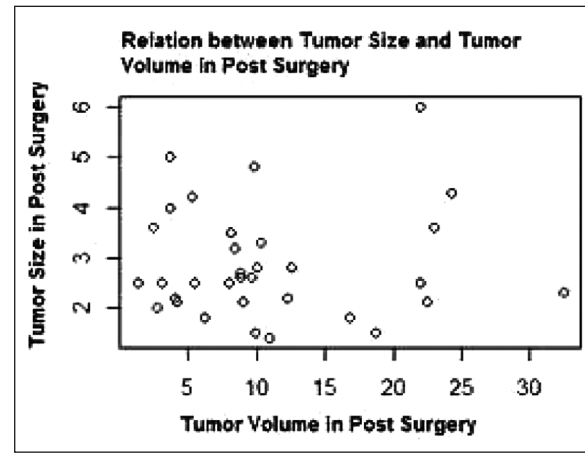

FIGURE 6: Relation between tumor size and tumor volume in post surgery.

TABLE 1: Descriptive Statistics about tumor size of the patients.

Sex	Baseline Measurements		Post Surgery Measurements	
	(Max, Min)	Mean(SD)	(Max, Min)	Mean(SD)
Male	(6.50,0.20)	3.60(1.20)	(6.00,1.50)	2.87(1.10)
Female	(5.50,2.40)	3.52(1.05)	(4.80,1.40)	2.82(1.10)

The classical test is performed to test the level of CCC in tumor data. Table 2 and Table 3 reveal the estimates of CCC through covariates adjusted model on tumor volume and tumor size respectively. The test is performed to check whether the null hypothesis that the concordance correlation coefficient is zero, i.e. $\rho_{ccc} = 0$. The cccUst function in "cccrm" package of R i386 3.1.1 is applied and test the null hypothesis to perform the classical test.

The Bayesian counterparts of estimates through posterior estimates on tumor volume and size separately provided in Table 4 and Table 5 respectively.

In Bayesian the same models are selected to fit the correlation coefficient to measure the associations. It implies that the precision about the methods are moderate. The correlation coefficients are not very much different from calculated classical

TABLE 2: Estimates of concordance correlation coefficients on tumor volume.

Selected Variable	ρ_{ccc}	SE(ρ_{ccc})	95%CI	Z	SE(Z)
Male	0.89	0.00	(0.87,0.91)	1.46	0.04
Female	0.84	0.01	(0.82,0.86)	1.23	0.04

TABLE 3: Estimates of concordance correlation coefficients on tumor size.

Selected Variable	ρ_{ccc}	SE(ρ_{ccc})	95%CI	Z	SE(Z)
Male	0.85	0.01	(0.81,0.88)	1.26	0.05
Female	0.87	0.01	(0.84,0.90)	1.36	0.05

TABLE 4: Posterior estimates of CCC on tumor volume for all patients.

Parameter	Mean	SD	2.5%	Median	97.5%
ρ_{ccc}	0.96	0.03	0.87	0.98	0.99
σ_w^2	431.5	15.57	402.2	431.2	463.1
σ_a^2	1.97	0.08	1.72	2.11	2.19
σ_b^2	0.10	0.51	0.00	0.00	0.47
σ_d^2	0.15	0.38	0.00	0.00	1.6
θ	9.67	27.26	-54.51	15.04	53.23

CCC detailed in Table 3. It can be concluded by having high estimates for accuracy.

Table 2 shows the CCC between two scanners on tumor volume are 0.89 (0.00) and 0.84 (0.01) for male and female patients respectively. Table 3 reveals the CCC estimates between CT and MRI on tumor size for male and female patients as 0.85(0.01) and 0.87(0.01) respectively. The estimates of CCC for male and females are found very close. The Bayesian counterpart of CCC's for tumor size and volume are computed separately for all patients. The male and females are not selected separately to compute the Bayesian counterpart of CCC. The posterior estimate of CCC is found to be 0.96 with 95% credible interval (0.87,0.99) on tumor volume (Table 4). Table 5 shows that posterior estimates of CCC on tumor size observed with 0.98 with 95% credible interval (0.95,0.99) . The variance components are obtained and detailed in Table4 and Table 5. In summary, the proposed computation method for estimating CCC tends to estimate the true CCC with less or equal standard error. The values are applied to obtain the BF_{10} in equation (18). The BF_{10} is calculated with 10.28. It is the evidence in favor of M_1 in comparison to model M_0.

DISCUSSION AND CONCLUSION

The CCC is now a useful tool for measuring agreement among observers on continuous variables. It is more attractive due to computational provisions through a result of the sample covariance, variances,

TABLE 5: Posterior estimates of CCC on tumor size for all patients.

Parameter	Mean	SD	2.5%	Median	97.5%
ρ_{ccc}	0.98	0.01	0.95	0.99	0.99
σ_w^2	98.02	3.53	91.66	97.9	105.2
σ_a^2	2.32	16.08	0.00	0.06	10.36
σ_b^2	0.55	1.29	0.00	0.05	4.77
σ_d^2	0.06	0.23	0.00	0.00	0.89
θ	82.34	1.82	76.84	82.24	85.24

and means of observers to the CCC.[1,21] However, there is a certain chance of getting biased estimates either on the CCC or its standard error.[22] The CCC into the generalized estimating equation through three different procedures has been extended.[16] The application of overall CCC and stratified CCC also been explored in detail recently.[15] The Generalized Concordance Correlation Coefficient through variance component method is found very simple.[23] The robust approximation to deal with CCC has also been elaborated.[15] The application of CCC has been found suitable in case of time to event problem by,[24] univariate censoring,[2] and longitudinal repeated measurements.[22,25] It is found suitable to estimate CCC through qualitative or quantitative data through variance components linear mixed model. Here, the generalized CCC (GCCC) has been defined through variance component approach into continuous data. The Bayesian inference is adopted for development of the computational algorithm. The idea of this approach is to fit the data into GLMM and thereafter extend the application through Bayesian. The approach illustrated in this work gives the researchers with the scope to find the most appropriate model for specific data and apply CCC to fulfill the desired hypothesis. It gives more information about statistical inference rather than mere p-values observed from classical approach. In addition to estimates about CCC, it also provides the estimates of variance components of CCC. The Bayesian estimation procedure is applied on ICC.[26] They adopted the beta-binomial model for ICC interpretation. They reported the conclusion through the credible interval. A Bayesian Estimator for calculation of CCC is applied in this study. It is found that the ICC values are generally not accompanied by confidence interval, which makes the impact of ICC limited towards estimation procedure.[27] In this work the model is formulated with MCMC. A total of 10,000 iterations are selected to generate the posterior estimates for parameters. The OpenBugs software is used to run the algorithm. It is clear that the techniques applied over here are quite simple and suitable to apply in continuous data with concordance problem. This paper has attempted to explore the Bayesian counterpart to compute CCC. It is aimed to explore the application of Bayesian approach to compute CCC. The application has been illustrated with tumor volume and tumor size measurements of astrocytoma brain patients measured through different types of imagings. It can be concluded that tumor size and tumor volume are highly concordant. The measurement of any one can be replicated in presences of others. Bayesian can be useful to get prominent evidence for test statistics in relation between variables. Bayes factor is useful for computation of CCC. It is useful to figure out the strength of the hypothesis. It can be considered as an easily interpretable tool to discover the relations.

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