The Development of Web-based Graphical User Interface for Learning and Fitting Generalized Estimating Equation with Spline Smoothers

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ABSTRACT

Statistical modeling (regression analyses) have been growing rapidly into various directions to accommodate various data conditions. For longitudinal or repeated measures data, one of the suitable models is GEE (Generalized Estimating Equation). In practice, to do complex modeling such as GEE, the use of statistical software is necessary and it is available on free open source software R. However, GEE modeling on R can only be access through command line interface (CLI), and most practical researchers very much rely on Graphical User Interface (GUI) based statistics software. To make access to GEE (both order 1 and 2) much easier, we developed, using Shiny toolkit, two types of web-based GUI, standard pull down menu type and e-module type (with narrative theories) that can be utilized for learning and fitting GEE. This paper discusses the features of the interfaces and illustrates the use of them.

Keywords: longitudinal data, Generalized Estimating Equation (GEE), exponential families, statistical modeling, correlated response, nonparametric, natural splines, shiny toolkit

INTRODUCTION

Statistical models have been developed into various directions to accommodate the objectives of researchers and the complexity of data (in term of sample size, the number, types and structure of variables involved). In practice, most applications of the models need statistics softwares. Majority of practical researches can only access models those are already implemented in commonly available GUIbased softwares, while actually, statistics theories grows much more rapidly than those readily implemeted in those type of softwares. This situation worries statisticians (Wallace *et al.*, 2012) that *“**practitioners continue to use inappropriate or suboptimal methods due to their being restricted to what is made available via GUIs”.***

New statistical methods are most frequently implemented or tested using open source R, and R has rich collections of the most recent (currently developed) or advanced statistical methods. However, all of them (including GEE) are still based on script or CLI, hence they cannot be utilized by majority of ‘practitioners’. For ordinary and occasional R users, even installing R with extended specific packages are also not simple.

The need for developing GUI for R, were already recognized arround last decade and several GUIs have been developed such as Rcommander which covers most basic statistics (Fox, 2005), RKWard (Rodiger *et al.*, 2012), and Deducer (Fellows, 2012). R Commander and Deducer have plug-in system to facilitate other programmers to extend the coverage. However, GEE has yet not been implemented either in the core or as plug-ins of the above GUIs.

The development of Web-based GUI has becoming easier since the release of shiny framework (Chang *et al.* 2015). Such framework has been implemented for unifying regression analysis (in pulldown menu type) for independent/ univariate responses (Tirta, *et al.* 2017). In this paper we develop web-GUI and in e-tutorial/e-module type. for easier, friendlier access and guided application of GEE (order 1 and order 2) both in pull down menus and e-module types. In addition we extend the GEE by combining with spline smoother on the mean model.

The rest of the paper is organized as follows: section II briefly summarizes theory of GEEs, section III describes the main methods or tools, section IV discusses the results and numerical illustration and section V concludes the results of the study.

REVIEW OF GEE

GEE Order 1

Original GEE (later known as GEE 1 or GEE order 1) was formally introduced by Liang and Zeger and Zeger and Liang in 1986. GEE can be considered as extension of GLM (Generalized Linear Model, McCullagh & Nelder, 1989) to account for correlation in the responses. These type of responses are commonly found in repeated meassurement or longitudinal data. The type of distributions of data considered in this model are mainly those from exponential family distribution with corresponding valid link functions (McCullagh & Nelder, 1989). The mean responses are also modeled similarly to GLM with appropriate link function, *g*, as given in equation (1).

$$g(\mu_i) = \sum_{j=0}^{p} x_{ij}\beta_j \qquad (1)$$

for *p* number of predictors.

The most common correlation structures available for GEE are: (a) exchangeable (uniform) with 1 correlation parameter (cp), (b) AR (auto regressive)-1 with 1 cp, (c). Independence no cp (identic with GLM) and (d) unstructured with (k^2-k)/2 cp's, for responses with *k* cluster/ repeated measurement. The form of the correlation matrices are as given in equation 2(a)-2(d).

$$\text{(a)} \begin{pmatrix} 1 & \alpha & L & \alpha \\ \alpha & 1 & L & \alpha \\ M & M & O & M \\ \alpha & \alpha & L & 1 \end{pmatrix}, \text{(b)} \begin{pmatrix} 1 & \alpha & L & \alpha^{k-1} \\ \alpha & 1 & L & \alpha^{k-2} \\ M & M & O & M \\ \alpha^{k-1} & \alpha^{k-2} & L & 1 \end{pmatrix}$$

$$\text{(c)} \begin{pmatrix} 1 & 0 & L & 0 \\ 0 & 1 & L & 0 \\ M & M & O & M \\ 0 & 0 & L & 1 \end{pmatrix}, \text{(d)} \begin{pmatrix} 1 & \alpha_{12} & L & \alpha_{1k} \\ \alpha_{21} & 1 & L & \alpha_{2k} \\ M & M & O & M \\ \alpha_{k1} & \alpha_{k2} & L & 1 \end{pmatrix} \text{(2)}$$

GEE Order 2

In GEE (order 1), the scale parameter ϕ is considered as constant. GEE order 2 extends the GEE with possibility of modeling the scale parameter to be dependant upon some predictors (in our case are limited to linear predictors). That is, in addition to model for mean, there is also model for scale parameter as given in equation (3)

$$\phi = \sum_{j=0}^{q} x_{ij}\gamma_j . \qquad (3)$$

As being well known, that misspesification of correlation structure in GEE 1, does not influence the point estimates of the regression parameter *β*, however it does influence their efficiency as indicated by their standard error (Hidayati *et al.*). Therefore it is still important to check the best correlation structure as well as the model for the scale parameter. In addition to the model of scale parameter, GEE2 also allows the correlation to have one of two available link functions, these are identity and Fizsher.

Considering Smoother for the mean model

Modeling regression parameter as linear with composition of link function, sometime is not sufficient to account for nonlinearlity in the predictors. In other words, there is a need to have model that can be considerd as extention of GAM for GEE. Recently, there are many sugesstion in the discussion forum to include natural or b-spline smoother in the model. This is possible since natural and b-spline are quite flexible in R to be combined with other model (such as classes of lm() and glm(), and gee ()).

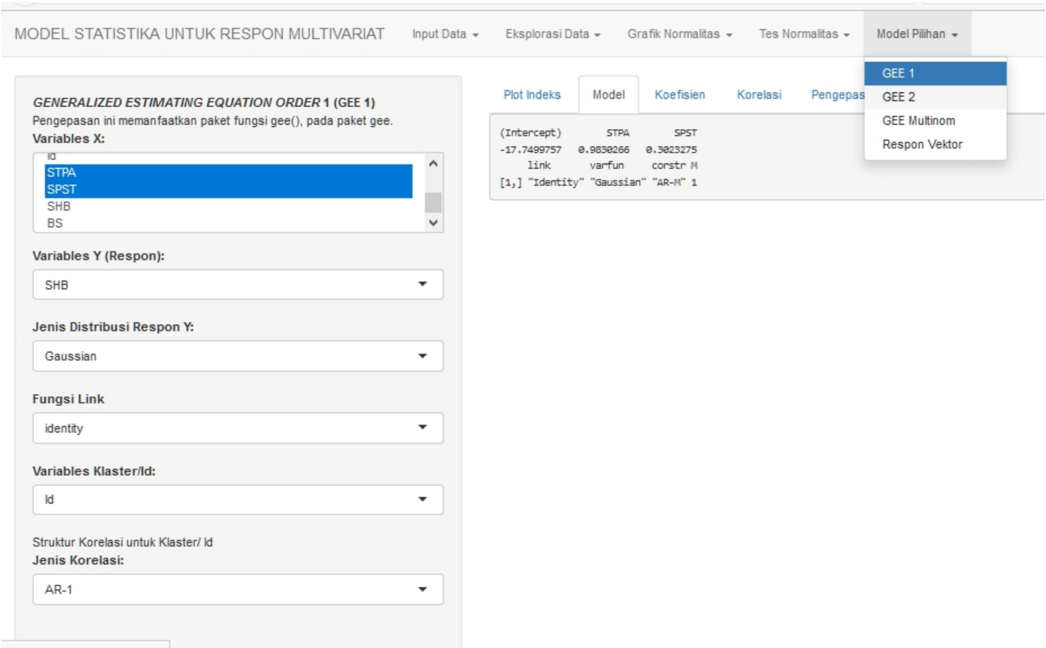
METHODS

The web-based interfaces are built using shiny toolkit applied on R-shiny server from Rstudio group (Chang *et al.*, 2015). We develop two types of web-GUI interfaces: standard pull down menu type and e-tutorial/ e-module type for modeling longitudinal data, using GEE. The pulldown menu type consst of 2 main file, ui.r (for communication with user) and server.r (for communication with R server), while for e-module type the ui.r is replaced by index.html (where in this html file we can put several extension such as theory, step by step procedure by utilizing html features). Therefore, in addition to computational features (as in pulldown menu type), the e-module type has description of theory and narration for guiding users in every step of modeling and interpreting the outputs.

The main packages involved are (i) geepack (Yan, 2002; Jsgaard *et al.*, 2006), especially the geese() and geeglm() functions, (ii) ggplot2 (Wickham, 2009) for ploting the smoother, (iii) psych (Revelle, 2016) for ploting diagram correlation and splines (R Core Team, 2016) for nonparametric modelling of the mean.

RESULTS AND DISCUSSION

The developed interfaces are already uploaded on our 'virtual statistics laboratory'. The pull down menus type can be accessed at http://statslab-rshiny.fmipa.unej.ac.id/ RProg/MSD/ (See Fig 1) and for e-modul type, it can be accessed athttp://statslab-shiny.fmipa.unej.ac.id/JORS/GEE/ (Fig 2).



GENERALIZED ESTIMATING EQUATION ORDER **1 (GEE 1)**

Pengepasan ini memanfaatkan paket fungsi gee(), pada paket gee.

Variables X: Id, STPA, SPST, SHB, BS (STPA and SPST selected)

Variables Y (Respon): SHB

Jenis Distribusi Respon Y: Gaussian

Fungsi Link: identity

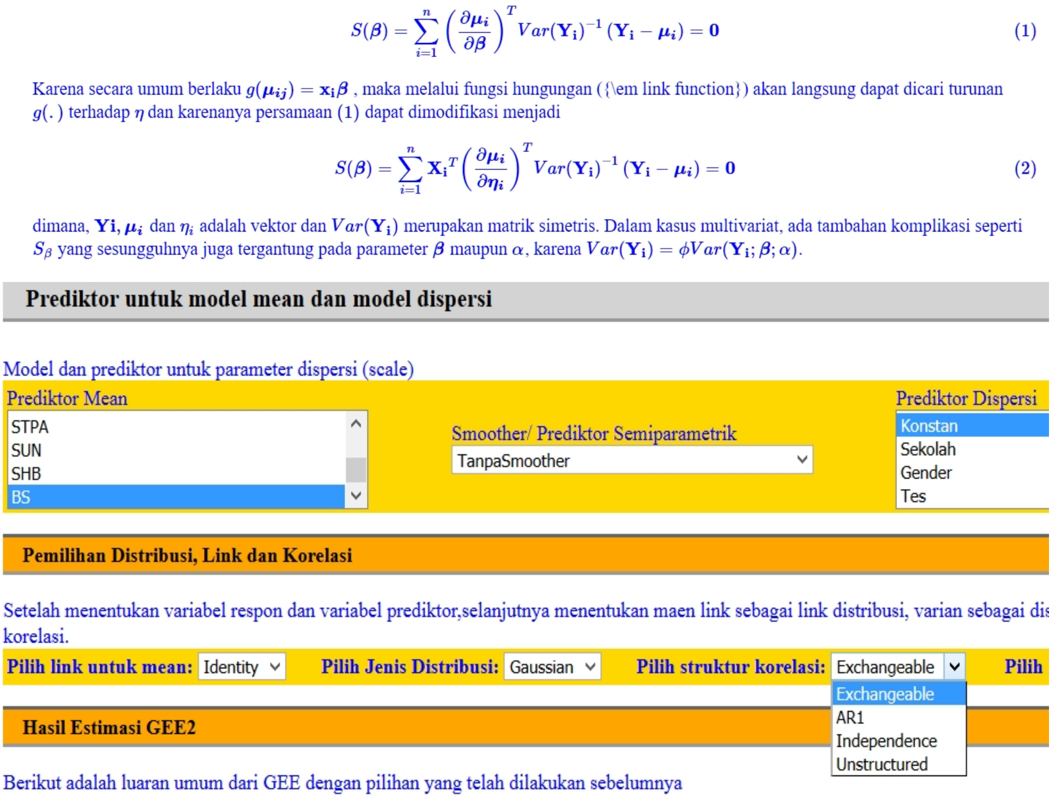
Variables Klaster/Id: Id

Struktur Korelasi untuk Klaster/ Id

Jenis Korelasi: AR-1

```
(Intercept)        STPA       SPST
-17.7499757  0.9830266  0.3023275
       link       varfun     corstr M
[1,] "Identity" "Gaussian" "AR-M" 1
```

Figure 1. The appearance of the pulldown menu type. User can easily chooseariables, type of distributions, correlation structure


$$S(\beta)=\sum_{i=1}^{n}\left(\frac{\partial\boldsymbol{\mu}_i}{\partial\boldsymbol{\beta}}\right)^{T} Var(\mathbf{Y_i})^{-1}(\mathbf{Y_i}-\boldsymbol{\mu}_i)=\mathbf{0} \qquad (1)$$

Karena secara umum berlaku $g(\boldsymbol{\mu}_{ij})=\mathbf{x}_i\boldsymbol{\beta}$, maka melalui fungsi hungungan ({\em link function}) akan langsung dapat dicari turunan $g(.)$ terhadap η dan karenanya persamaan (1) dapat dimodifikasi menjadi

$$S(\beta)=\sum_{i=1}^{n}\mathbf{X_i}^{T}\left(\frac{\partial\boldsymbol{\mu}_i}{\partial\eta_i}\right)^{T} Var(\mathbf{Y_i})^{-1}(\mathbf{Y_i}-\boldsymbol{\mu}_i)=\mathbf{0} \qquad (2)$$

dimana, $\mathbf{Yi}, \boldsymbol{\mu}_i$ dan η_i adalah vektor dan $Var(\mathbf{Y_i})$ merupakan matrik simetris. Dalam kasus multivariat, ada tambahan komplikasi seperti S_β yang sesungguhnya juga tergantung pada parameter $\boldsymbol{\beta}$ maupun α, karena $Var(\mathbf{Y_i})=\phi Var(\mathbf{Y_i};\boldsymbol{\beta};\alpha)$.

Prediktor untuk model mean dan model dispersi

Model dan prediktor untuk parameter dispersi (scale)

Prediktor Mean: STPA, SUN, SHB, BS (BS selected)

Smoother/ Prediktor Semiparametrik: TanpaSmoother

Prediktor Dispersi: Konstan, Sekolah, Gender, Tes (Konstan selected)

Pemilihan Distribusi, Link dan Korelasi

Setelah menentukan variabel respon dan variabel prediktor,selanjutnya menentukan maen link sebagai link distribusi, varian sebagai dis korelasi.

Pilih link untuk mean: Identity **Pilih Jenis Distribusi:** Gaussian **Pilih struktur korelasi:** Exchangeable **Pilih**

Hasil Estimasi GEE2

Berikut adalah luaran umum dari GEE dengan pilihan yang telah dilakukan sebelumnya

Figure 2. The appearance of theory and guided options for predictor, family and correlation structures in e-module type

Data Ilustration

As illustration, we simulated data having both continuous (SHB) and binary responses (BS) which are measurred repeatedly (in the form of five Tests,T1-T5). To calculate the correlation matrix and to display correlation diagram (among the repeated responses), the name for id and for the repeated observations must be properly chosen. The following is the correlation matrix and correlation diagram (Fig 3) between repeated observations. This correlation matrix or diagram can give rough idea on the candidate of the suitable type of correlation structure (in this case AR-1 seems appropriate, slightly decreases as the test distance further away). Note that on the web, for the same name user may find slightly different data since they are randomly simulated.

```
   T1    T2    T3    T4    T5
T1 1.000 0.951 0.834 0.793 0.785
T2 0.951 1.000 0.905 0.858 0.818
T3 0.834 0.905 1.000 0.943 0.891
T4 0.793 0.858 0.943 1.000 0.943
T5 0.785 0.818 0.891 0.943 1.000
```

We check the possibility of including smoother in the mean model and inspect the scatter plot of some predictors vs response. After comparing the graphs, we see thatvariable STPA with df =3 seems worth to include in the mean model (Fig 4). For distribution, link and correlation structure, we can easily select the menus for these choices (see Fig 2).

Table 1. Main computational features of the Interfaces

No	Steps	Input Menus	Output	Packages
1	Data explorations	1. Internal Database 2. Import Data	Summary of data Correlation matrix Correlation diagram	stats stats
		3. Smoother exploration	Natural- Smoother graphics	psy ggplot2
2	Model fitting	4. Variable input (Y, Xs for means, Xs for scale)		Geepack (geese, geeglm)
		5. Family and links as in GLMs)	Estimates of β Estimate of α	Geepack (geese, geeglm)
		6. Smoother component		splines
3	Model Selection	QIC	QIC (does not account for model for scale)	MuMIn

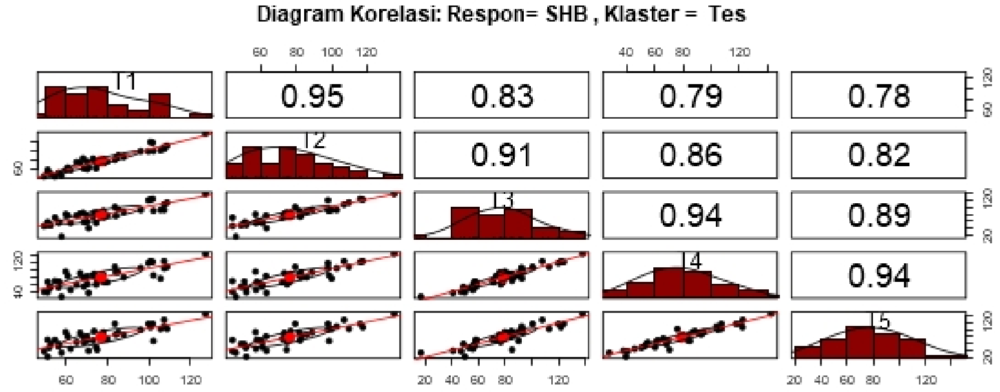


Figure 3. Correlation Diagram of the Repeated Responses

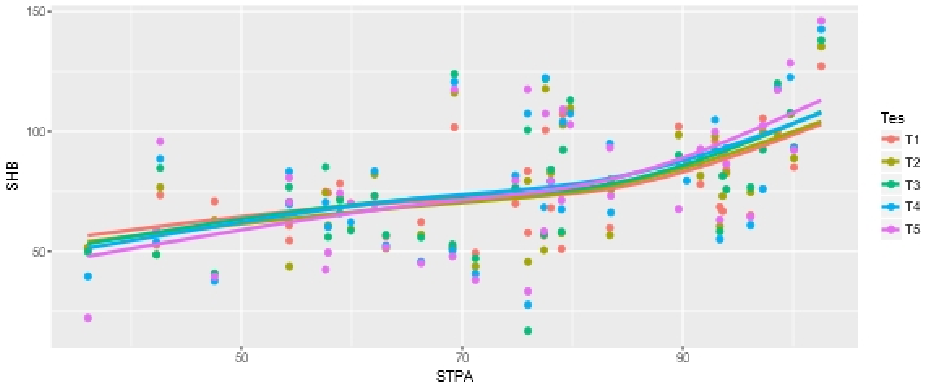


Figure 4. Smoother graphics of predictor (STPA) vs Response using natural cubic sline with df=3

The interpretation of the outputs is as usual by checking the p-value (for the significance of the parameter) and the value of QIC for checking the goodness of fit of the model. In this illustration, all the regression coefficient (for both mean and scale parameter) are significant (p-val<5%). User can modify (change) the model (family, correlation structure etc) and compare the value of the QIC (Note that model for scale parameter does not affect QIC, so for scale model we only check their p-values). The results for some tested models are summarized in Table 2, follows by the full output of what is considered as the best model. In modelling with GEE, a predictor cannot be at the same time as linear and nonparametric predictor (in our interface using natural spline). In practice, for prediction purposes, the repeated measurement (in this illustration is Test) may be retained in the model although their parameters are not significant especially where prediction for every level of the repeated factor are needed.

Table 2. Comparison of the QIC values for some tested models

Mean Predictors	Scale predictors	CorStr	QIC
Gaussian			
STPA SUN	SUN	Exch	1224.713
s(STPA) SUN	SUN	Exch	1277.158
STPA s(SUN)	SUN	Exch	1230.296
STPA SUN	SUN	Ar1	1224.804
s(STPA) SUN	SUN	Ar1	1277.787
STPA s(SUN)	SUN	Ar1	1230.56

In this illustration, we found that the QIC values (i) under Gaussian (identity) and Gamma (log) are simmilar, (ii) without smoother are slightly smaller, (iii) with exchangeable correlation structure are slightly smaller.

```
$mean (estimates)
             estimate    san.se       wald           p
(Intercept) 12.4124717 11.5776244  1.14941705 0.2836712146
TesT2       -0.7975178  1.1823131  0.45500458 0.4999678898
TesT3        0.5604951  2.5716382  0.04750331 0.8274660888
TesT4        0.9635519  2.7915540  0.11914016 0.7299689376
TesT5        0.8370444  2.7818546  0.09053742 0.7634950413
STPA         0.6055147  0.1578732 14.71066235 0.0001253356
SUN          0.2710924  0.1132546  5.72958620 0.0166814129
$correlation
      estimate     san.se     wald p
alpha 0.7842216 0.04402325 317.3316 0
$scale
             estimate    san.se     wald         p
(Intercept) 177.971103 172.87004 1.059887 0.3032410
SUN           3.193302   2.40771 1.759024 0.1847463
QIC.QIC
  1224.713
```

The final model can be expressed as follows

$$E(\mathbf{Y}) = E\begin{pmatrix} y1 \\ y2 \\ y3 \\ y4 \\ y5 \end{pmatrix}$$

$$= \begin{pmatrix} 12.4125 \\ 12.4125 - 0.7975 \\ 12.4125 + 0.5605 \\ 12.4125 - 0.9635 \\ 12.4125 - 0.8370 \end{pmatrix} + 0.6055STPA + 0.2711SUN$$

and
scale=177.97+3.1933*SUN
Overall, the response Y has gaussian distribution with identity link and among the repeated observations have exchangeable type of correlation structure with estimated correlation parameters equal 0.78.

Discussion
Our web GUI interfaces fill the gap of the absence of GUI for GEE (both order 1 and 2) in R. In term of available of choices of components, our web-GUI offers all of the common choices and the output of geese() function (ready for modeling GEE1 and GEE2). In addition (which are not part of geepack package) we also offer (ii) correlation matrix and correlation diagram, (iii) smoother model and graphics, and (iv) QIC as guidance for choosing a better model. Users can utilized those option without worrying about the syntax of all used functions, or even about installing them on their computer. The e-module type not only describe summary of theory (as found in commonly available e-module, such as one of popular online text book on statistics) (StatSoft, Inc., 2013), but also present proper mathematics notation and offer the users to dynamically choose different data (including their own data) and follow step by step checking various models and interpretation of the output.

Limitation and future development
Our web-GUI has some limitation including: (i) responses distributions are limited to exponential family distributions, (ii) model for scale is limited to linear model with identity link, (iii) QIC does not count for model for scale. We have recently initiated extending the interfaces to include GEE for nominal or ordinal multinomial responses through multgee package (Touloumis, 2015) and possibly vector generalized linear and additive model (VGAM) (Yee, 2016) and these features will be properly added in near future. For e-module type the structure of description of the theory and the step of modelling need to be continuously improved by considering user's feedback.

CONCLUSION

Our web-based GUI on GEE can be accessed with various type of gadgets and browser without worrying about scripting, collecting and installing R and related packages. Our web-GUI offer all important options of geese() as if it is accessed via script. In addition, the web also calculate and offer sample correlation and correlation diagram, and QIC of each chosen model. User are also possible to accomodate smoother (using natural cubic spline) in modeling mean responses.

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