PRELIMINARY REPORT

On Estimation of ED50 using Generalized Linear models and Generalized Additive models

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SUMMARY

To estimate the median effective dose (ED₅₀), we model the dose-response curve by using generalized linear models and generalized additive models as their extension. The estimation of ED₅₀ in generalized linear models has been known but not so for generalized additive models. We compare the result from nonparametric fitting of a generalized additive model with those of generalized linear models.

1. Introduction

When dealing with quantal responses, it is often the case that estimation of the value of the dose at which the response probability is 50% is of interest. It is called the median effective dose, ED₅₀, for short. (It is sometimes referred to as the median lethal dose, LD₅₀, when the response corresponds to the death of study subjects.) More generally, we may be interested in estimating the dose causing 100 α % of subjects to respond, ED α with 0 $\leq\alpha\leq$ 1. This kind of inverse prediction is also known as a calibration problem in some contexts.

The probability of response at dose d can be often viewed as

$$\alpha = \int_{-\infty}^d f(x)dx$$

where the $f(x)$ is called the tolerance distribution. The choice of a normal distribution as the tolerance distribution leads to a probit model, a logistic distribution corresponds to a logistic model, and an extreme value distribution leads to a complementary log-log model (See Finney (1971), Cox and Snell (1989) and Chambers and Cox (1967)).

Key words: Dose-response curves; ED₅₀; Generalized linear models; Generalized additive models; Nonparametric regression.

It is now possible to discuss those models in a unified way under generalized linear models. Suppose that n_i subjects are exposed to a dose d_i of stimuli and out of n_i subjects, y_i responses occur. Letting p_i be the response probability at dose d_i , generalized linear models specify the link function,

$$g(p_i) = \beta_0 + \beta_1 d_i. \quad (1)$$

When the link function is logit, we have a logistic model;

$$g(p_i) = \text{logit}(p_i) = \log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 d_i. \quad (2)$$

When the link function is the inverse cumulative standard normal distribution, we have a probit model;

$$g(p_i) = \Phi^{-1}(p_i) = \beta_0 + \beta_1 d_i. \quad (3)$$

For a complementary log-log model, the link function is

$$g(p_i) = \log[-\log(1-p_i)] = \beta_0 + \beta_1 d_i. \quad (4)$$

Generalized linear models have been extensively used for modeling response probabilities (see McCullagh and Nelder (1986)) and the computer program have been implemented in general package softwares such as GLIM (Baker and Nelder (1978)), S (Becker, Chambers and Wilks (1988)) and SAS so that they are readily available.

Recently, generalized additive models (GAM, for short) have been introduced as an extension of the generalized linear models (Hastie and Tibshirani (1986, 1990)). Generalized additive models replace the linear components in the link function by additive components,

$$g(p_i) = \gamma + s(d_i), \quad (5)$$

where s is an arbitrary function. This is essentially a nonparametric regression. The $s(\cdot)$ is an unspecified function that is estimated nonparametrically using a scatterplot smoother in an iterative fashion called the local scoring algorithm. The S language now includes some functions for fitting generalized additive models (Chambers and Hastie (1992)).

In this paper, we estimate the dose-response curve by those models, then from the estimated dose-response curve, we obtain the estimate of the median effective dose (ED_{50}) or more generally, $100\alpha\%$ effective dose (ED_α) with $0 \leq \alpha \leq 1$. (Kelly and Rice (1990) discuss the application of monotone smoothing to dose-response curves.) A calibration problem (or inverse prediction) in general has been discussed and the results have been known for an ordinal regression model and a generalized linear model but few studies have been done for a calibration problem in a generalized additive model. We present a simple way to find ED_α and compare the results with those from a generalized linear model numerically. In the next section, the estimation methods are discussed and those methods are illustrated by an experimental data in Section 3. Also two simulation results are shown to give some insights into the behavior of the estimates, followed by a brief discussion in Section 4.

2. Estimation

It is well known that the maximum likelihood estimation for the parameter $\beta = (\beta_0, \beta_1)$ in an (exponential family) generalized linear model is equivalent to using an iterative reweighted least squares procedures (Green (1984), McCullagh and Nelder (1989)) in which adjusted dependent variable

$$z_i = \eta_i^{(k)} + y_i - n_i p_i^{(k)} \frac{g'(p_i^{(k)})}{n_i}$$

are regressed on d_i with weights

$$w_i^{(k)} = \frac{n_i}{p_i^{(k)}(1 - p_i^{(k)})[g'(p_i^{(k)})]^2}$$

at the k -th iteration, where $g(p_i) = \eta_i$ and the superscript (k) indicates the values obtained at the k -th iteration. The deviance

$$D(\mathbf{y}, \hat{\mathbf{p}}) = 2 \sum [y_i \log \left(\frac{y_i}{n_i \hat{p}_i} \right) + (n_i - y_i) \log \left(\frac{n_i - y_i}{n_i - n_i \hat{p}_i} \right)] \quad (6)$$

may be used to see the goodness of fit of the model.

On the other hand, a generalized additive model can be fitted using the local scoring procedure that is accomplished by replacing the weighted linear regression part in the iterative reweighted least squares by some local scatterplot smoothing procedure such as running-line smoother, smoothing splines, locally weighted smoother (Cleveland (1979)), kernel smoother and so on. We will not give the detailed discussion of smoothing here since it is given elsewhere (Hastie and Tibshirani (1990), Whaba (1990), de Boor (1978), Silverman (1985), Eubank (1988), Ramsay (1988), for example). Convergence and consistency of the algorithm have been shown by Brieman and Friedman (1985) under mild regularity conditions. Stone (1986) has proved that a unique best additive approximation exists for any exponential family models and he has also discussed the rate of convergence of the procedure.

Once a dose-response curve has been estimated, we can obtain the estimate of ED_{α} by inverting the curve in theory at least. Specifically, for a generalized linear model with the link function $g(p)$, the estimate of $ED_{\alpha}=d_{\alpha}$ is given by

$$\hat{d}_{\alpha} = \frac{g(\alpha) - \hat{\beta}_0}{\hat{\beta}_1}. \quad (7)$$

Its standard error may be obtained approximately by the delta method as follows,

$$se(\hat{d}_{\alpha}) = [\text{Var}(\hat{\beta}_0) + \hat{d}_{\alpha}^2 \text{Var}(\hat{\beta}_1) + 2\hat{d}_{\alpha} \text{Cov}(\hat{\beta}_0, \hat{\beta}_1)]^{1/2} / \hat{\beta}_1^2 \quad (8)$$

And for a generalized additive model with a smoother $s(d)$, we have the estimate of $ED_{\alpha}=d_{\alpha}$,

$$\hat{d}_{\alpha} = \hat{s}^{-1}(g(\alpha) - \hat{\gamma}), \quad (9)$$

where $\hat{s}^{-1}(t) = \inf\{x : \hat{s}(x) \geq t\}$. Since $\hat{s}$ is made up of nonparametric smoothing terms, it is not easy to find $\hat{s}^{-1}$, we use the fitted value $\hat{p}_i$ corresponding to d_i . Then we simply connect those fitted values by some known functions such as piecewise linear function. From the curve connecting those fitted values, we can find the $\hat{d}_{\alpha}$. Also, it is not possible to obtain the standard error for this estimator in a closed form so that we may resort to a bootstrap estimate of the standard error (Efron (1982, 1986)).

An approximate $100(1-\beta)\%$ confidence interval, $C_{glm}(1-\beta)$ for ED_α for a generalized linear model approach can be found using Fieller's method (Fieller (1954)) as follows,

$$C_{glm}(1-\beta) = \{x : [\hat{\beta}_0 + \hat{\beta}_1 x - g(\alpha)]^2 \leq z_{\beta/2}^2 v(x)\}, \quad (10)$$

where $v(x) = \text{Var}(\hat{\beta}_0) + x^2 \text{Var}(\hat{\beta}_1) + 2x \text{Cov}(\hat{\beta}_0, \hat{\beta}_1)$ and $z_{\beta/2}$ is an upper $\beta/2$ quantile of the standard normal distribution.

A bootstrap confidence interval can be based on a Monte Carlo resampling of B independent replications with the bootstrap distribution G^* of the estimates. An approximate $100(1-\beta)\%$ bootstrap confidence interval, $C_{boot}(1-\beta)$ for ED_α is given by

$$C_{boot}(1-\beta) = [G^{*-1}(\beta/2), G^{*-1}(1-\beta/2)]. \quad (11)$$

3. Numerical Results

To illustrate the procedures described in Section 2, we discuss an example from an experiment and two simulation results here.

Example 1;

In an experiment discussed in Bliss(1935), the response of the confused flour beetle to gaseous carbon disulphide (CS₂) was evaluated. After the five hours' exposure at eight levels of doses (measured in *mg/l*), the number killed, y_i , was recorded in a batch of n_i insects. The data are shown in Table 1. The plot of the proportions, $\hat{p}_i = y_i / n_i$, against the (log) dose is given in Figure 1. The curves fitted by a logistic model, a probit model, a complementary log-log model and a generalized additive model with a logit link function(GAM for short) using a smoothing spline are shown in Figure 2 along with the observed proportions. The GAM curve here is simply a result of connecting the fitted values by piecewise linear function. The logistic curve (the broken line) and the probit curve (the dot-dashed line) are almost identical and the complementary log-log curve (the dashed line) and the GAM curves (the solid line) are a bit

different from the logistic and probit curves. The estimated ED_{50} and ED_{90} as well as the estimated coefficients and the deviances are summarized in Table 2. The bootstrap estimates of the standard errors are obtained from a Monte Carlo resampling of $B=500$ replications. For comparison, the approximate standard error of ED_{50} and ED_{90} for the logistic model are computed both by a delta method and a bootstrap method. The value 0.00386 and 0.00619 of the standard error computed by the delta method is not too different from the value 0.00401 and 0.00593, respectively, of the bootstrap method. Table 3 gives 95% confidence intervals for the ED_{50} and the ED_{90} . Again, the confidence intervals obtained by Fieller's method and by a bootstrap method are shown for the logistic model. Fieller's method gives (1.764, 1.780) for the ED_{50} and (1.825, 1.850) for the ED_{90} that is fairly close to (1.764, 1.779) and (1.825, 1.847), respectively, obtained from the bootstrap distribution. We note that the different link functions in GAM make little differences.

Table 1. BEETLE MORTALITY DATA

Dose d_i ($\log_{10}CS_2$)	# of beetles n_i	# killed, y_i
1.6907	59	6
1.7242	60	13
1.7552	62	18
1.7842	56	28
1.8113	63	52
1.8369	59	53
1.8610	62	61
1.8839	60	60

Table 2. Estimates

model	logistic model	probit model	complementary log-log model	GAM(spline)
β_0	-60.717	-34.935	-39.572	*
s.e. (β_0)	5.180	2.647	3.239	*
β_1	34.2703	19.728	22.041	*
s.e. (β_1)	2.912	1.487	1.799	*
Deviance	11.232	10.120	3.446	1.675
d.f.	6	6	6	3
ED50	1.772	1.771	1.779	1.782
s.e.(ED50)	0.00386 (0.00401)*	0.00381	0.00401	0.00507*
ED90	1.836	1.836	1.833	1.832
s.e.(ED90)	0.00619 (0.00593)*	0.01272	0.00449	0.00605*

(* indicates the bootstrap estimates of standard error)

Table 3 95% Confidence Intervals

model	ED50	ED90
logistic model	(1.764, 1.780)	(1.825, 1.850)
	(1.764, 1.779)*	(1.825, 1.847)*
probit model	(1.763, 1.778)	(1.826, 1.849)
complementary log-log model	(1.770, 1.786)	(1.825, 1.843]
GAM(spline)	(1.771, 1.790)*	(1.821, 1.844)*

(* indicates the bootstrap confidence intervals)

Simulation study 1;

We suppose that the true dose-response curve is given by the following logistic curve,

$$\log\left(\frac{p_i}{1-p_i}\right) = -5.0 + 2.0d_i. \quad (12)$$

Hence the true ED₅₀ is 2.5. We further assume the levels of dose at which the observations are taken are 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, and the number of the subjects at each dosage level, n_i , is 50.

They are summarized in Table 4 and The dashed line in Figure 3 is the true curve. We apply the models discussed so far to each of 500 replicates of a set of simulated observations.

Table 4.

dose(d_i)	0.5	1.0	2.0	3.0	4.0	5.0
n_i	50	50	50	50	50	50
probability	0.018	0.047	0.269	0.731	0.953	0.993

The summary statistics of the estimated ED_{50} for each model are shown in Table 5 and the box-plot for each model is given in Figure 4. The logistic and the probit model result in a very close value of 2.503 to the true ED_{50} whereas the complementary log-log model gives a biased estimate of 2.697. On the other hand, the GAM(with a logit link) estimate is 2.506 that is not far from the true value of 2.5. The box-plots also point out the resemblance of the logistic, the probit and the generalized additive model. Figure 5–8 are the normal probability plots of the 500 estimates of ED_{50} for the logistic, the probit, the complementary log-log, and the generalized additive model. Except for a few points at both ends, they look reasonably linear.

Table 5. Results of 500 replicates for Simulation 1.

model	logistic model	probit model	complementary log-log model	GAM(spline)
mean	2.503	2.503	2.697	2.506
min	2.246	2.226	2.432	2.189
1st Q	2.435	2.438	2.633	2.441
median	2.504	2.501	2.692	2.502
3rd Q	2.567	2.568	2.764	2.570
max	2.876	2.885	3.105	2.907
s.d.	0.1003	0.1003	0.103	0.103

Simulation study 2;

Here, we perturb the dose-response curve of the (12) as follows,

$$\log\left(\frac{p_i}{1-p_i}\right) = -5.0 + 2.0d_i + \varepsilon_i \quad \varepsilon_i \sim N(0,1.1) \quad (13)$$

We simulated the model 500 times. The result in fitting the logistic and the generalized additive model(with a logit link) to 500 replicates are shown in Table 6. The estimate from the logistic model seems to be less influenced by the perturbation and its standard deviation is smaller than that of GAM estimates which may reflect the overdispersed nature of the model (13)..

Table 6. Results of 500 replicates

model	logistic model	GAM(spline)
mean	2.495	2.541
min	1.651	1.346
1st Q	2.288	2.286
median	2.499	2.527
3rd Q	2.715	2.821
max	3.348	3.785
s.d.	0.3015	0.4640

4. Discussion

Since the true dose-response relationship will never be known, any parametric form is a part of assumptions. A nonparametric regression approach of a generalized additive model can be used as an alternative to a parametric approach. The numerical experiments discussed in Section 3 shows that the estimates obtained from a generalized additive model are fairly reasonable. On the other hand, a penalty from misspecification of a parametric model may be severe as seen in the case of the complementary log-log model in Simulation study 1. Although

the computation is heavy for a generalized additive models, the advance of the computing facilities may ease the burden.

Although the normal probability plots suggest the approximate normality of the estimators, statistical as well as numerical properties are not yet known very much for a generalized additive model approach, much researches needs to be done and the rigorous theory of asymptotic is yet to be developed.

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beetle mortality data

Figure 1

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Figure 2

Figure 3

SIMULATION 1

Figure 4 ED50

SIMULATION 1

Figure 5
SIMULATION 1

Figure 6

SIMULATION 1

Figure 7

SIMULATION 1

Figure 8

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