COMPARISON OF BINARY REGRESSION MODELS
FOR THE OUTCOME OF PEDIATRIC
LIVER TRANSPLANTATION

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Abstract: In this paper we consider four models for binary regression analysis and their application to the prediction of lethal outcome in pediatric liver transplantation. We also compare the performance of the MATLAB® codes `fitnlm` and `lsqcurvefit` [4] used for this purpose.

AMS Subject Classification: 62J20, 62G25, 97M60
Key Words: binary regression analysis; prediction; transplantation; MATLAB

1. Introduction

In the recent two years, various mathematical models have been employed in the studies on the spread of Covid-19, just to mention a few works as for example, [1], [3], [7], [10]. Among these, a number of sigmoid models have been considered in [2] for modeling of the consecutive waves of the Covid-19 pandemic.

Some of these models are appropriate for the modeling of the outcome in the early postoperative period of pediatric liver transplantation. In particular the fractional power model seems suitable for this purpose. The numerical

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determination of the parameters of the models leads to a highly nonlinear computational problem. The solution of this problem depends on the algorithm implemented as well as on the initial guess. For illustration of these phenomena we compare the performance of two MATLAB® codes [4] on particular sets of data.

2. Binary regression

2.1. Statement of the problem

Let the data $\mathbf{X} = [x_1, x_2, \ldots, x_N]$, $\mathbf{Y} = [y_1, y_2, \ldots, y_N]$ be given. Usually the elements of the vector $\mathbf{X}$ are ordered so as

$$x_1 \le x_2 \le \cdots \le x_N, \ \ y_k \in \{0, 1\}.$$

The inequalities $x_k \le x_{k+1}$ (instead of the usual $x_k < x_{k+1}$) reflect the fact that there may be repeated arguments. The variable y is binary and takes values $y_k = 0$ (absence of the corresponding property), or $y_k = 1$ (presence of the corresponding property).

The binary nonlinear regression model is a function

$$y = R(\mathbf{c}, x), \ x \in [x_1, x_N], \tag{1}$$

where $\mathbf{c} = [c_1, c_2, \ldots, c_n]$ $(n < N)$ is n-vector parameter which has to be determined using the data $(\mathbf{X}, \mathbf{Y})$. In the simplest case this is done by minimizing the quadratic cost

$$Q(\mathbf{c}) = \|R(\mathbf{c}, \mathbf{X}) - \mathbf{Y}\|^2 = \sum_{k=1}^{N} \left(R(\mathbf{c}, x_k) - y_k \right)^2, \tag{2}$$

where $R(\mathbf{c}, \mathbf{X}) = [R(\mathbf{c}, x_1), R(\mathbf{c}, x_2), \ldots, R(\mathbf{c}, x_N)]$. Denote by

$$\text{RMSE} = \sqrt{\frac{Q(\mathbf{c})}{N}}$$

the root mean square error (RMSE).

2.2. Logistic model

The widely used *standard logistic model* $R = L$ is

$$L(a, b, x) = \frac{1}{1 + \exp(ax + b)}, \tag{3}$$

where $\mathbf{c} = [a, b]$ is the parameter vector.

Note that the application of the *generalized logistic model*

$$L_g(a, b, n, x) = \frac{1}{(1 + \exp(ax + b))^n}$$

for binary regression meets serious problems. Since

$$L_g(a, b, 1, x) = L(a, b, x),$$

the standard model is a particular case of the generalized problem. Hence one should expect that the value of the quadratic cost $Q(\mathbf{c})$ for the generalized model L_g should be less than or equal to the corresponding value for the standard model L.

However, the function $\mathbf{c} \mapsto Q(\mathbf{c})$ has rather complicated behavior and the numerical procedure may find local minimums for the generalized model with larger values of RMSE compared to the values of RMSE for the standard model.

2.3. Fractional power model

The *generalized fractional power model*, or the *generalized Hill model*, has the form

$$F_g(a, b, n, x) = \frac{x^{an}}{(x^a + b)^n},$$

where $\mathbf{c}_g = [a, b, n]$ is the vector parameter. When $n = 1$ we have the *standard fractional power model*

$$F(a, b, x) = \frac{x^a}{x^a + b} \tag{4}$$

with vector parameter $\mathbf{c} = [a, b]$.

2.4. Inverse tangent model

The *inverse tangent model* had been considered in [8] for the binary regression analysis of early postoperative period in liver children transplantation. The *generalized form* of this model is

$$T_g(a, b, n, x) = \left(\frac{1}{\pi} \mathrm{atan}(ax + b) + \frac{1}{2} \right)^n,$$

where $\mathbf{c}_g = [a, b, n]$ is the vector parameter. When $n = 1$ we have the *standard inverse tangent model*

$$T(a, b, x) = \frac{1}{\pi} \mathrm{atan}(ax + b) + \frac{1}{2} \tag{5}$$

with vector parameter $\mathbf{c} = [a, b]$.

2.5. Gompertz model

The *Gompertz model*

$$G(a, b, x) = \exp(-\exp(ax + b))$$

is the limit case of the generalized logistic model written in a special form. The vector parameter for the Gompertz model is $\mathbf{c} = [a, b]$.

Note that the generalized form $G(a, b, x)^n$ $(n > 0)$ of the Gompertz model is again a Gompertz model since

$$G(a, b, x)^n = G(a, \beta, x), \;\; \beta = b + \log(n).$$

The connection between the generalized models R_{g} and standard models R is

$$R_{\mathrm{g}}(a, b, n, x) = R(a, b, x)^n,$$
$$R(a, b, x) = R_{\mathrm{g}}(a, b, 1, x).$$

3. MATLAB® codes for binary regression

The parameters of the models are computed by the MATLAB® command `fitnlm` in the form

```
>> c = fitnlm(X,Y,R,c0)
```

Here `R = @(c,x)` is the description of the model (1) and $\mathbf{c}_0$ is the initial guess for the value of the vector parameter $\mathbf{c}$. For example, in case (3) we have

```
>> R = @(c,x) 1./(1 + exp(c(1)*x + c(2)))
```

Another MATLAB® function

```
>> c = lsqcurvefit(R,c0,X,Y)
```

can also be used to compute the vector parameter $\mathbf{c}$.

The accuracy of the models is estimated by the value RMSE of the quadratic mean square error as well as by the p–value.

Let for example $n = 12$ and let the data be given at Table 1 below.

X	0.1	0.3	0.7	1.1	1.6	1.9	2.3	4.2	5.0	8.4	10.0	13.1
Y	0	0	0	1	0	1	1	1	1	1	0	1

Table 1: Data

Model	c(1)	c(2)	RMSE	p–value
F	2.24	1.36	0.433	0.00138
G	−1.53	1.50	0.435	0.00145
L	−2.09	2.77	0.438	0.00154
T	8.86	−8.07	0.442	0.00169

Table 2: Comparison of models

The coefficients of the models, the values of RMSE and the p–values are presented at Table 2. The results are given with up to three significant decimal digits which corresponds to the accuracy of the data.

The order of models according to both the criterion RMSE and the p–value is 1) F, 2) G, 3) L and 4) T. We see that the model F is superior to the other three models.

With the fractional model we have

$$y = \frac{x^{2.24}}{x^{2.24} + 1.36}.$$

4. Prediction of mortality

In this section we compare the performance of the four models described in Sections 2.2–2.5 to the prediction of mortality in early postoperative periods after pediatric liver transplantation (LT). The use of the logistic model for this purpose has been considered in [9, 8, 6].

The Model for Early Allograft Function (MEAF) is the first statistically confirmed score for diagnosis of Early Allograft Dysfunction (EAD). It is a scale from 0 to 10 which is advantageous as it makes it possible to grade the severity of the dysfunction [5]. Scoring is based on graft survival at different intervals and is made by a calculation containing ALAT (alanine aminotransferase), INR (International Normalized Ratio) and total bilirubin in the blood at the 3rd postoperative day.

Multiple researches in transplant centers over the world proved that MEAF has an advantage over other definitions of EAD and use it over the other ones. The mean scores in patients are reported as 5.02, with more severe EAD at scores above 6. The first data set $(\mathbf{X}_1, \mathbf{Y})$ considered below contains the MEAF results for 26 children with LT in "Lozenets" Hospital.

The Model for End-Stage Liver Disease score in the post transplant period (pMELD) was used as a predictor of mortality in the early postoperative period. pMELD can help in assessing the need for re-transplantation. Uzunova et al. [6] published results of a retrospective study of liver transplant children using pMELD as a predictor of lethal outcome after liver transplantation. An univariate analysis was used and the constructed binary models using pMELD on postoperative day 5 (data $(\mathbf{X}_2, \mathbf{Y})$) predicted disadvantageous outcome after LT with good statistical significance ($p < 0.05$).

The data $\mathbf{X}_1, \mathbf{X}_2, \mathbf{Y}$ are presented at Tables 3–5.

$\mathbf{X}_1$	3.23	8.26	7.44	9.33	7.74	6.99	6.93	6.20	7.17
$\mathbf{X}_2$	7	12	18	20	24	20	14	13	16
$\mathbf{Y}$	1	1	0	0	1	1	1	1	1

Table 3: Data for MEAF and pMELD

The coefficients of the models as well as the RMSE and p-values are given at Table 6.

As in the previous case the fractional power model F is superior to the other three models relative to both the RMSE and the p–value. The other three models show approximately equal behavior. The computed parameters of the models are given at Table 6. The comparison of the performance of the models is summarized at Table 7.

With the data set $\mathbf{X}_1$ the fractional power model is

$$y = \frac{x^{0.422}}{x^{0.422} + 1.14},$$

$\mathbf{X}_1$	5.68	6.97	8.50	4.92	5.47	6.83	8.01	2.79	5.56
$\mathbf{X}_2$	21	32	23	18	12	20	31	16	25
$\mathbf{Y}$	0	0	1	1	1	1	0	0	1

Table 4: Data for MEAF and pMELD (cont.)

$\mathbf{X}_1$	5.96	5.35	7.20	5.10	9.65	3.66	7.51	7.22
$\mathbf{X}_2$	22	19	19	16	31	22	22	23
$\mathbf{Y}$	1	0	0	0	1	1	1	1

Table 5: Data for MEAF and pMELD (cont.)

Data	Mod.	c(1)	c(2)	RMSE	p–value
$\mathbf{X}_1$	L	-5.43×10^{-2}	-2.83×10^{-1}	0.495	2.9×10^{-6}
$\mathbf{X}_2$	L	6.00×10^{-2}	-1.84	0.487	2.0×10^{-6}
$\mathbf{X}_1$	F	4.22×10^{-1}	1.14	0.494	2.8×10^{-6}
$\mathbf{X}_2$	F	-1.19	1.57×10^{-2}	0.486	1.9×10^{-6}
$\mathbf{X}_1$	T	5.33×10^{-2}	1.81×10^{-1}	0.495	2.9×10^{-6}
$\mathbf{X}_2$	T	-5.15×10^{-2}	1.59	0.488	2.0×10^{-6}
$\mathbf{X}_1$	G	-4.57×10^{-2}	-5.60×10^{-1}	0.495	2.9×10^{-6}
$\mathbf{X}_2$	G	4.94×10^{-2}	-1.86	0.487	2.0×10^{-6}

Table 6: Performance of models

Data	RMSE	p–value
$\mathbf{X}_1$	$F, L = T = G$	$F, L = T = G$
$\mathbf{X}_2$	$F, L = G, T$	$F, L = T = G$

Table 7: Comparison of models

while for the data $\mathbf{X}_2$ the fractional power model is

$$y = \frac{x^{-1.19}}{x^{-1.19} + 0.00157} = \frac{1}{1 + 0.00157\, x^{1.19}}.$$

5. Conclusions

1. The results obtained by the MATLAB$^{\circledR}$ codes `fitnlm` and `lsqcurvefit` coincide up to three significant decimal digits. Both codes are sensitive relative to the initial guess $\mathbf{c}_0$ for the vector parameter $\mathbf{c}$. The codes may stop at a local minimum which is different from the optimum value of $\mathbf{c}$.

2. The logistic model and the inverse tangent model are symmetric in the sense that they are odd functions relative to the point with coordinates $x = -b/a$, $y = 0.5$, while the fractional power model and the Gompertz model are non-symmetric.

3. Hence, in view of 2, for non-symmetric data (which is usually the case in the analysis of mortality in the early post-operative period) the performance of the fractional power model and the Gompertz model are superior to the logistic model and the inverse tangent model.

4. The p–value in all cases considered in this paper is of order 10^{-6} and the root mean square error is less than 0.5. The latter is typical for binary regression models.

5. It is useful to draw the graphs of the functions $x \mapsto R(\mathbf{c}, x)$, $x \in [x_1, x_N]$, in order to detect possible local minimums for $\mathbf{c}$ different from the optimal one.

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