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Estimation of Safe Doses: Critical Review of the Hockey Stick Regression Method

by Takemi Yanagimoto* and Eiji Yamamoto†

The hockey stick regression method is a convenient method to estimate safe doses, which is a kind of regression method using segmented lines. The method seems intuitively to be useful, but needs the assumption of the existence of the positive threshold value. The validity of the assumption is considered to be difficult to be shown.

The alternative methods which are not based on the assumption, are given under suitable dose-response curves by introducing a risk level. Here the method using the probit model is compared with the hockey stick regression method. Computational results suggest that the alternative method is preferable. Furthermore similar problems in the case that response is measured as a continuous value are also extended.

Data exemplified are concerned with relations of SO_2 to simple chronic bronchitis, relations of photochemical oxidants to eye discomfort and residual antibiotics in the lever of the chicks. These data was analyzed by the original authors under the assumption of the existence of the positive threshold values.

Introduction

Many techniques and methods for estimation of safe doses have been proposed and discussed as a current topic of biostatistics. Estimation of safe doses concerning various chemical compounds is important, even though it is very difficult.

The hockey stick (HS) regression method is an interesting which was proposed by Hasselblat and others (*1*) to obtain maximum no-adverse-health-effect concentration of photochemical oxidants. The HS regression method is a kind of regression method using segmented curves (*2, 3*), and has attracted many researchers' attention.

In this paper we study properties of the HS regression method, especially validity of it. For this purpose, the HS model was compared with other regression models like the probit model and the log-log linear model. For the latter model, a risk level is used to define a safe dose. A risk level was used previously (4) and has been supported by subsequent researchers.

A safe dose does not mean here a dose which causes no harmful effects, and therefore can not be used directly as a standard by the administration. It should be considered as a criterion for evaluation of safety.

The HS regression model and its method is reviewed. Data on which the current standard of SO_2 is partly based are analyzed and discussed. A reanalysis of relationships between photochemical oxidant and eye discomfort is given. In these two examples the HS model and the probit model are compared. Some conclusions and suggestions are obtained, and two related topics are discussed.

Hockey Stick Regression Method

The HS regression function is defined as a dose-response curve as follows. For some x_0

$$\begin{aligned} f(x) &= \beta_0 && \text{for } x \le x_0 \\ &= \beta_1 + \beta_2 x && \text{for } x > x_0 \end{aligned} \qquad (1)$$

This means that for a suitable dose x_0, $f(x)$ remains constant for any x less than x_0 and increases linearly as x increases for any x more than x_0. The dose x_0 is considered as a physiological threshold value. β_0 represents a spontaneous or baseline response which is caused by background stimuli. The main purpose is to get a suitable estimator of x_0. When x_0 means

*Institute of Statistical Mathematics, 4-6-7 Minami-Azabu, Minato-ku, Tokyo 106, Japan.
†Okayama University of Science, 1-1 Ridaicho, Okayama-Si, Okayama 700, Japan.

really a safe dose, a lower confidence limit is preferable.

An assumption of existence of a threshold value is necessary to consider x_0 as a safe dose, on which the HS regression model is based. This assumption seems to be serious, since we have no proof of existence of threshold values of substances surrounding us such as food additives and environmental pollutants which many human beings are exposed to. Generally the HS method is only a operational one to obtain a value as the safe dose.

The method was studied previously (*1*) and used for getting relationships between daily maximum hourly oxidant levels and daily symptom rate reported by student nurses in Los Angeles (*5*), which will be discussed in detail below. The method is accepted by Japanese research workers, such as epidemiologists, who are interested in relationships between concentration of air pollutants and prevalence ratios from epidemiological surveys. These relationships are needed to obtain criteria on which air quality standards are based.

Let $(x_1, y_1), \ldots, (x_n, y_n)$ denote data where the x represent doses and the y are measures of responses. Responses are mainly measured by continuous real values or dichotomous values.

Firstly, suppose that response is continuous. The HS model is defined by

$$y_i = f(x_i) + \epsilon_i \qquad i = 1, 2, \ldots, n \qquad (2)$$

where $f(x)$ is defined in Eq. (1). ϵ_i $(i = 1, 2, \ldots, n)$ are mutually independent and are distributed according to $N(0, \sigma_i^2)$, respectively. σ_i possibly depend on n_i, respectively. Estimators $\hat{\beta}_0$, $\hat{\beta}_1$, and $\hat{\beta}_2$ of the parameters β_0, β_1, and β_2, respectively, are obtained by the maximum likelihood method. Sometimes a flat line β_0 and a linear line $\beta_1 + \beta_2 x$ are estimated by separated data. Data to estimate β_0 are considered as those of non-polluted areas. This case will be seen in the next section. Estimators are given by the least-square method separately. Generally, both lines are estimated simultaneously using the constrained least-square method.

Next, suppose response is dichotomous. The HS model is defined by

$$y_i \sim B_i\,[f(x_i)], \qquad i = 1, 2, \ldots, n \qquad (3)$$

where $B_i(p)$ denotes binomial distribution with its incidence probability p. Parameters are estimated by the maximum likelihood method.

An estimator $\hat{x}_0$ of an intersection x_0 is obtained by the estimators $\hat{\beta}_0$, $\hat{\beta}_1$, and $\hat{\beta}_2$. When x_0 is considered as a safe dose, $\hat{x}_0$ should be a lower limit of a confidence interval, in order to make a estimator conservative. A confidence interval is usually able to be calculated approximately.

Application to Chronic Bronchitis and SO_2

One of the most important criteria, which the current air quality standard of sulfur dioxide (SO_2) in Japan is based on, comes from epidemiological surveys. The surveys were conducted in Cities of Osaka, Akoh, and Yokkaichi (*6*). A prevalence ratio of positive simple chronic bronchitis for each area was obtained. Questionnaires were made according to them on respiratory symptoms given by British Medical Research Council (*7*). Thus chronic bronchitis is defined as persistent cough and phlegm.

The prevalence ratios were compared with average concentrations of SO_2 during the three years. These data are listed in Table 1. We cannot obtain exact sample size in each area and regard it as 2000 when necessary.

The original analysis (6) is as follows. The areas where the surveys were conducted are divided into the former eight areas which are considered as non-polluted areas and the latter nine polluted ones. Let y_i denote prevalance ratios, and x_i average concentrations of SO_2. The following HS model is assumed:

$$y_i = f(x_i) + \epsilon_i \qquad i = 1, \ldots, 17 \qquad (4)$$
$$\epsilon_i \sim N(0, \sigma^2)$$

Table 1. Average concentrations of SO_2 and prevalence ratios of chronic bronchitis.[a]

SO_2, mg/day/100 cm²	Prevalence ratio
0.21	0.035
0.28	0.033
0.27	0.031
0.15	0.030
0.15	0.029
0.14	0.027
0.13	0.027
0.14	0.025
3.4	0.078
2.75	0.059
2.75	0.052
2.1	0.048
1.6	0.038
1.55	0.037
1.15	0.032
1.0	0.027
0.9	0.024

[a]Data of Mantel and Bryan (*4*).

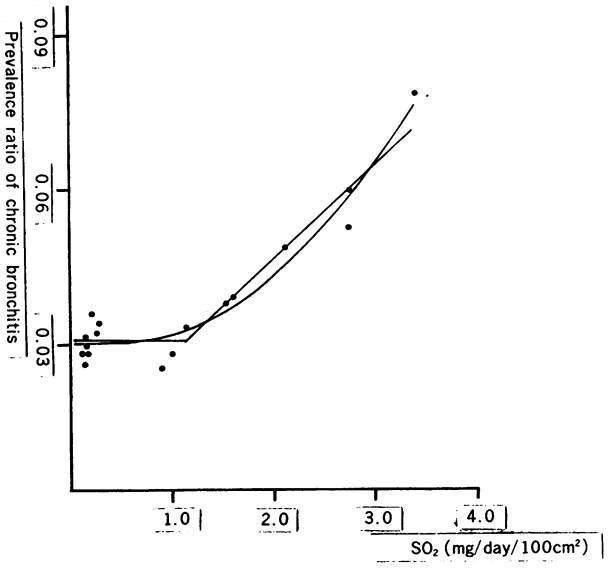

FIGURE 1. Data of SO_2 and chronic bronchitis, and fitted regression lines.

β_0 is estimated by data from the nonpolluted areas, while β_1 and β_2 by data from the polluted areas. Using the estimators $\hat{\beta}_0$, $\hat{\beta}_1$, and $\hat{\beta}_2$, the estimator $\hat{x}_0$ of x_0 is defined by

$$\hat{\beta}_0 = \hat{\beta}_1 + \hat{\beta}_2\hat{x}_0 \tag{5}$$

The fitted regression line is given by

$$\hat{\beta}_0 = 0.02963$$
$$\hat{\beta}_1 + \hat{\beta}_2 x = 0.00765 + 0.01898x \tag{6}$$

which is described in Figure 1. From this $\hat{x}_0$ is estimated at 1.160.

However, in order to consider $\hat{x}_0$ as a safety concentration, lower confidence limits of x_0 are preferable to the above estimator. For various assurance levels lower confidence limits are given in Table 2.

Though the above analysis is clear and simple, some conditions must be fulfilled. It is very difficult to consider the parameter x_0 as a safety concentration, even if the HS regression model is close to a "true" model, because a "true" regression line, if it exists, must be smoothly increasing.

Table 2. Lower confidence limits under the HS model with various kinds of assurance levels for data of Table 1.

Level α	Confidence limits
0.5	1.160
0.05	0.953
0.01	0.834
0.005	0.786

Probit Analysis

To avoid the difficulty mentioned above, we may use a model with a smoothly and increasing regression curve. The most popular model to interpret a dose-response relationship is the probit model. That is, a random variable Y which represents response of an individual under dose x, has its distribution

$$Y(x) \sim B_i[\beta_0 + (1 - \beta_0)\,\Phi\,(\beta_1 + \beta_2 \log x)] \tag{7}$$

where $\Phi\,(x)$ is the distribution function of the standard normal distribution. β_0 means a spontaneous prevalence ratio. β_0 is assumed to be positive, since chronic bronchitis is nonspecific. In fact, β_0 is considered about 0.03 in Japan, as Table 1 shows.

Since the probit model implies nonexistence of a positive threshold value, we need another definition of safety concentration instead of a threshold value. The value x_0 is defined by introducing a risk level ρ

$$\beta_0 + (1 - \beta_0)\,\Phi\,(\beta_1 + \beta_2 \log x_0) = \beta_0 + (1 - \beta_0)\,\rho \tag{8}$$

that is,

$$\log x_0 = [\Phi^{-1}\,(\rho) - \beta_1]/\beta_2 \tag{9}$$

This definition is in line with Mantel and Bryan (*4*) and others, who presented methods for estimating safe doses against carcinogenicity from experimental data. They have been studied by many researchers, especially for these five years. The most difficult problem is that of extrapolation, but fortunately, this problem does not occur here.

An estimator $\hat{x}_0$ of the safe dose x_0 is defined by a lower confidence limit with an assurance level $1 - \alpha$, that is, a lower confidence limit of LDρ with an assurance level $1 - \alpha$, which can be obtained by a well-known technique in the probit analysis.

Under the probit model, the fitted curve is given by

$$0.0289 + \Phi\,(-2.917 + 2.377 \log x), \tag{10}$$

which is described in Figure 1. The chi-square value of test for homogeneity is 4.761 with 14 degrees of freedom.

The proposed value $\hat{x}_0$ for different kinds of assurance levels are given in Table 3. Here we choose 0.01, 0.005, 0.001, 0.0005, and 0.0001 as risk levels. A very small value like 10^{-8} was adopted as a risk level by Mantel and Bryan (*4*) to estimate the safe dose against carcinogenicity. But we do not choose such a small risk level, since chronic bronchitis is not a serious disease, but may be only a symptom. On the other hand, cancer is a fatal one.

Tables 2 and 3 show that $\hat{x}_0$ obtained by the HS

Table 3. Lower confidence limits under the probit model with various kinds of risk and assurance levels for data of Table 1.

	Risk level ρ				
α	0.01	0.005	0.001	0.0005	0.0001
0.5	1.780	1.398	0.849	0.700	0.462
0.05	1.461	1.055	0.537	0.412	0.234
0.01	1.286	0.877	0.396	0.290	0.149
0.005	1.213	0.806	0.344	0.247	0.121

regression method is consequently according to $\hat{x}_0$ with a risk level about 0.005 or less.

Application to Los Angeles Nurse Study

Similar discussions can be made about data from the Los Angeles Nurse Study (5). The summary data are cited in Table 4. The authors used the HS regression method. The parameters β_0, β_1, and β_2 were estimated by the least-square method under the restriction that both lines are connected, that is, the three parameters are estimated simultaneously. Approximate confidence limits were also obtained.

The probit model with a positive spontaneous ratio is also applicable to these data. Here we discuss mainly analysis of eye discomfort, and add that of chest discomfort. Eye discomfort is a typical symptom caused by photochemical oxidants. Daily maximum hourly oxidant levels given as intervals in Table 3 are read as midpoints of intervals.

We compare the two models mentioned above. Suppose $Y(x)$ is a random variable which takes the value 1 if a student complains of the symptom under a daily maximum hourly oxidant level x, and has a value 0 if not. The HS regression model means here

$$Y(x) \sim B_i\,[f(x)] \tag{11}$$

where $f(x)$ is defined in Eq. (1). Another definition with normally distributed random error is discussed later. the probit model means

$$Y(x) \sim B_i[\beta_0 + (1 - \beta_0)\,\Phi\,(\beta_1 + \beta_2 \log x)] \tag{12}$$

The maximum likelihood estimators of β_0, β_1, and β_2 under the HS regression model are given by

$$\hat{\beta}_0 = 0.0540$$
$$\hat{\beta}_1 + \hat{\beta}_2 x = -0.03575 + 0.5873x \tag{13}$$

Those under the probit model are given by

$$\hat{\beta}_0 + (1 - \hat{\beta}_0)\,\Phi\,(\hat{\beta}_1 + \hat{\beta}_2 \log x) = 0.0523 + 0.9477\,\Phi\,(0.402 + 3.307 \log x) \tag{14}$$

These two are described in Figure 2. As the figure shows, the probit model is fitted better. Chi-square values are 6.436 under the probit model, and 21.534 under the HS regression model with common 6 degrees of freedom. This implies that the HS regression model is statistically significant with level 5%.

Lower confidence limits under the probit model with various kinds of assurance levels and risk levels are given in Table 5. Lower confidence limits with an assurance level 0.5 are reduced to point estimators. The maximum likelihood estimator $\hat{x}_0$ under the HS model is 0.153. We do not calculate confidence

Table 4. Relationship of average daily percent of adjusted symptoms to photochemical oxidant levels.

Daily maximum hourly oxidant level, ppm	No. of days	Average daily percent of symptom reported, %[a]	
		Eye discomfort	Chest discomfort
≤0.04	229	5.0	1.8
0.05-0.08	184	5.4	1.8
0.09	35	5.6	1.9
0.10-0.14	176	5.9	1.8
0.15-0.19	144	6.9	1.7
0.20-0.24	63	9.2	1.6
0.25-0.29	25	11.2	2.0
0.30-0.39	9	17.8	2.3
0.40-0.50	3	31.8	5.8

[a]Data of Hammer et al. (5).

[b]All days on which the symptom was reported along with "feverish" "chilly" or "temperature" are excluded.

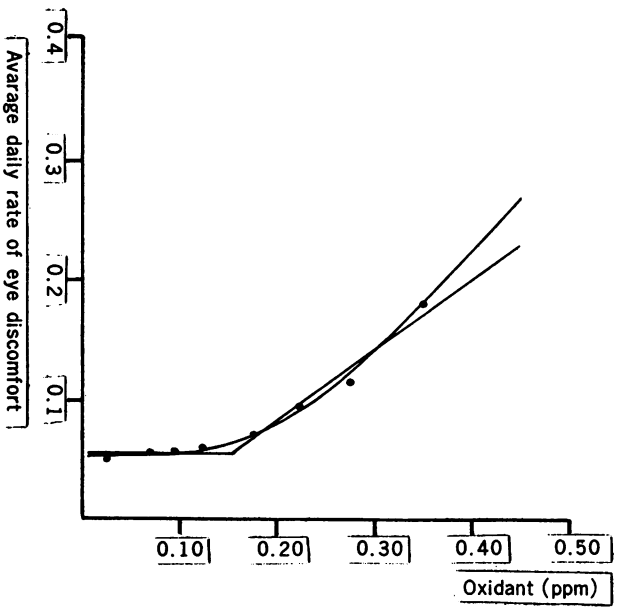

FIGURE 2. Data of photochemical oxidant and eye discomfort, and fitted regression lines.

Table 5. Lower confidence limits under the probit model with various kinds of risk and assurance levels for data of Table 2.

	Risk level ρ				
α	0.01	0.005	0.001	0.0005	0.0001
0.5	0.150	0.126	0.088	0.076	0.057
0.05	0.134	0.110	0.073	0.062	0.044
0.01	0.127	0.103	0.066	0.055	0.038
0.005	0.124	0.100	0.063	0.053	0.036

intervals, since test for homogeneity is statistically significant.

To apply the HS model to these data, we need to modify an assumption to the error term. Here the binomial distribution in Eq. (11) is replaced by a normal distribution. Let $Y(x)$ be a random variable which represents incidence ratio of students with positive symptom on a day with maximum hourly oxidant level x. The distribution of $Y(x)$ is given as follows

$$Y(x) \sim f(x) + \epsilon \qquad \epsilon \sim N(0, \sigma^2) \tag{15}$$

This model is available, if disturbance comes not only from variation among individuals but other various causes, for example meteorological factors, errors from surveys, and so on. The latter can be essential, since the quality of epidemiological data is limited to some extent.

This modified model seems to be applicable. This means that the HS procedure is robust. The estimators of the parameters are given by

$$\hat{\beta}_0 = 0.0541$$
$$\hat{\beta}_1 + \hat{\beta}_2 x = -0.0172 + 0.491x \tag{16}$$

which implies $\hat{x}_0 = 0.145$. This is similar to the estimated value in the HS model under binomial distribution. Further detailed analysis is omitted here.

Similar results have been obtained also in the case of chest discomfort. Both the probit model and the HS model under binomial distribution are well fitted. Chi-square values for homogeneity with their common 6 degrees of freedom are 1.533 and 1.673, respectively. The probit model is preferable in this case, too.

Discussion

Some conclusions and suggestions can be given through the above applications and other experiences.

The HS method is of omnibus use. In fact, the model is often well fitted as the simple linear regression. The defect is lack of scientific and medical interpretations of x_0. It is hoped that intersection of both lines means a safe dose. But for this purpose we need a certain physiological proof. That is, it is necessary to show existence of the positive threshold value. If otherwise, x_0 does not necessarily have special meanings. Practically the model is often assumed only for convenience. It is usually convinced that the dose-response curve is smoothly increasing, even in the case that the HS model is assumed.

A model with a smoothly increasing regression curve can delete this serious problem, but brings another one. A curve regression model does not present a point which suggests a safe dose directly. Thus a risk level is introduced to define a safe dose. This definition is more natural than that by an intersection in the HS model.

The trouble is about how we choose a suitable family of regression curves. Fortunately, we have many conventional models of dose-response relationships, for example, the probit model, the logit model, and so on. Our two examples show the probit model is well fitted, even though the data are obtained not from experiments but from epidemiological surveys.

The polynomial regression models are frequently used, when the linear regression model is not well fitted, but they are not applicable to our problem. In fact, the regression model using the polynomial of order 3 is well fitted to both data, but the estimated regression curves are unacceptable.

Related Problems

There are many related problems to comparisons between the HS model and the probit model. In this section we are going to deal with two examples.

Inverse Estimation of Regression Analysis

The most popular technique for analysis of bivariate data is the linear regression method. The inverse estimation of linear regression is often used to estimate safe doses. Let $(x_1, y_1), \ldots, (x_n, y_n)$ denote data. Under the linear regression model

$$y = \beta_0 + \beta_1 x + \epsilon \qquad \epsilon \sim N(0, \sigma^2) \tag{17}$$

an estimated regression line is written by

$$y = \hat{\beta}_0 + \hat{\beta}_1 x \tag{18}$$

An estimated safe dose $\hat{x}_0$ is defined by

$$y_0 = \hat{\beta}_0 + \hat{\beta}_1 \hat{x}_0 \tag{19}$$

where y_0 is given by another criterion, for example a

standard by the administration or a detection threshold of chemical analysis. The HS method is reduced to this one, when β_0 is known. Of course, a lower confidence limit is preferred to the above definition $\hat{x}_0$.

This method is not seen in the literature by statisticians, but really often used. This simple method also should be used after careful considerations. We will give a practical example.

A result of an experiment on residual antibiotics in growing chick's organ is presented in Table 6 (*18*).

The chicks were sacrificed after 4 weeks on diets containing various levels of kanamycin, and the kanamycin potency was determined by bioassay. We concentrate on figures in the blood. The threshold sensitivity is 0.1 μg potency/ml blood.

Our purpose is to obtain suitable estimator of safe levels. Now at first we ignore figures in the first column for simplicity which are below the threshold sensitivity. This does not change the following discussion. Let $(x_1, y_1), \ldots, (x_{20}, y_{20})$ denote data in Table 6, where x_i are dietary levels and v_i are residues in the blood. The log-log linear model is assumed, that is, for $i = 1, \ldots, 20$

$$\log y_i = \beta_0 + \beta_1 \log x_i + \epsilon_i \qquad \epsilon_i \sim N(0, \sigma^2) \tag{20}$$

Let $Y(x)$ be a random variable which represents residue of kanamycin on a dietary level x. Using an assurance level α, a risk level ρ, and a threshold level τ, a safe dose x_0 is defined by

$$x_0 = \max\{x | \Pr[\Pr(Y(x) > \tau) \leq \rho | (x_1, y_1), \ldots, (x_n, y_n)] \geq 1 - \alpha\} \tag{21}$$

Table 6. Content of kanamycin after 4 weeks on diets containing various levels of kanamycin.[a]

	Potency, μg/ml				
Organ	Diet 20 μg/g	Diet 1000 μg/g	Diet 4000 μg/g	Diet 8000 μg/g	Diet 16000 μg/g
Blood	0[b]	0.11	0.30	0.85	1.45
	0	0.10	0.27	0.66	2.00
	0	0.10	0.30	0.65	1.50
	0	0.11	0.72	1.50	2.90
	0	0.60	0.27	1.03	2.90
Liver	0	0.50	3.30	5.15	11.75
	0	0	3.70	5.05	9.25
	0	0	3.45	10.05	15.25
	0	0.52	3.03	8.25	15.50
	0	0.65	3.09	8.25	16.00

[a]Data of Yoshida (*8*).
[b]No kanamycin was detected.

Table 7. Lower confidence limits with various kinds of three levels for data in Table 6.

		Threshold level τ		
α	Risk level ρ	0.1	0.05	0.01
0.5	0.01	213.00	102.22	18.60
	0.005	185.28	88.95	16.18
	0.001	139.11	66.78	12.15
0.05	0.01	72.03	29.13	3.50
	0.005	58.64	23.76	2.86
	0.001	38.35	15.57	1.89
0.01	0.01	31.31	11.22	1.01
	0.005	24.14	8.66	0.78
	0.001	14.08	5.07	0.46

The definition means that it holds with probability $1 - \alpha$ that the ratio of chicks in which the residue is higher than a threshold value τ is less than ρ. The procedure to get $\hat{x}_0$ was obtained exactly by Takeuchi (*9*). An approximate one was also given there.

For the data in Table 6, $\hat{x}_0$'s are calculated with various kinds of three levels, which are listed in Table 7. On the other hand, lower confidence limits of $\hat{x}_0$ defined in Eq. (19) give fatal results.

Linear-Plateau Model

The linear-plateau model is analytically equivalent to the HS model. The regression function in the linear-plateau model is a reverse form of that in the HS model. That is, it is written by

$$f(x) = \beta_1 + \beta_2 x \quad x \leq x_0 \qquad = \beta_0 \quad x > x_0 \tag{22}$$

The model was used in the field of agriculture to estimate the optimum fertilizer rate (*10*) and the optimum harvest time (*11*). The model was proposed after comparing with the quadratic, square root and exponential models. The model was recommended by these authors, since the estimator $\hat{x}_0$ in the model tends to be smaller than the maximum point of the fitted quadratic curve and that of the square root curve. It was concluded that $\hat{x}_0$ is suitable for these purposes.

Now we study on the model from the viewpoint of comparison with a model with a smoothly increasing regression function.

Suppose that the true regression curve $f(x)$ is quadratic, that is

$$f(x) = \beta_0 + \beta_1 x - \beta_2 x^2 \tag{23}$$

and that predictor variables are suitably allocated. The linear-plateau model is possibly well fitted, and

$\hat{x}_0$ is smaller than the maximum point of the fitted quadratic curve $\hat{\beta}_1/2\hat{\beta}_2$.

Next, suppose that true regression curve f(x) is strictly increasing in x, for example

$$f(x) = \beta_1/(\beta_2 + \exp\{-\beta_3 x\}) \tag{24}$$

and that predictor variables are suitably allocated. Even in this case the linear-plateau model can be well fitted and an estimator $\hat{x}_0$ is obtained, though $f(x)$ does not take the maximum value at $x = x_0$.

These seem to correspond to the relationships between the HS model and the probit model. Thus we conjecture that another approach introducing risk levels are available. The alternative method must be more flexible and natural.

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