

# Monotone Local Linear Quasi-Likelihood Response Curve Estimates<sup>1)</sup>

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## Abstract

In bioassay, the response curve is usually assumed monotone increasing, but its exact form is unknown, so it is very difficult to select the proper functional form for the parametric model. Therefore, we should probably use the nonparametric regression model rather than the parametric model unless we have at least the partial information about the true response curve. However, it is well known that the nonparametric regression estimate is not necessarily monotone. Therefore the monotone transformation technique is of course required. In this paper, we compare the finite sample properties of the monotone transformation methods which can be applied to the local linear quasi-likelihood response curve estimate.

*Keywords* : Local linear quasi-likelihood estimate; Monotone nonparametric estimate; Response curve.

## 1. Introduction

In bioassay, different concentrations of a chemical compound are applied to experimental animals, and the all-or-none reaction of the animals are then recorded. For example, in pharmacology the effective action of a drug or vaccine is treated by an animal experiment, where the deaths or other all-or-none reactions of the animals are recorded after exposure to the drug at various levels.

Let  $x_i$  be the dose level for the  $i$ th subject. If the  $i$ th subject reacts at  $x_i$ , then the binary response variable  $Y_i$  is encoded by  $Y_i = 1$ , and if no reaction, then  $Y_i = 0$ . We assume that

$$P(Y_i = 1|X_i = x_i) = p(x_i) = 1 - P(Y_i = 0|X_i = x_i), \quad i = 1, \dots, n. \quad (1.1)$$

Here the function  $p(\cdot)$  denotes the response curve and we further assume that  $p$  is strictly monotone increasing. The statistical aim is the estimation of the response curve.

There are two main approaches for the estimation of the response curve. One is

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the parametric approach and the other is the nonparametric approach. It is well known that the convergence rate of the mean squared error for the parametric estimator is  $O(n^{-1})$  if the true model follows the assumed one, whereas the corresponding rate for the nonparametric estimator is usually  $O(n^{-\delta})$  for some number  $\delta \in (0,1)$ . However, if an incorrect parametric model is used, then the mean squared error for the parametric estimator does not even converge to zero, so the nonparametric estimator is much better than the parametric one in this case.

In many literature of bioassay, it has been pointed out that biological mechanisms of a drug action are usually so complicated that the form of the response curve is completely unknown, so the selection of the proper functional form for the parametric estimator is not an easy task. For this reason, numerous authors have proposed estimating the response curve nonparametrically. Kappenman (1987) proposed nonparametric dose response curve estimation procedure which is based on an estimator first proposed by Copas (1983). But his main interest is the use of it for the estimation of the ED50. The ED100 $\alpha$  is the dose level at which 100 $\alpha\%$  of the subjects react, so it is defined as  $ED100\alpha = p^{-1}(\alpha)$ .

Müller and Schmitt (1988) proposed a kernel estimator for the dose response curve. Their estimator is just Gasser and Müller kernel estimator with binary response variable. It is known that the local polynomial regression estimator has several more appealing features than the traditional kernel regression estimators. The better performance near boundaries is one of them (Fan, 1992). Park (1999) considered the local linear regression estimator as the response curve estimator and compared the finite sample performance with Müller and Schmitt's kernel response curve estimator. However, these estimators ignore the binary nature of the response, so they have some problems as the estimator of  $P(Y=1|X=x)$ . The obvious one is that the fitted curve is not guaranteed to lie in the interval (0,1). To overcome these difficulties, a generalization of the weighting mechanism is needed. Fan, Heckman, and Wand (1995) proposed the locally weighted quasi-likelihood estimators in one-parameter exponential family. Park and Park (2006) considered the estimation problem of ED100 $\alpha$  and compared the finite sample performance of parametric and nonparametric estimator. They chose the local linear quasi-likelihood estimator as the nonparametric estimator and the logit model as the parametric estimator.

Nonparametric response curve estimate is not necessarily monotone, especially in the small sample situation. Therefore the monotonizing transformation technique is of course required. There are several monotonizing transformation techniques for the nonparametric regression discussed in the literature. The most widely used

method for getting isotonic regression is the Pool Adjacent Violators Algorithm (PAVA). Friedman and Tibshirani (1984) recommended first smoothing and then isotonizing the nonparametric estimate by the PAVA. Mukerjee (1988) suggested the reverse sequence. Mammen (1991) derived theoretical results for both approaches. Kappenman (1987) proposed the monotone nonparametric regression estimation procedure by controlling the bandwidth. Recently Dette, Neumeyer, and Pilz (2003) proposed using the inverse of a density estimate from the estimated curve to obtain a monotone estimate of the regression function in a general nonparametric regression model.

These transformation techniques might change the shape of the estimated response curve dramatically in the small sample situation, so our aim here is to compare the finite sample properties of the monotone transformation methods which can be applied to the local linear quasi-likelihood estimator. In this paper, we consider the method in Friedman and Tibshirani (1984), the one in Kappenman (1987), and the one in Dette, Neumeyer, and Pilz (2003, 2005). These three methods produce the estimates which are asymptotically first order equivalent, so it is worthy to compare their finite sample properties. In fact, Dette and Pilz (2004) compared the finite sample properties of their method with the PAVA in the continuous response variable regression model and argued that their method has the better performance. We want to make sure that their method is still competitive in the response curve estimation problem.

In Section 2 we review three monotone nonparametric estimates briefly. In Section 3 we report the results of a simulation study to show the finite sample properties of three estimators. We present a summary of our findings in Section 4.

## 2. Three monotone nonparametric estimators

Consider the binary response model (1.1), where  $Y_1, \dots, Y_n$  are assumed to be independent and the dose response curve  $p$  is assumed to be strictly increasing and  $p \in C^2([0, 1])$ .

In the parametric generalized linear model it is usual to model a transformation of the regression function  $E(Y|X=x) = p(x)$  as linear and the model is given by

$$\eta(x) = \beta_0 + \beta_1 x = g(p(x)) \quad (2.1)$$

where  $g$  is the link function. There are many practical circumstances in which even though the full likelihood is unknown, one can specify the relationship between the mean and variance (Fan, Heckman, and Wand, 1995). Suppose the conditional variance is modeled as  $\text{Var}(Y|X=x) = V(p(x))$  for some specific function  $V$ . In this case estimation of the mean can be achieved by replacing the

conditional log-likelihood by a quasi-likelihood function  $Q(p(x), y)$  which satisfies

$$\frac{\partial}{\partial w} Q(w, y) = \frac{y - w}{V(w)}, \quad (2.2)$$

and estimating  $\beta_0$  and  $\beta_1$  by maximizing the quasi-likelihood

$$\sum_{i=1}^n Q(g^{-1}(\beta_0 + \beta_1 X_i), Y_i). \quad (2.3)$$

Since we deal with binary response,  $V(p) = p(1-p)$  and in this case the quasi-likelihood method coincides with the Bernoulli log-likelihood method.

Fan, Heckman, and Wand (1995) proposed the local quasi-likelihood using kernel weights, which is given by

$$\sum_{i=1}^n Q(g^{-1}(\beta_0 + \beta_1(X_i - x)), Y_i) K\left(\frac{X_i - x}{h}\right) \quad (2.4)$$

where  $h$  is the bandwidth and  $K$  is the kernel function. Maximizing (2.4) with respect to  $\beta_0$  and  $\beta_1$  leads to the maximum local linear quasi-likelihood estimate

$$\hat{\eta}(x; h) = \hat{\beta}_0 \quad (2.5)$$

and the local linear quasi-likelihood response curve estimate can be computed by applying the inverse link function

$$\hat{p}(x; h) = g^{-1}(\hat{\eta}(x; h)). \quad (2.6)$$

The local linear quasi-likelihood estimator  $\hat{p}(x; h)$  has very nice properties (Fan, Heckman, and Wand 1995), so we would like to use  $\hat{p}(x; h)$  as our response curve estimator. In the small sample situation, however,  $\hat{p}(x; h)$  is not necessarily monotone, so the monotone transformation is of course required. There are several monotone transformation techniques discussed in the literature, and we need the methods which can be applied to  $\hat{p}(x; h)$ . Among others, we consider the method in Friedman and Tibshirani (1984), the one in Kappenman (1987), and the one in Dette, Neumeier, and Pilz (2005).

The method in Friedman and Tibshirani (1984) can be summarized as follows. Suppose we have a set of  $n$  points  $\{(x_1, \hat{p}(x_1)), \dots, (x_n, \hat{p}(x_n))\}$  where  $x_1 \leq x_2 \leq \dots \leq x_n$  and  $\hat{p}(x)$  is the local linear quasi-likelihood estimate. The problem is to find  $\{\tilde{p}(x_1), \dots, \tilde{p}(x_n)\}$  to minimize  $\sum_{i=1}^n (\hat{p}(x_i) - \tilde{p}(x_i))^2$  subject to the monotone restriction  $\tilde{p}(x_1) \leq \tilde{p}(x_2) \leq \dots \leq \tilde{p}(x_n)$ . Such a solution exists and can be obtained from the PAVA. The basic idea of the PAVA is the following. Starting with  $\hat{p}(x_1)$ , we move to the right and stop if the pair  $(\hat{p}(x_i), \hat{p}(x_{i+1}))$  violates the monotone restriction, that is,  $\hat{p}(x_i) > \hat{p}(x_{i+1})$ . We pool  $\hat{p}(x_i)$  and  $\hat{p}(x_{i+1})$  by replacing them with their average. Call this average

$\tilde{p}(x_i) = \tilde{p}(x_{i+1}) = (\hat{p}(x_i) + \hat{p}(x_{i+1}))/2$ . We then move to the left to make sure that  $\hat{p}(x_{i-1}) \leq \tilde{p}(x_i)$ . If not, we pool  $\hat{p}(x_{i-1})$  with  $\tilde{p}(x_i)$  and  $\tilde{p}(x_{i+1})$ , replacing all three with their average. We continue to the left until the monotone requirement is satisfied, then proceed again to the right. This process of pooling the first violator and back-averaging is continued until we reach the right edge. The solution at each  $x_i$ ,  $\tilde{p}(x_i)$ , are then given by the last average assigned to the point at  $x_i$ . We denote this estimate as  $\hat{p}_P(x)$ . There is one thing we can notice about  $\hat{p}_P(x)$ : if  $\hat{p}(x_i)$ 's are already monotone, then the PAVA reproduces the original data, so  $\hat{p}_P(x_i) = \hat{p}(x_i), \forall i$ .

The method in Kappenman (1987) is rather simple. Suppose the local linear quasi-likelihood estimate  $\hat{p}(x_i; h)$  is not monotone. Then it is quite clear that there exists a value  $h_0$  such that  $\hat{p}(x_i; h)$  is monotone as long as  $h \geq h_0$ . This is true because the local linear estimate converges to a straight line as  $h$  goes to infinity. The monotone local linear quasi-likelihood estimates is then defined by  $\hat{p}(x_i; h_0), i = 1, \dots, n$ . We denote this estimate as  $\hat{p}_K(x)$ .

Dette, Neumeyer, and Pilz (2005) proposed a method for the estimation of the effective dose level curve,  $p^{-1}(\alpha)$  using the general framework developed in their earlier work (Dette, Neumeyer, and Pilz 2003) in the context of estimating a monotone regression function. Let  $\hat{p}(i/N)$  denote the local linear quasi-likelihood response curve estimator at the point  $i/N, i = 1, \dots, N$  with the kernel function  $K_r$  and the bandwidth  $h_r$ . It is not necessary that the number  $N$  coincides with the sample size  $n$ , particularly if  $n$  is small. Then they define the estimator of the effective dose level curve as

$$\hat{p}_I^{-1}(\alpha) \equiv \frac{1}{Nh_d} \sum_{i=1}^N \int_{-\infty}^{\alpha} K_d \left( \frac{\hat{p}(i/N) - u}{h_d} \right) du \tag{2.7}$$

The kernels  $K_r$  and  $K_d$  are assumed to be symmetric with compact support, say  $[-1, 1]$ , and  $h_r$  and  $h_d$  are corresponding bandwidths converging to 0 with increasing sample size  $n$ . They also assume that  $K_d$  is two times continuously differentiable and positive. Because the kernel  $K_d$  is positive, the estimate  $\hat{p}_I^{-1}(\alpha)$  is obviously isotonic. Therefore the monotone estimate of the response curve,  $\hat{p}_I(x)$  is simply obtained by reflection of  $\hat{p}_I^{-1}(\alpha)$  at the line  $\alpha = x$ .

### 3. Finite sample properties

#### 3.1 Models and evaluation

Mammen (1991) showed that  $\hat{p}_P(x)$  is asymptotically equivalent with the unconstrained estimator  $\hat{p}(x)$  in the first order. Dette, Neumeier, and Pilz (2003) also showed that  $\hat{p}_I(x)$  exhibits the same first order asymptotic behavior as the unconstrained estimator  $\hat{p}(x)$ . Therefore three monotone estimator,  $\hat{p}_P(x)$ ,  $\hat{p}_I(x)$ , and  $\hat{p}_K(x)$  are asymptotically equivalent, so it is of interest to compare their finite sample properties for estimating different styles of the response curve.

As the true response curve, we used the following 8 models:

1. The logit model,  $p_1(x) = [1 + \exp(5 - 15x)]^{-1}$
2. The skewed logit model,  $p_2(x) = [1 + \exp(5 - 10x)]^{-2}$
3. The complementary log-log model,  $p_3(x) = 1 - \exp[-\exp(-5 + 8x)]$
4. The normal mixture model,  $p_4(x) = 0.5\Phi((x - 0.3)/0.05) + 0.5\Phi((x - 0.7)/0.05)$
5. The normal mixture model,  $p_5(x) = 0.3\Phi((x - 0.3)/0.05) + 0.7\Phi((x - 0.7)/0.05)$
6. The Weibull model,  $p_6(x) = 1 - \exp[-(15x)^{0.5}]$
7. The piece-wise linear model,

$$p_7(x) = \begin{cases} 2x & \text{if } 0 \leq x < 0.3 \\ 0.4x + 0.48 & \text{if } 0.3 \leq x < 0.8 \\ x & \text{if } 0.8 \leq x \leq 1 \end{cases}$$

8. The piece-wise constant model,

$$p_8(x) = \begin{cases} 0.2 & \text{if } 0 \leq x < 0.5 \\ 0.8 & \text{if } 0.5 \leq x \leq 1 \end{cases}$$

The model  $p_1(x)$  to  $p_6(x)$  are the most widely used models for the binary data and their shapes are different from each other. The model  $p_1(x)$  is a symmetric sigmoid curve, and  $p_2(x)$  and  $p_3(x)$  are non-symmetric sigmoid curves, and  $p_4(x)$  is a symmetric non-sigmoid curve with three inflection points, and  $p_5(x)$  is a non-symmetric non-sigmoid curve with three inflection points, and  $p_6(x)$  is a non-symmetric strictly concave curve. Both  $p_7(x)$  and  $p_8(x)$  were included since they are not an element of  $C^2([0,1])$  which is an interesting case because we assume  $p \in C^2([0,1])$ .

The design points  $x_i$ 's for each model were determined by Uniform(0,1) pseudo random numbers. The sample sizes under consideration were  $n = 20, 50, 100$ . Dette and Pilz (2004) considered  $n = 50$  and  $n = 80$  cases only, so we actually considered more various circumstances. For the generation of the binary responses, Uniform(0,1) pseudo random numbers were constructed again and compared with  $p(x_i)$  for the respective models.

The local linear quasi-likelihood estimate,  $\hat{p}(x)$  was computed by R function *locfit* (Loader, 1999) in the *locfit* package. The bandwidth for  $\hat{p}(x)$  was chosen by the generalized cross validation method, which was done by R function *gcv* in the *locfit* package. An Epanechnikov kernel was used for the kernel function.

The density regression estimate,  $\hat{p}_d(x)$  was computed by R function *monreg* in the *monreg* package. For both  $K_r$  and  $K_d$ , the Epanechnikov kernel was used. The bandwidth  $h_r$  was also chosen by the generalized cross validation method. For the bandwidth  $h_d$ , Dette, Neumeier, and Pilz (2005) recommended the use of  $h_d = h_r^2$ , so we just followed it. For the number  $N$  in (2.7) we used  $N = 101$ .

To compare the performance of each estimator, the Monte Carlo mean integrated squared error (MISE) was computed as the average of

$$\int_0^1 (\hat{p}_*(x) - p(x))^2 dx \tag{2.8}$$

over  $m = 2000$  simulation samples where  $\hat{p}_*(x)$  denotes one of three monotone estimates. The Monte Carlo integrated squared bias (ISB) was also computed as

$$\int_0^1 (\bar{p}_*(x) - p(x))^2 dx \tag{2.9}$$

where  $\bar{p}_*(x)$  is the average of  $\hat{p}_*(x)$  over  $m = 2000$  simulation samples.

To support the validity of our simulation results we have to estimate the standard error of our MISE estimates. Let  $M_i$  denote the integrated squared error of  $i$ th simulation sample and let  $\bar{M}$  denote the average of  $M_i$  over  $m = 2000$ . The the standard error of the MISE estimates can be estimated by

$$SE = \sqrt{\frac{1}{m(m-1)} \sum_{i=1}^m (M_i - \bar{M})^2}. \tag{2.10}$$

A rough approximation to the relative error in each MISE estimate could then be obtained using  $2 \times SE / \bar{M}$ , and in our simulation, relative errors in each MISE estimate were estimated to be at most 5%, so they are not significant factors in interpreting the simulation results.

### 3.2 Comparison

Simulation results are reported in <Table 1> which contains the Monte Carlo MISE and ISB of three monotone estimates for each model. We can notice that  $\hat{p}_K(x)$  has much smaller MISE than other two monotone estimators in most cases. For  $p_4(x)$ ,  $p_5(x)$ , and  $p_8(x)$ ,  $\hat{p}_P(x)$  has smaller MISE than  $\hat{p}_K(x)$  at  $n = 100$  case only. Therefore in terms of MISE, it turns out that  $\hat{p}_K(x)$  is superior to both

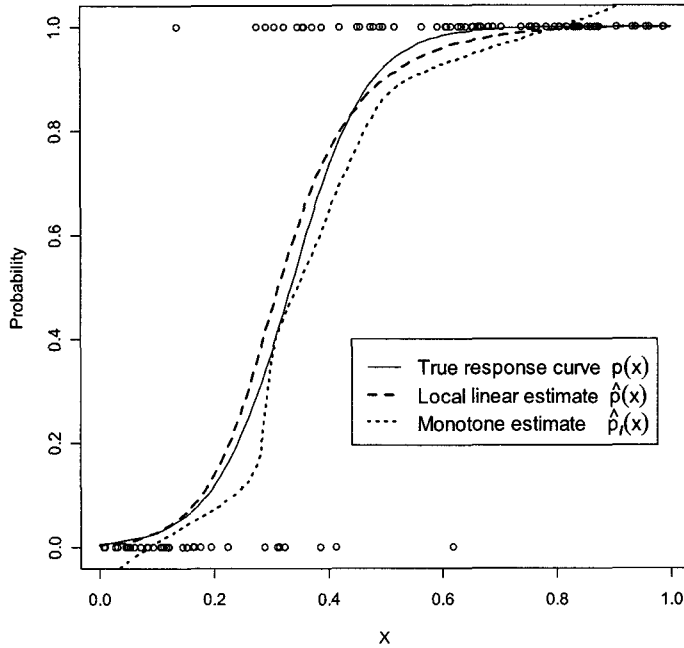
$\hat{p}_P(x)$  and  $\hat{p}_I(x)$ . We also can notice that except the case of  $p_2(x)$  with  $n=20$ ,  $\hat{p}_P(x)$  has much smaller ISB for all cases. Therefore in terms of ISB,  $\hat{p}_P(x)$  performs much better than other two monotone estimators.

<Table 1> MISE and ISB of three monotone estimators

	$n$	MISE			ISB		
		$\hat{p}_K(x)$	$\hat{p}_P(x)$	$\hat{p}_I(x)$	$\hat{p}_K(x)$	$\hat{p}_P(x)$	$\hat{p}_I(x)$
$p_1$	20	0.0126	0.0170	0.0346	0.0002	0.0002	0.0046
	50	0.0059	0.0068	0.0182	1.9e-5	4.7e-5	7.1e-4
	100	0.0030	0.0034	0.0144	5.0e-6	1.3e-5	1.6e-3
$p_2$	20	0.0136	0.0255	0.0356	0.0002	0.0005	0.0022
	50	0.0064	0.0092	0.0187	9.8e-5	7.5e-5	6.5e-4
	100	0.0030	0.0035	0.0133	8.3e-5	5.8e-5	1.5e-3
$p_3$	20	0.0144	0.0200	0.0356	0.0009	0.0003	0.0024
	50	0.0064	0.0080	0.0166	0.0003	0.0002	0.0005
	100	0.0034	0.0038	0.0108	0.0002	0.0001	0.0008
$p_4$	20	0.0206	0.0302	0.0376	0.0071	0.0053	0.0057
	50	0.0117	0.0117	0.0186	0.0057	0.0033	0.0045
	100	0.0074	0.0065	0.0104	0.0043	0.0026	0.0034
$p_5$	20	0.0203	0.0272	0.0390	0.0077	0.0037	0.0069
	50	0.0109	0.0112	0.0185	0.0052	0.0028	0.0044
	100	0.0070	0.0061	0.0107	0.0039	0.0022	0.0031
$p_6$	20	0.0176	0.0226	0.0234	0.0039	0.0030	0.0053
	50	0.0093	0.0110	0.0157	0.0022	0.0016	0.0031
	100	0.0063	0.0066	0.0156	0.0024	0.0017	0.0038
$p_7$	20	0.0241	0.0337	0.0382	0.0051	0.0044	0.0091
	50	0.0114	0.0131	0.0277	0.0030	0.0020	0.0105
	100	0.0066	0.0072	0.0184	0.0022	0.0014	0.0063
$p_8$	20	0.0345	0.0389	0.0600	0.0157	0.0098	0.0282
	50	0.0246	0.0220	0.0482	0.0168	0.0097	0.0293
	100	0.0214	0.0157	0.0333	0.0172	0.0088	0.0193

The finite sample properties of  $\hat{p}_I(x)$  is rather disappointing. Its values of MISE and ISB are not even close to the values of its competitors. In fact, we didn't expect such a poor performance of  $\hat{p}_I(x)$  as the estimator of  $p(x)$ , because Dette, Neumeier, and Pilz (2005) showed that for the estimation of  $p^{-1}(\alpha)$  problem,  $\hat{p}_I^{-1}(\alpha)$  is competitive with the method based on the PAVA by the simulation study. Therefore it is worthwhile to investigate the reason why  $\hat{p}_I(x)$  has the poor finite sample properties and we think that the <Figure 1> gives us the clue.



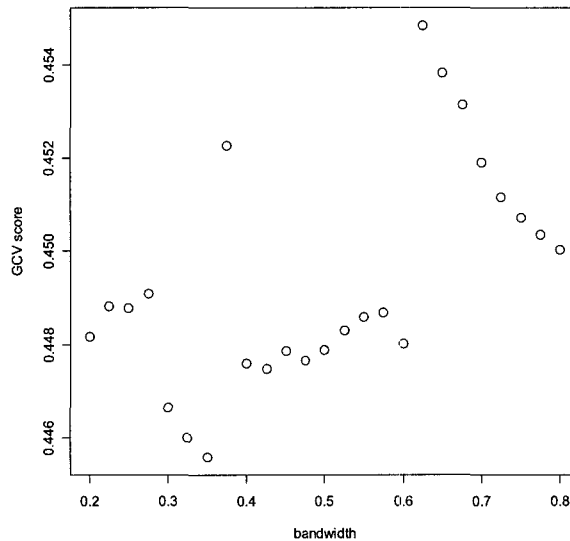


<Figure 1> Estimated dose response curves for typical data set of the model  $p_1(x)$

In <Figure 1>, the solid line represents the true response curve which is the logit model,  $p_1(x)$ . The dashed line represents the local linear quasi-likelihood estimate,  $\hat{p}(x)$ . Since  $\hat{p}(x)$  is already monotone, both  $\hat{p}_K(x)$  and  $\hat{p}_P(x)$  are represented by the dashed lines, too. The dotted line represents  $\hat{p}_I(x)$ . We can notice that even though  $\hat{p}(x)$  is monotone,  $\hat{p}_I(x)$  and  $\hat{p}(x)$  are not the same, and we believe that this is one of the undesirable properties of  $\hat{p}_I(x)$ . In <Figure 1>,  $\hat{p}(x)$  is constructed by the bandwidth  $h = 0.35$  and as we can see in <Figure 2>, the GCV score for the data set in <Figure 1> is minimized at  $h = 0.35$ . Therefore  $\hat{p}(x)$  in <Figure 1> can be considered as the "optimal" nonparametric estimate for the given data set, and in this point of view  $\hat{p}_I(x)$  should reproduce the original monotone nonparametric estimate, but this is not the case.

Another problem of  $\hat{p}_I(x)$  is that it is not guaranteed to lie in the interval  $(0,1)$ . In fact, we can notice that  $\hat{p}_I(x) \leq 0$  for  $x \leq 0.08$  and  $\hat{p}_I(x) \geq 1$  for  $x \geq 0.81$  in <Figure 1>. We believe that this is the crucial problem for the estimator of the response curve.

We showed the problems of  $\hat{p}_I(x)$  only for the case of  $p_1(x)$  in <Figure 1>, but just the same problems were observed at every other models.



<Figure 2> Generalized cross validation plot for the data set in <Figure 1>

#### 4. Conclusion

In bioassay, the response curve is usually assumed to be monotone increasing, but its exact form is unknown, so it is very difficult to select the proper functional form for the parametric model. Therefore, we should probably use the nonparametric regression model rather than the parametric model unless we have at least the partial information about the true response curve. However, the disadvantage of nonparametric regression is that the nonparametric regression estimate is not necessarily monotone, especially in the small sample situation. Therefore the monotonizing transformation technique is of course required.

A Monte Carlo study was done under various circumstances to compare the performance of the existing monotonizing transformation methods. In terms of the MISE,  $\hat{p}_K(x)$  is turned out the superior method, whereas in terms of the ISB,  $\hat{p}_P(x)$  is. Even though Dette, Neumeier, and Pilz (2005) strongly recommended the use of  $\hat{p}_I(x)$ , it turned out that the performance of  $\hat{p}_I(x)$  is very poor. To improve the performance of  $\hat{p}_I(x)$  as the response curve estimator, we believe that two problems pointed out in the previous section have to be resolved.

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