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Dose–Response Curve Estimation: A Semiparametric Mixture Approach

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Summary. In the estimation of a dose–response curve, parametric models are straightforward and efficient but subject to model misspecifications; nonparametric methods are robust but less efficient. As a compromise, we propose a semiparametric approach that combines the advantages of parametric and nonparametric curve estimates. In a mixture form, our estimator takes a weighted average of the parametric and nonparametric curve estimates, in which a higher weight is assigned to the estimate with a better model fit. When the parametric model assumption holds, the semiparametric curve estimate converges to the parametric estimate and thus achieves high efficiency; when the parametric model is misspecified, the semiparametric estimate converges to the nonparametric estimate and remains consistent. We also consider an adaptive weighting scheme to allow the weight to vary according to the local fit of the models. We conduct extensive simulation studies to investigate the performance of the proposed methods and illustrate them with two real examples.

Key words: Bootstrap; Dose–response curve; Effective dose; Nonparametric method; Parametric model; Weighted average.

1. Introduction

Dose–response experiments are routinely conducted in pharmacology and toxicology to study the relationship between the dose of an agent and the probability of an induced response (e.g., toxicity or efficacy). At a given dose x, we typically assume that the response Y is a Bernoulli variable with probability $p(x)$. We are often interested in estimating the dose–response curve $p(x)$, and in addition, the effective dose (ED), defined as $\text{ED}_\alpha = p^{-1}(\alpha)$ with $0 < \alpha < 1$, where $p^{-1}(\cdot)$ is the inverse function of $p(\cdot)$. In other words, the ED_α is the dose at which the probability of response is α. Pharmacologic studies typically focus on the $\text{ED}_{0.5}$ (i.e., $\alpha = 0.5$), and toxicology studies are often interested in estimating the ED_α for a smaller α.

In general, we can classify the methods for estimating the dose–response curve into the parametric and the nonparametric families. Parametric methods assume a parametric model $p(x, \boldsymbol{\theta})$ for the dose–response curve, where $\boldsymbol{\theta}$ is a vector of unknown parameters. Commonly used parametric models include probit and logit functions (Bliss, 1934; Berkson, 1944; McCullagh and Nelder, 1989; Morgan, 1992). It is well known that if the parametric model is correctly specified, the inference based on the maximum likelihood estimator (MLE) is efficient. However, in many cases, it is difficult to correctly specify the parametric form of the dose–response curve because the biological mechanism of drug action or toxicity may be complex and the form of the dose–response curve is unknown *a priori*. When the parametric model is misspecified, the corresponding curve estimate may be severely biased. Morgan (1992) provided a comprehensive review of the parametric estimation methods for dose–response curves.

To enhance the robustness of the estimation of the dose–response curve, many nonparametric methods have been proposed. Schmoyer (1984) derived a constrained MLE under the assumption that the dose–response curve is sigmoid. Müller and Schmitt (1988) proposed a kernel estimator for the dose–response curve. Kelly and Rice (1990) estimated the dose–response curve nonparametrically using regression B-splines. Mukhopadhyay (2000) developed a fully Bayesian nonparametric approach based on the Dirichlet process prior. Dette, Neumeyer, and Pilz (2005) constructed the composition of a nonparametric estimate of the quantile response curve and the classical density estimate. Park and Park (2006) proposed a kernel method using the local quasi-likelihood approach. Bornkamp and Ickstadt (2009) considered a Bayesian nonparametric estimate of continuous monotonic dose–response curves based on a mixture of shifted and scaled parametric probability distribution functions. Dette and Scheder (2010) compared the finite-sample performance of various nonparametric estimators. Nonparametric methods are flexible and the shape of the dose–response curve is mainly determined by the data. In general, nonparametric estimates are consistent under widely applicable regularity conditions. However, compared with parametric models, nonparametric methods are less efficient; and it is difficult to extrapolate the dose–response curve beyond the range of the observed dose levels.

To retain the advantages of parametric and nonparametric approaches, we construct a semiparametric estimate of the

dose–response curve as a weighted average of the two. The weight is chosen by minimizing the mean integrated squared error (MISE), such that strength can be adaptively borrowed across the two methods. The proposed semiparametric estimator has appealing features: when the parametric model is correctly specified, the semiparametric curve estimate skews toward the parametric estimate and thus achieves high efficiency; when the parametric assumption is violated, the semiparametric estimate assigns more weight to the nonparametric estimate, and still maintains consistency.

The mixture of a parametric estimate and a nonparametric estimate has been investigated for continuous response variables (Einsporn, 1987). Olkin and Spiegelman (1987) developed a similar approach for density estimation. Kouassi and Singh (1997) extended the parametric and nonparametric mixing to estimate the hazard function with censored data. Mays, Birch, and Starnes (2001) further studied the model-robust regression method for continuous outcomes based on mixing the parametric and nonparametric fits. That method has been applied successfully to various settings including linear mixed models (Waterman, Birch, and Schabenberger, 2007), the dual model for replicated and nonreplicated responses (Pickle et al., 2008; Robinson, Birch, and Starnes, 2010), and the multiresponse optimization problem (Wan and Birch, 2011). Also see Ghouch and Genton (2009) for recent development in this area. In the context of dose–response curve estimation with binary outcomes, Nottingham and Birch (2000) proposed a model-robust quantal regression method, which combines the parametric and nonparametric predictions with the use of a mixing parameter. Our work extends their method in several important aspects, which include proposing different mechanisms to estimate the mixing parameter based on the observed data, developing a new class of local mixing estimators, and establishing asymptotic properties for the proposed estimators.

The rest of the article is organized as follows. In Section 2, we propose two classes of semiparametric estimators that combine the parametric and nonparametric estimates using a global or a local mixing parameter, and describe the corresponding estimation procedures. We present simulation studies to examine the performance of the proposed methods in Section 3, and illustrate our methods with two real examples in Section 4. We conclude with a brief discussion in Section 5. Technical details are given in the Web Appendices.

2. Parametric and Nonparametric Mixing

2.1 *Global Semiparametric Estimator*

Let $p(x,\hat{\boldsymbol{\theta}})$ denote a parametric estimate of the dose–response curve based on the MLE $\hat{\boldsymbol{\theta}}$, and let $\tilde{p}(x)$ denote a nonparametric estimate. By mixing the two, we propose a semiparametric estimator of the dose–response curve,

$$p_\pi(x,\hat{\boldsymbol{\theta}}) = \pi p(x,\hat{\boldsymbol{\theta}}) + (1-\pi)\tilde{p}(x), \tag{1}$$

which is a weighted average of the parametric and nonparametric estimates of $p(x)$, with an unknown weight $\pi \in [0,1]$. This semiparametric estimator allows both the parametric and nonparametric estimates to simultaneously contribute to the estimation of the dose–response curve, and each contribution is determined by the weight π. By estimating π through a suitable way, a higher weight is assigned to the estimate that fits the data better, therefore the resulting semiparametric estimator inherits both efficiency and robustness from the two methods. The semiparametric estimator in (1) forms a general class of estimators because various available parametric estimates (e.g., probit or logistic models) and nonparametric estimates (e.g., spline or kernel methods) can be used to construct $p_\pi(x,\hat{\boldsymbol{\theta}})$.

Let $x_{\min}$ and $x_{\max}$ denote the minimum and maximum doses under investigation, respectively. We estimate the weight π by minimizing the MISE,

$$\mathrm{MISE}(p_\pi(x,\hat{\boldsymbol{\theta}})) = \mathrm{E}\left[\int_{x_{\min}}^{x_{\max}} \{p_\pi(x,\hat{\boldsymbol{\theta}}) - p(x)\}^2\,\mathrm{d}x\right]. \tag{2}$$

In Web Appendix A, we show that

$$\hat{\pi} = \frac{\int \{\mathrm{MSE}(\tilde{p}(x)) - \mathrm{covb}(x)\}\,\mathrm{d}x}{\int \{\mathrm{MSE}(p(x,\hat{\boldsymbol{\theta}})) + \mathrm{MSE}(\tilde{p}(x)) - 2\mathrm{covb}(x)\}\,\mathrm{d}x}, \tag{3}$$

where the mean squared errors (MSEs) of $p(x,\hat{\boldsymbol{\theta}})$ and $\tilde{p}(x)$ are $\mathrm{MSE}(p(x,\hat{\boldsymbol{\theta}})) = \mathrm{E}(p(x,\hat{\boldsymbol{\theta}}) - p(x))^2$ and $\mathrm{MSE}(\tilde{p}(x)) = \mathrm{E}(\tilde{p}(x) - p(x))^2$, and $\mathrm{covb}(x) = \mathrm{cov}(p(x,\hat{\boldsymbol{\theta}}),\tilde{p}(x)) + \mathrm{bias}(p(x,\hat{\boldsymbol{\theta}}))\mathrm{bias}(\tilde{p}(x))$. For ease of exposition, we refer to (1) as a global semiparametric estimator because it is estimated by minimizing the MISE, a global discrepancy measure, and π does not depend on dose x.

Despite the closed form, the calculation of $\hat{\pi}$ is challenging because the bias, MSE, and covariance of $p(x,\hat{\boldsymbol{\theta}})$ and $\tilde{p}(x)$ depend on the unknown dose–response curve $p(x)$. One way of circumventing this difficulty is to replace the true dose–response curve with its consistent estimate $p^*(x)$, for example, using the nonparametric estimator $\tilde{p}(x)$, and then estimate the bias, MSE, and covariance based on the bootstrap procedure as follows.

1. Generate B bootstrap samples stratified by the dose x, that is, sample y with replacement at each of the doses independently. We do not resample the dose x together with y because the doses are typically fixed by the design in dose–response studies.
2. For the bth bootstrap sample, calculate the parametric estimate $p^{(b)}(x,\hat{\boldsymbol{\theta}})$ and nonparametric estimate $\tilde{p}^{(b)}(x)$, for $b = 1, \ldots, B$.
3. Estimate the bias and MSE of $p(x,\hat{\boldsymbol{\theta}})$ by

$$\mathrm{bias}(p(x,\hat{\boldsymbol{\theta}})) \approx \frac{1}{B}\sum_{b=1}^{B}\{p^{(b)}(x,\hat{\boldsymbol{\theta}}) - p^*(x)\},$$

$$\mathrm{MSE}(p(x,\hat{\boldsymbol{\theta}})) \approx \frac{1}{B}\sum_{b=1}^{B}\{p^{(b)}(x,\hat{\boldsymbol{\theta}}) - p^*(x)\}^2;$$

the bias and MSE of $\tilde{p}(x)$ by

$$\mathrm{bias}(\tilde{p}(x)) \approx \frac{1}{B}\sum_{b=1}^{B}\{\tilde{p}^{(b)}(x) - p^*(x)\},$$

$$\mathrm{MSE}(\tilde{p}(x)) \approx \frac{1}{B}\sum_{b=1}^{B}\{\tilde{p}^{(b)}(x) - p^*(x)\}^2;$$

and the covariance between $p(x,\hat{\boldsymbol{\theta}})$ and $\tilde{p}(x)$ by

$$\operatorname{cov}(p(x,\hat{\boldsymbol{\theta}}),\tilde{p}(x)) \approx \frac{1}{B}\sum_{b=1}^{B}\{p^{(b)}(x,\hat{\boldsymbol{\theta}})-p^{*}(x)\}\{\tilde{p}^{(b)}(x)-p^{*}(x)\}.$$

Once we obtain these estimates based on the bootstrap samples, it is straightforward to take a numerical integration of these quantities over the range of $(x_{\min}, x_{\max})$ to obtain $\hat{\pi}$.

By minimizing the MISE, the resulting $\hat{\pi}$ automatically adjusts the weights assigned to the parametric and nonparametric estimates to reflect their closeness to the true dose–response curve. The closer is the estimate to the true curve, the higher weight is assigned. The global semiparametric estimator $p_{\hat{\pi}}(x,\hat{\boldsymbol{\theta}})$ has the following asymptotic property.

THEOREM 1: *Under the regularity conditions given in Fahrmeir and Kaufmann (1985), when the parametric model is correctly specified, $\hat{\pi}$ converges to* 1, *and thus $p_{\hat{\pi}}(x,\hat{\boldsymbol{\theta}})$ converges in probability to the parametric estimate $p(x,\hat{\boldsymbol{\theta}})$; when the parametric model is misspecified, $\hat{\pi}$ converges to* 0, *and thus $p_{\hat{\pi}}(x,\hat{\boldsymbol{\theta}})$converges in probability to the nonparametric estimate $\tilde{p}(x)$.*

The proof of Theorem 1 is briefly outlined in Web Appendix B. As a consequence, if the parametric assumption is reasonably satisfied, the semiparametric estimator $p_{\hat{\pi}}(x,\hat{\boldsymbol{\theta}})$ would enjoy high efficiency due to its closeness to the parametric estimator $p(x,\hat{\boldsymbol{\theta}})$. On the other hand, if the parametric assumption does not hold, $p_{\hat{\pi}}(x,\hat{\boldsymbol{\theta}})$ converges to the nonparametric estimator $\tilde{p}(x)$ and maintains a consistent estimator of $p(x)$. Moreover, as our semiparametric estimator is a mixture of the parametric and nonparametric estimates, it can estimate the ED_α outside the range of the observed doses, for which nonparametric methods often fail. For such extrapolation, we naturally set $\pi = 1$ and thus solely rely on the parametric component to predict the ED_α.

2.2 *Local Semiparametric Estimator*

The global semiparametric estimator assigns a constant weight π to the parametric estimate according to the global fit of the underlying parametric model. However, in some cases, although the parametric model does not characterize the entire dose–response curve well, it may still provide a good local fit to certain regions of the curve. Thus, it may be desirable to assign weights adaptively according to the local fit of the parametric and nonparametric models. Toward this goal, we propose a locally weighted semiparametric estimator

$$p_{\pi(x)}(x,\hat{\boldsymbol{\theta}}) = \pi(x)p(x,\hat{\boldsymbol{\theta}}) + (1-\pi(x))\tilde{p}(x), \tag{4}$$

in which the weight $\pi(x)$ depends on x in contrast to using a constant weight in (1).

To estimate the unknown weight $\pi(x)$, we minimize the MSE of $p_{\pi(x)}(x,\hat{\boldsymbol{\theta}})$ at each given dose x,

$$\mathrm{MSE}(p_{\pi(x)}(x,\hat{\boldsymbol{\theta}})) = \mathrm{E}[\{p_{\pi(x)}(x,\hat{\boldsymbol{\theta}})-p(x)\}^2],$$

which leads to

$$\hat{\pi}(x) = \frac{\mathrm{MSE}(\tilde{p}(x)) - \mathrm{covb}(x)}{\mathrm{MSE}(p(x,\hat{\boldsymbol{\theta}})) + \mathrm{MSE}(\tilde{p}(x)) - 2\mathrm{covb}(x)}.$$

Similar to (3), $\hat{\pi}(x)$ depends on the bias, MSE, and covariance of $p(x,\hat{\boldsymbol{\theta}})$ and $\tilde{p}(x)$, which can be approximated using the bootstrap procedure. In addition, following similar arguments as those in the proof of Theorem 1, it can be shown that the local semiparametric estimator possesses the same asymptotic property: when the parametric model is correctly specified, $p_{\hat{\pi}(x)}(x,\hat{\boldsymbol{\theta}})$ converges in probability to the parametric estimate $p(x,\hat{\boldsymbol{\theta}})$, and when the parametric model is misspecified, $p_{\hat{\pi}(x)}(x,\hat{\boldsymbol{\theta}})$ converges in probability to the nonparametric estimate $\tilde{p}(x)$.

Once we obtain a semiparametric estimator of the dose–response curve, say, the global $p_{\hat{\pi}}(x,\hat{\boldsymbol{\theta}})$, the ED_α can be estimated by $p^{-1}_{\hat{\pi}}(\alpha,\hat{\boldsymbol{\theta}})$. As the $\widehat{\mathrm{ED}}_\alpha$ does not have a closed form, we can use the numerical grid search to estimate ED_α. However, the estimator $\widehat{\mathrm{ED}}_\alpha$ might not be uniquely defined when $p_{\hat{\pi}}(x,\hat{\boldsymbol{\theta}})$ is not monotone. Following the work of Müller and Schmitt (1988), we can average over all the values of x satisfying $p_{\hat{\pi}}(x,\hat{\boldsymbol{\theta}}) = \alpha$ as the estimate of the ED_α. Local estimators of the ED_α can be pursued in a similar way based on $p_{\hat{\pi}(x)}(x,\hat{\boldsymbol{\theta}})$.

2.3 *Isotonic Semiparametric Estimator*

In some cases, such as toxicology studies, the dose–response curve is often assumed to be nondecreasing. Thus, it is desirable to incorporate such monotonic constraint into the proposed semiparametric estimators. One possibility is to impose the monotonicity condition on both $p(x,\hat{\boldsymbol{\theta}})$ and $\tilde{p}(x)$. However, this approach works only for the global semiparametric estimator in (1); but fails for the local estimator in (4) because the monotonicity of $p(x,\hat{\boldsymbol{\theta}})$ and $\tilde{p}(x)$ may not necessarily translate into the monotonicity of $p_{\hat{\pi}(x)}(x,\hat{\boldsymbol{\theta}})$ when the weight $\pi(x)$ depends on x. Therefore, we propose imposing the monotonicity condition directly on the semiparametric estimators, a strategy applicable to both the global and local estimators. Specifically, we apply the pool-adjacent-violator algorithm (PAVA) to $p_{\hat{\pi}}(x,\hat{\boldsymbol{\theta}})$ and $p_{\hat{\pi}(x)}(x,\hat{\boldsymbol{\theta}})$ at the prespecified fine grid of doses to obtain isotonic estimators of the dose–response curve (Barlow et al., 1972). The estimate of the dose–response curve at an arbitrary point between two adjacent doses is obtained by linear interpolation. The PAVA-transformed estimator can be further smoothed using the spline or kernel method (Müller and Schmitt, 1988; Mammen, 1991). Because the PAVA-transformed estimate may not be strictly monotonic, several different values of x may lead to the same response probability α. In this case, we average over the values of these x's to estimate the ED_α.

3. Simulation Study

We investigated the numerical performance of the proposed semiparametric estimators of the dose–response curve. We simulated data from the four true dose–response models:

$$\begin{aligned}
\text{Probit 1}: &\quad p(x) = \Phi\left(\frac{x-0.5}{0.25}\right),\\
\text{Probit 2}: &\quad p(x) = \Phi\left(\frac{x-0.5}{0.5}\right),\\
\text{Weibull}: &\quad p(x) = 1-\exp\left(-x^{0.52876}\right),\\
\text{Mixture}: &\quad p(x) = 0.64946\times\Phi\left(\frac{x-0.4}{0.13546}\right)\\
&\qquad + 0.35054\times\Phi\left(\frac{x-1.0}{0.13546}\right),
\end{aligned}$$

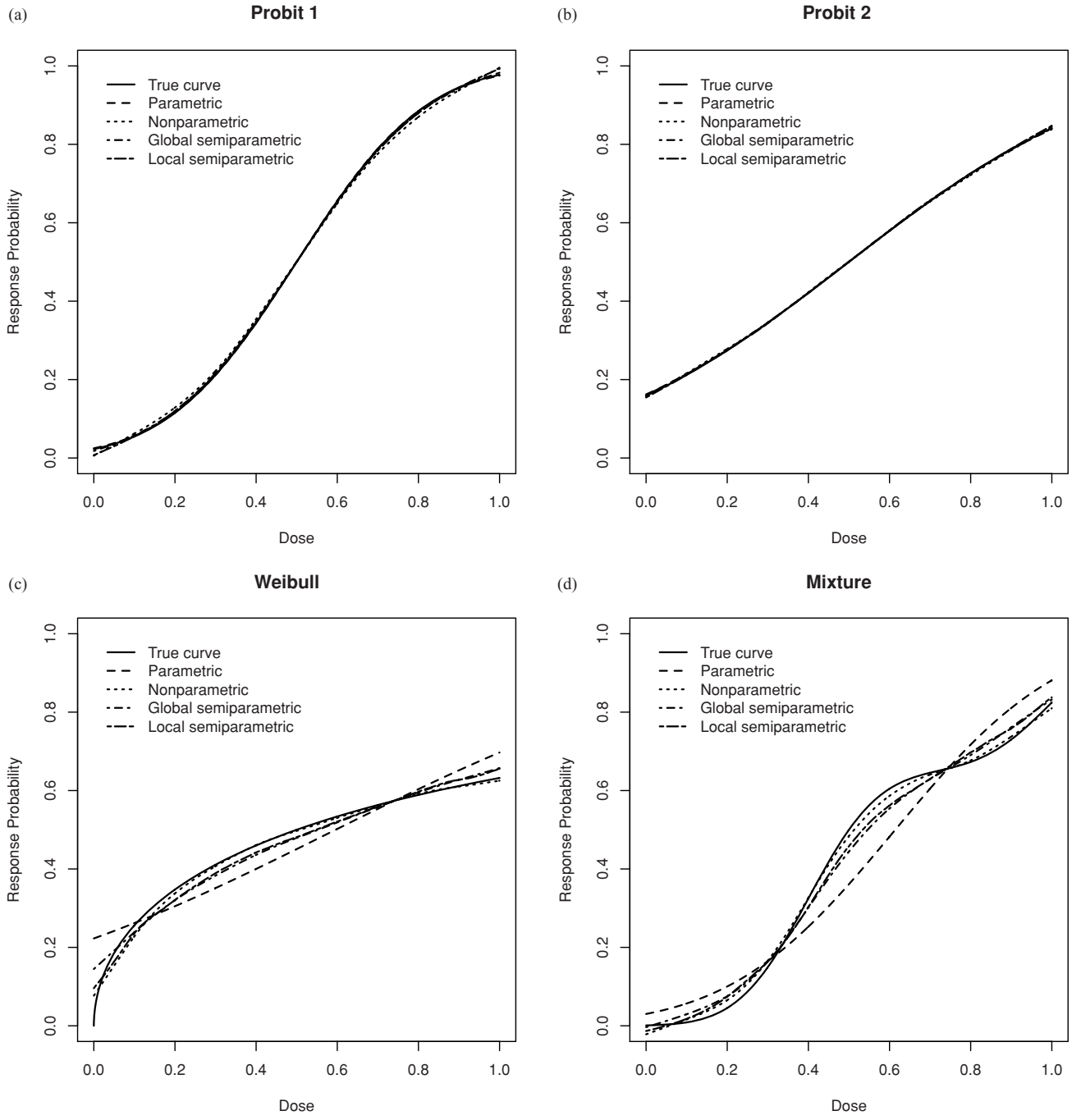

Figure 1. Averaged estimates of the dose–response curve using the parametric probit, nonparametric kernel, and the proposed global and local semiparametric methods.

where the model parameters were chosen so that $\mathrm{ED}_{0.5} = 0.5$; see Figure 1 for the shapes of the four dose–response curves. We simulated 10 outcomes from Bernoulli distributions with probability $p(x)$ at each of the 20 equally spaced doses $x = (d-1)/19$, for $d = 1, \ldots, 20$. We took the probit model as the basis for the parametric estimate, and considered three nonparametric estimates: the smoothing spline, the kernel estimate of Müller and Schmitt (1988), and the local quasi-likelihood kernel estimate of Park and Park (2006). These three nonparametric estimates were computed using the functions of `gam`, `glkerns`, and `locfit` in the `R` packages, respectively. We used the generalized cross-validation to choose the smoothing parameter for the smoothing spline (Green and Silverman, 1994), and the automatically adapted global plug-in bandwidth in the kernel methods (Gasser, Kneip, and Koehler, 1991). By mixing the probit parametric curve estimate with each of the three aforementioned nonparametric estimates, we obtained three global and three local

Table 1

Bias and mean squared error (MSE) of the estimated ED_α under the parametric probit model, nonparametric smoothing spline (SS), kernel (KE), and quasi-likelihood (QL), and the proposed global and local semiparametric methods with 10 *subjects at each of* 20 *equally spaced doses*

		Values of α for ED_α									
True model	Method	0.1	0.2	0.3	0.4	0.5	0.1	0.2	0.3	0.4	0.5
		Bias ($\times 10^{-3}$)					MSE ($\times 10^{-3}$)				
Probit 1	Probit	0	0	0	0	0	2	1	1	1	1
	Smoothing spline	−12	−8	−6	−4	−1	3	2	2	2	2
	Global-semi$^{(SS)}$	−7	−5	−4	−2	−1	2	2	1	1	1
	Local-semi$^{(SS)}$	−5	−5	−4	−2	−1	2	2	1	1	1
	Kernel	−17	−9	−6	−4	−1	4	3	2	2	2
	Global-semi$^{(KE)}$	−6	−4	−4	−2	0	2	2	1	1	1
	Local-semi$^{(KE)}$	−4	−4	−3	−2	−1	2	2	1	1	1
	Quasi-likelihood	−35	−37	−23	−10	−1	3	3	2	1	1
	Global-semi$^{(QL)}$	−28	−27	−17	−8	−1	2	2	2	1	1
	Local-semi$^{(QL)}$	−27	−35	−18	−7	−1	2	3	2	1	1
Probit 2	Probit	−17	−11	−7	−4	−1	17	9	5	3	2
	Smoothing spline	174	29	−3	−1	−2	32	5	7	6	6
	Global-semi$^{(SS)}$	−5	−6	−7	−2	−2	19	8	6	4	4
	Local-semi$^{(SS)}$	−1	−3	−5	−2	−2	20	8	6	4	4
	Kernel	183	37	0	−1	−1	35	6	8	7	7
	Global-semi$^{(KE)}$	−8	−8	−8	−2	−2	19	8	6	4	3
	Local-semi$^{(KE)}$	1	−1	−4	−2	−1	20	9	6	4	4
	Quasi-likelihood	175	21	−14	−4	−2	32	4	5	5	4
	Global-semi$^{(QL)}$	0	−8	−13	−4	−2	20	8	5	4	4
	Local-semi$^{(QL)}$	−2	−8	−14	−4	−2	20	8	5	4	4
Weibull	Probit	−456	−142	33	116	103	269	47	13	20	17
	Smoothing spline	17	28	29	21	38	1	2	5	13	31
	Global-semi$^{(SS)}$	−278	1	32	40	49	190	9	5	12	25
	Local-semi$^{(SS)}$	−163	16	33	42	53	130	4	5	13	26
	Kernel	22	32	44	53	61	1	3	11	23	35
	Global-semi$^{(KE)}$	−354	−31	36	67	67	224	19	7	15	23
	Local-semi$^{(KE)}$	−206	0	40	65	63	140	10	7	16	25
	Quasi-likelihood	13	29	50	50	39	1	3	5	9	21
	Global-semi$^{(QL)}$	−349	−17	49	58	52	229	20	6	10	21
	Local-semi$^{(QL)}$	−321	−8	46	58	55	218	17	6	11	21
Mixture	Probit	−62	11	58	94	116	6	1	4	10	15
	Smoothing spline	−26	−13	−1	12	29	2	1	1	2	4
	Global-semi$^{(SS)}$	−29	−9	8	25	44	2	1	1	2	5
	Local-semi$^{(SS)}$	−33	−4	9	22	41	2	1	1	2	5
	Kernel	−18	−7	0	11	31	2	1	2	2	6
	Global-semi$^{(KE)}$	−26	−1	16	32	53	2	1	2	3	6
	Local-semi$^{(KE)}$	−34	0	15	27	46	3	1	2	3	6
	Quasi-likelihood	−63	−38	−9	18	43	5	2	1	2	4
	Global-semi$^{(QL)}$	−63	−34	−3	24	50	5	2	1	2	5
	Local-semi$^{(QL)}$	−61	−20	−1	24	49	5	2	1	2	5

semiparametric estimators. For ease of exposition, we use Global-semi$^{(SS)}$, Global-semi$^{(KE)}$, and Global-semi$^{(QL)}$ to denote the global semiparametric estimators with smoothing spline, kernel, and quasi-likelihood estimates as the nonparametric mixing components, respectively; and similarly Local-semi$^{(SS)}$, Local-semi$^{(KE)}$, and Local-semi$^{(QL)}$ for the corresponding local semiparametric estimators. We took 500 bootstrap samples to compute the global weight π and the local weight $\pi(x)$, and conducted 1000 simulations under each of the dose–response models. For each replicated data set, we estimated the ED_α for $\alpha = (0.1, 0.2, 0.3, 0.4, 0.5)$. Because the ED_α may not be estimable using the nonparametric method when it is located outside of the observed dose range, we also recorded the percentage of the nonestimable ED_α when using the nonparametric methods. In the simulation, we did not impose the monotonicity assumption on the estimates. The computer code for implementing the proposed methodology is available on the author's website `http://odin.mdacc.tmc.edu/~yyuan/`.

Table 1 shows the bias and MSE of the estimated ED_α using the parametric, three nonparametric, three global semiparametric, and three local semiparametric methods. For the nonparametric method, the bias and MSE were obtained for those ED_α within the observed dose range only, while

Table 2
Percentage of the nonestimable ED_α using the nonparametric methods

	Smoothing spline					Kernel					Quasi-likelihood				
α	0.1	0.2	0.3	0.4	0.5	0.1	0.2	0.3	0.4	0.5	0.1	0.2	0.3	0.4	0.5
20 dose levels with 10 subjects per dose															
Probit 1	0.7	0	0	0	0	1.2	0	0	0	0	0	0	0	0	0
Probit 2	70.3	21.7	1.5	0	0	65.4	20.4	1.0	0	0	70.6	21.2	1.7	0	0
Weibull	23.9	0.7	0	0	0.2	30.8	3.8	0	0	0.2	55.6	6.5	0.1	0	0.7
Mixture	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5 dose levels with 10 subjects per dose															
Probit 1	0.2	0	0	0	0	1.7	0	0	0	0	0.2	0	0	0	0
Probit 2	25.7	4.2	0.1	0	0.2	61.6	21.9	3.1	0	0.4	25.7	4.2	0.1	0	0.2
Weibull	0	0	0	0.1	2.0	47.9	11.6	0.7	0.8	7.7	0	0	0	0.1	2.4
Mixture	0	0	0	0	0	0	0	0	0	0.2	0	0	0	0	0.2
5 dose levels with 20 subjects per dose															
Probit 1	0.1	0	0	0	0	0.1	0	0	0	0	0.1	0	0	0	0
Probit 2	53.7	7.0	0	0	0	68.3	18.3	0.8	0	0	54.1	7.0	0	0	0
Weibull	0	0	0	0	0	41.5	4.9	0	0.1	5.0	0	0	0	0	2.3
Mixture	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 2 presents the percentage of the ED_α lying outside of the observed dose range. The proposed semiparametric estimators for the ED_α inherited the desirable features from both parametric and nonparametric methods, which was generally comparable to the better one between the parametric and the nonparametric estimators, regardless of the type of the nonparametric method used or whether the parametric model assumption held or not. In particular, when the parametric model was correctly specified as in probit models 1 and 2, the parametric estimates performed the best with the smallest MSEs, while the nonparametric estimates exhibited substantial biases and relatively large MSEs. The MSEs of the proposed semiparametric estimators were uniformly smaller than those of the corresponding nonparametric estimators, and were comparable to those of the parametric estimators. For instance, under probit model 1, when the smoothing spline or the kernel estimate was used as the nonparametric component, the MSEs of semiparametric estimates were half of those of nonparametric estimates for the $ED_{0.3}$, $ED_{0.4}$, and $ED_{0.5}$, and were the same as those of parametric estimates. Under probit model 2, the semiparametric estimates also outperformed the corresponding nonparametric estimates with smaller MSEs, especially for the $ED_{0.4}$ and $ED_{0.5}$. In addition, the proposed semiparametric methods could estimate the ED_α in all of the scenarios, while the percentage of the nonestimable ED_α using nonparametric methods ranged from 65.4% to 70.6% for $\alpha = 0.1$, and 20.4% to 21.7% for $\alpha = 0.2$ under the true model of probit 2, as shown in Table 2.

When the true dose–response curve followed a Weibull or a mixture model, the nonparametric estimate of the ED_α remained consistent as expected. However, the parametric probit model resulted in substantial biases and MSEs due to model misspecification. The proposed global and local semiparametric estimators were slightly inferior to the corresponding nonparametric estimator, but substantially outperformed the parametric estimator. Under the Weibull model, the semiparametric estimates of the $ED_{0.1}$ had much larger MSEs than the corresponding nonparametric estimate because in approximately 23.9%, 30.8%, and 55.6% of the simulations, the $ED_{0.1}$ could not be estimated using the smoothing spline, kernel, or quasi-likelihood approach. In these cases, the semiparametric methods completely relied on the misspecified parametric model to predict the $ED_{0.1}$ by taking $\pi = 1$ or $\pi(x) = 1$, which thus led to relatively large biases and MSEs. When the nonparametric estimates were available, such as for the $ED_{0.3}$, $ED_{0.4}$, and $ED_{0.5}$, the semiparametric approaches performed similarly to the nonparametric methods. Figure 1 illustrates a graphical comparison of the averaged estimates of the dose–response curve, from which we can see that the parametric model works well if it is correctly specified, but deviates from the true curve if the model is misspecified; and nonparametric estimators typically match the true curve closely; and the proposed semiparametric estimators lie in between. Under probit models, all of the curve estimates are indistinguishable, but under the Weibull and mixture models, semiparametric and nonparametric methods can capture some local curvatures that parametric models would miss.

To investigate the case with sparse doses, we carried out a simulation study with five unequally spaced doses (i.e., $x =$ 0, 0.1, 0.25, 0.5, and 1). At each dose, 10 or 20 subjects were treated (see Tables 3 and 4, respectively). We observe a similar pattern of the estimation results as those with 20 doses. Semiparametric estimators offer an adaptive compromise between parametric and nonparametric estimators: when the parametric models were correctly specified as probit models, the semiparametric estimates outperformed the corresponding nonparametric estimates; and when the parametric models were misspecified as a Weibull or a mixture model, the semiparametric estimates yielded smaller MSEs than the parametric counterparts.

To gain a deeper insight to the behaviors of the semiparametric estimators, Figure 2 shows the weights π and $\pi(x)$ of Global-semi$^{(KE)}$ and Local-semi$^{(KE)}$ under the four dose–response models with 20 dose levels. When the parametric probit models were correctly specified as in Figure 2a and b, the weights used in the global and local semiparametric

Table 3

Bias and mean squared error (MSE) of the estimated ED_α under the parametric probit model, nonparametric smoothing spline (SS), kernel (KE), and quasi-likelihood (QL), and the proposed global and local semiparametric methods with 10 *subjects at each of five unevenly spaced doses*

		Values of α for ED_α									
True model	Method	0.1	0.2	0.3	0.4	0.5	0.1	0.2	0.3	0.4	0.5
		Bias ($\times 10^{-3}$)					MSE ($\times 10^{-3}$)				
Probit 1	Probit	21	10	3	−4	−10	10	5	4	4	5
	Smoothing spline	−14	−11	−1	9	19	11	10	9	12	15
	Global-semi$^{(SS)}$	11	0	1	6	11	8	6	7	8	10
	Local-semi$^{(SS)}$	19	6	2	6	11	9	6	7	9	11
	Kernel	−30	−27	3	32	49	5	7	9	10	10
	Global-semi$^{(KE)}$	−30	−24	4	29	43	5	7	8	9	10
	Local-semi$^{(KE)}$	−16	−24	1	27	43	5	7	8	9	9
	Quasi-likelihood	−13	−17	−8	3	13	8	8	8	9	10
	Global-semi$^{(QL)}$	7	−7	−7	2	8	7	6	7	8	9
	Local-semi$^{(QL)}$	14	0	−4	1	7	8	5	6	8	9
Probit 2	Probit	−4	−2	1	2	4	170	56	17	13	33
	Smoothing spline	214	55	3	−6	−16	56	20	25	33	36
	Global-semi$^{(SS)}$	15	22	13	13	13	58	27	20	21	25
	Local-semi$^{(SS)}$	37	31	18	14	10	61	27	20	20	25
	Kernel	207	54	19	31	35	46	11	17	20	19
	Global-semi$^{(KE)}$	18	9	6	26	28	174	53	17	18	36
	Local-semi$^{(KE)}$	10	6	6	20	24	172	55	16	17	36
	Quasi-likelihood	226	51	−11	−24	−25	59	13	17	25	28
	Global-semi$^{(QL)}$	20	22	6	1	2	58	24	17	18	21
	Local-semi$^{(QL)}$	28	25	9	3	6	61	25	17	18	21
Weibull	Probit	−269	11	161	223	190	288	70	53	83	110
	Smoothing spline	57	86	110	141	68	12	28	50	89	84
	Global-semi$^{(SS)}$	−74	72	115	144	120	98	21	41	63	91
	Local-semi$^{(SS)}$	41	72	117	133	103	8	20	45	61	81
	Kernel	41	64	101	142	95	6	13	33	64	48
	Global-semi$^{(KE)}$	−201	29	107	150	150	187	30	34	70	107
	Local-semi$^{(KE)}$	−193	30	107	146	142	183	28	34	65	106
	Quasi-likelihood	52	79	93	105	32	7	18	33	60	58
	Global-semi$^{(QL)}$	5	72	102	121	104	33	16	33	53	100
	Local-semi$^{(QL)}$	40	67	102	128	117	4	14	33	57	102
Mixture	Probit	−3	55	92	118	132	8	8	14	21	27
	Smoothing spline	−6	5	15	33	46	5	5	7	12	19
	Global-semi$^{(SS)}$	1	17	36	52	62	5	5	7	11	17
	Local-semi$^{(SS)}$	4	21	33	47	59	5	5	7	12	18
	Kernel	−59	−21	26	64	91	6	6	9	13	18
	Global-semi$^{(KE)}$	−57	−16	30	67	93	6	6	9	14	19
	Local-semi$^{(KE)}$	−39	−4	34	67	93	6	6	9	13	19
	Quasi-likelihood	−12	−3	10	29	47	5	4	6	10	18
	Global-semi$^{(QL)}$	−5	5	22	40	56	4	4	6	10	17
	Local-semi$^{(QL)}$	0	14	26	44	58	5	4	7	11	17

approaches were quite close: both assigned weights around 0.7 to the parametric estimate. When the parametric models were misspecified as in Figure 2c and d, the weights used in global and local semiparametric estimators were very different. Using the global semiparametric approach, the weight is a constant. For the Weibull model, the parametric and nonparametric estimates are balanced with a weight of 0.5, while for the mixture model, a higher weight of 0.63 was assigned to the nonparametric estimate. Using the local semiparametric approach, the weight varies according to the local fit of the parametric and nonparametric models. For example, under the mixture model in Figure 2d, around the region where the parametric estimate was close to the true dose–response curve, such as at doses 0.29 and 0.75, a higher weight was assigned to the parametric estimate due to its high efficiency, whereas in the region where the parametric estimate severely deviated from the true dose–response curve, such as at doses 0.51 and 0.92, the weight assigned to the parametric estimate sharply decreased.

4. Applications

For illustration, we applied the proposed methods to two real data examples. In these applications, we imposed a probit model as the parametric component and used the kernel estimate of Müller and Schmitt (1988) for the nonparametric

Table 4

Bias and mean squared error (MSE) of the estimated ED_α under the parametric probit model, nonparametric smoothing spline (SS), kernel (KE), and quasi-likelihood (QL), and the proposed global and local semiparametric methods with 20 *subjects at each of five unevenly spaced doses*

True model	Method	Values of α for ED_α									
		0.1	0.2	0.3	0.4	0.5	0.1	0.2	0.3	0.4	0.5
		Bias ($\times 10^{-3}$)					MSE ($\times 10^{-3}$)				
Probit 1	Probit	7	4	2	0	−2	3	2	2	2	2
	Smoothing spline	−4	−1	0	8	18	7	5	5	6	8
	Global-semi$^{(SS)}$	5	0	−1	5	11	4	3	3	4	5
	Local-semi$^{(SS)}$	11	6	2	4	9	5	3	3	4	6
	Kernel	−31	−29	1	34	56	2	4	5	7	8
	Global-semi$^{(KE)}$	−29	−26	1	30	50	2	3	5	6	7
	Local-semi$^{(KE)}$	−24	−27	−1	28	45	2	3	4	6	7
	Quasi-likelihood	−5	−7	−6	5	15	6	4	4	5	6
	Global-semi$^{(QL)}$	5	−3	−5	5	12	4	3	3	4	5
	Local-semi$^{(QL)}$	10	2	−4	1	8	5	2	3	4	5
Probit 2	Probit	−12	−7	−3	0	3	21	10	6	5	6
	Smoothing spline	191	27	−3	11	16	41	10	16	18	20
	Global-semi$^{(SS)}$	3	5	3	9	14	25	11	10	11	13
	Local-semi$^{(SS)}$	14	12	3	10	14	28	13	10	12	14
	Kernel	181	27	4	33	43	34	5	10	13	12
	Global-semi$^{(KE)}$	7	−3	0	25	35	25	9	9	11	11
	Local-semi$^{(KE)}$	−2	−5	−1	21	31	23	9	9	11	11
	Quasi-likelihood	198	32	−6	1	7	44	8	13	14	15
	Global-semi$^{(QL)}$	7	8	0	4	9	25	11	9	11	11
	Local-semi$^{(QL)}$	10	6	0	5	10	27	11	9	10	11
Weibull	Probit	−233	24	157	204	158	87	14	33	52	42
	Smoothing spline	30	39	48	74	49	3	7	19	45	59
	Global-semi$^{(SS)}$	−15	38	80	119	88	16	5	22	42	46
	Local-semi$^{(SS)}$	26	38	73	106	73	2	5	20	40	45
	Kernel	19	42	68	100	79	1	4	12	37	39
	Global-semi$^{(KE)}$	−152	36	79	113	104	70	6	14	39	46
	Local-semi$^{(KE)}$	−134	34	80	114	101	62	6	15	36	46
	Quasi-likelihood	34	46	47	60	34	2	5	13	32	46
	Global-semi$^{(QL)}$	21	45	72	97	69	1	5	16	34	43
	Local-semi$^{(QL)}$	29	42	75	104	75	1	5	17	35	45
Mixture	Probit	−14	48	88	116	132	3	5	10	17	22
	Smoothing spline$^{(SS)}$	2	1	7	16	20	3	2	3	4	8
	Global-semi$^{(SS)}$	2	12	24	36	42	2	2	3	6	9
	Local-semi$^{(SS)}$	0	15	21	32	39	2	2	3	6	9
	Kernel	−63	−30	15	54	83	5	3	4	8	12
	Global-semi$^{(KE)}$	−61	−27	18	57	85	5	3	4	8	12
	Local-semi$^{(KE)}$	−48	−12	22	57	84	5	3	4	8	12
	Quasi-likelihood	−1	−5	1	13	23	3	2	2	4	8
	Global-semi$^{(QL)}$	−1	1	11	25	36	2	2	3	5	9
	Local-semi$^{(QL)}$	−2	8	14	29	40	2	2	3	6	9

part. By adaptively mixing these two, we obtained the proposed global and local semiparametric estimators.

4.1 *Labeling Index and Remission Study*

Lee (1974) reported a study with 27 cancer patients to determine the dose–response relationship between the labeling index (LI) and remission. The "dose" variable LI varied between 8 and 28, representing the percentage of cells that were labeled, which measured the proliferative activity of cells after a patient received an injection of tritiated thymidine. The binary response indicated whether a patient had achieved remission or not. Of particular interest in that study was to estimate the $ED_{0.5}$, the dose at which 50% of the cells were labeled.

To obtain isotonic smooth curve estimates, we applied the PAVA-transformation to the nonparametric and semiparametric estimates and then smoothed the transformed estimates using smoothing spline. Figure 3a shows the estimates of the dose–response curve. The curve estimates using the two semiparametric methods are very close to the nonparametric estimate and demonstrate some local features that are not captured by the parametric model. For example, the semiparametric estimates indicate that the probability of remission is close to 0 when LI is between 8 and 14, which is

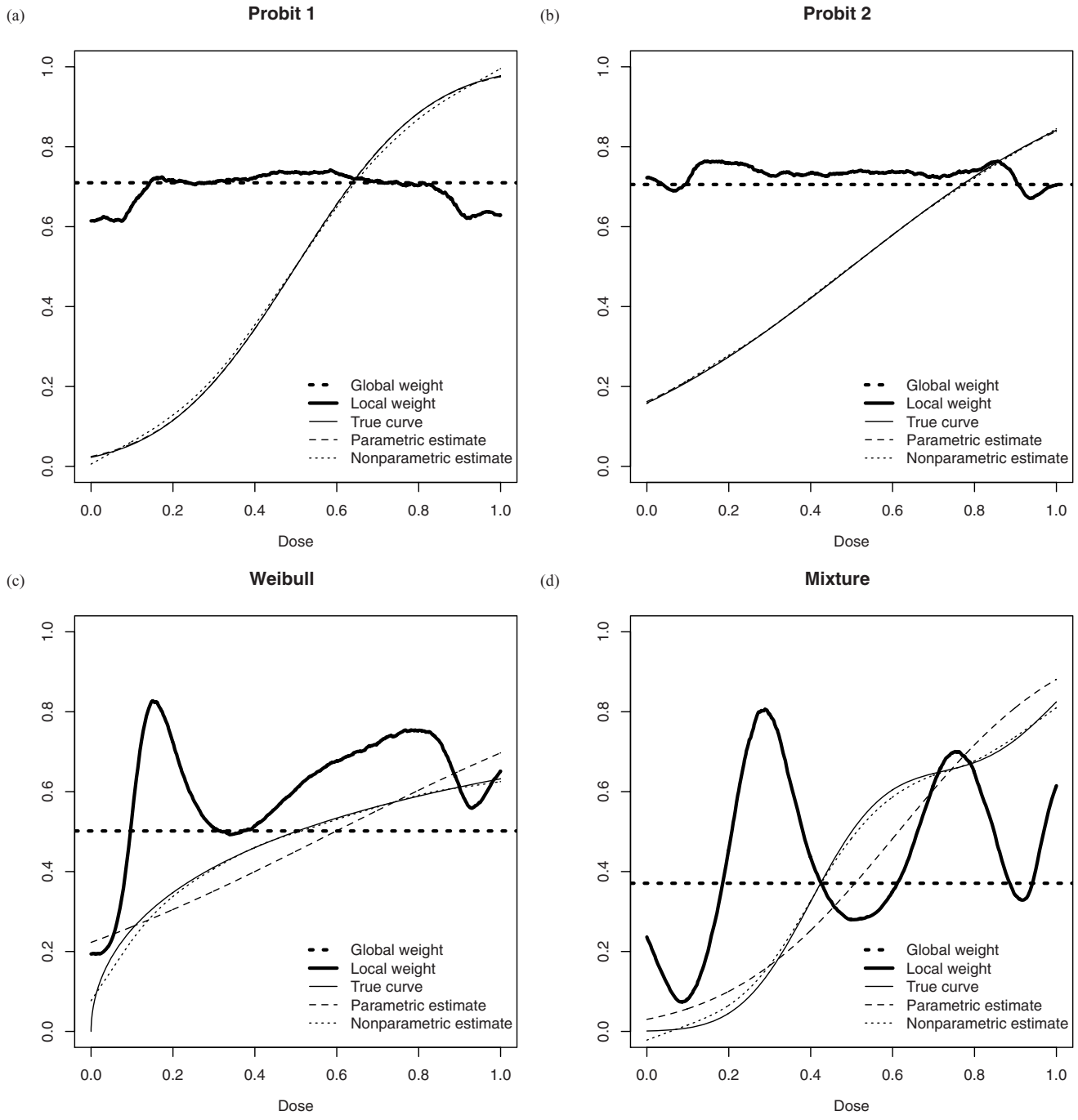

Figure 2. Weights π and $\pi(x)$ in the global and local semiparametric estimators under four dose–response models. The true dose–response curve, parametric estimator, and nonparametric estimator are also shown for reference.

more consistent with the observed data (no remission was observed in this range of LI). The similarity between the semiparametric and the nonparametric estimates can be explained by large weights assigned to the nonparametric estimate as shown in Figure 3b. Specifically, for the global semiparametric estimator, the weight assigned to the nonparametric component was 0.91. For the local semiparametric estimator, the weight varied according to the agreement between the parametric and nonparametric estimates. In the areas where the parametric and nonparametric estimates were close to each other, such as around LI = 23 and 38, the majority of the weight was assigned to the parametric estimate due to its high efficiency. In the regions where the parametric and nonparametric estimates were very different, such as for LI lying in the ranges of (16, 20) and (25, 35), the nonparametric estimate received most of the weight because of its flexibility and consistency. The estimate of the $ED_{0.5}$ under the parametric probit model was 26.38 and that using the

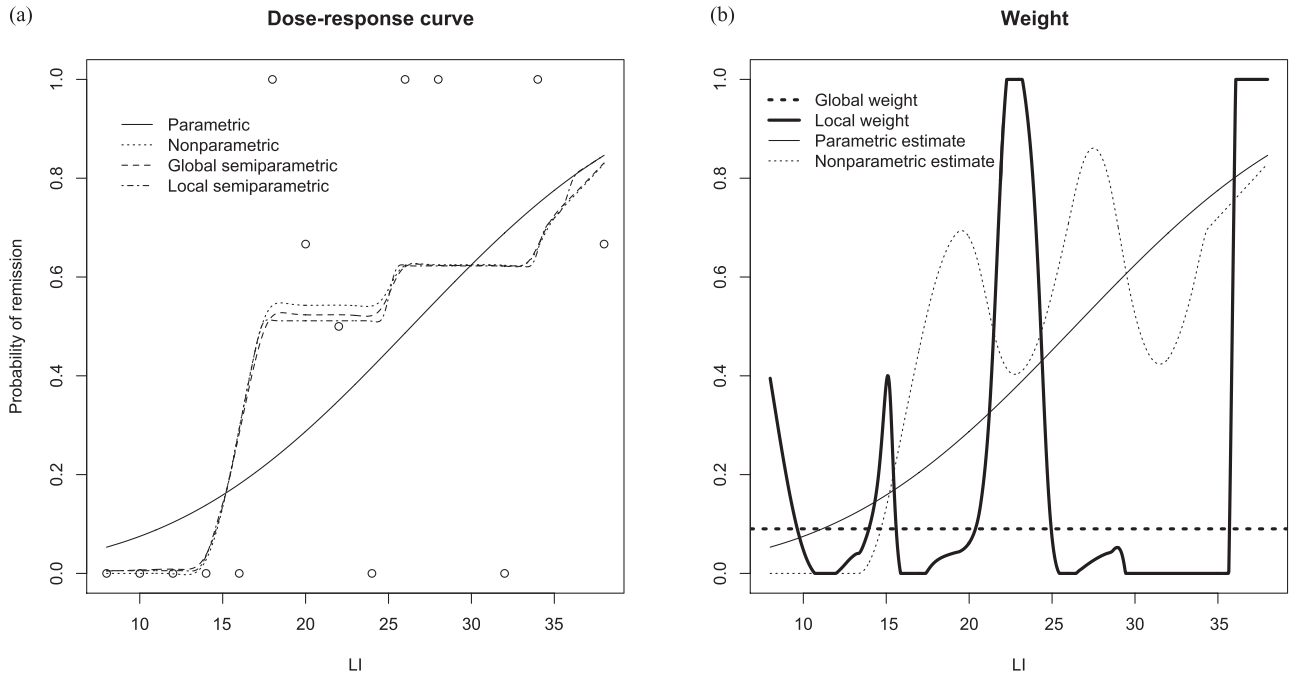

Figure 3. The labeling index and remission study: panel (a) shows the isotonically transformed estimates of the dose–response curve using the parametric, nonparametric, and the proposed global and local semiparametric methods, with the observed rates of remission given as dots; and panel (b) displays weights π and $\pi(x)$ in the global and local semiparametric estimates, respectively. The parametric and nonparametric estimators without isotonic transformation are also shown for reference.

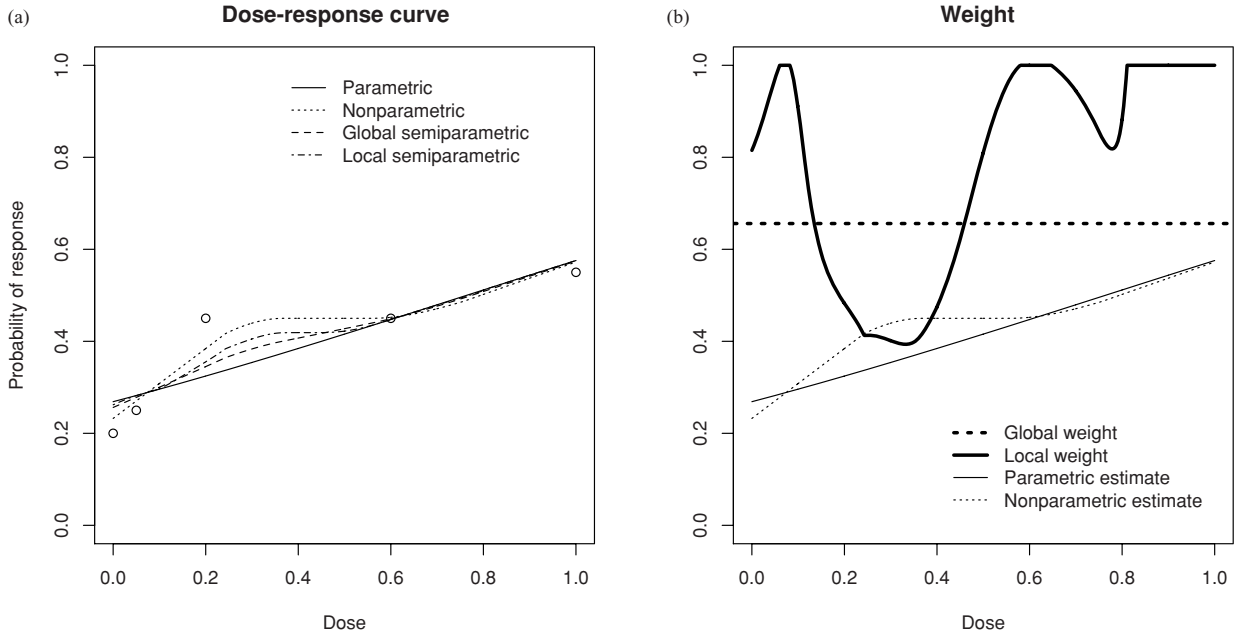

Figure 4. Estimates of the dose–response curve for the phase II trial. Panel (a) shows the estimates of the dose–response curve using the parametric, nonparametric, and the proposed global and local semiparametric methods, with the observed response rates given as dots; and panel (b) displays weights π and $\pi(x)$ in the global and local semiparametric estimates, respectively. The parametric and nonparametric estimators are also shown for reference.

nonparametric kernel method was 17.28. Our global and local semiparametric estimators of the $ED_{0.5}$ were 17.49 and 17.28, respectively, quite close to the nonparametric estimate. As a comparison, Agresti (2002) applied a logistic regression model to the same data and obtained an estimate of 26.05 for the $ED_{0.5}$. Therefore, the parametric probit or logit model may result in substantial bias for this data set.

4.2 *Phase II Dose Finding Study*

Bretz, Pinheiro, and Branson (2005) presented a parallel-group clinical trial with a total of 100 patients equally randomized to either placebo or one of four active doses (coded as 0.05, 0.2, 0.6, and 1, respectively). We coded a patient as a responder ($Y = 1$) if his/her value of the (continuous) efficacy measure was larger than 0.8; otherwise as a nonresponder ($Y = 0$).

Figure 4a shows the estimated dose–response curves using the parametric, nonparametric, and global and local semiparametric methods. The estimated probability of response increases rapidly from 0 to 0.2, and thereafter increases gradually with the dose. For doses below 0.5, we observe some differences between the parametric and nonparametric curve estimates, while the two curves are almost identical for doses above 0.6. Overall, the two semiparametric estimates lie between the parametric and nonparametric curves, and both of them are slightly closer to the parametric estimate due to relatively more weights assigned to the parametric model, as shown in Figure 4b. For the global semiparametric estimator, the weight assigned to the parametric part is 0.63; and for the local semiparametric estimator, when the parametric and nonparametric estimates are close to each other (e.g., around the doses of 0.07 and 0.6), the weight for the parametric estimate is almost 1.

5. Conclusions

We have proposed global and local semiparametric estimates of a dose–response curve in the form of a weighted average of a parametric and a nonparametric estimate. The weight is adaptively chosen according to the model fit: a higher weight is given to the model that fits the data better. When the parametric assumption holds, the semiparametric estimate skews toward the parametric estimate, and thus achieves high efficiency; when the parametric model deviates far from the true curve, the semiparametric estimate comes close to the nonparametric estimate and remains consistent. In the local semiparametric method, the weight is further allowed to vary according to the local fit of the models.

As a compromise between the global and local semiparametric estimators for the dose–response curve, the moving average semiparametric estimator takes the form of

$$p_{\pi(x_1,x_2)}(x,\hat{\boldsymbol{\theta}}) = \pi(x_1,x_2)p(x,\hat{\boldsymbol{\theta}}) + (1-\pi(x_1,x_2))\tilde{p}(x)$$

with a moving window (x_1, x_2) satisfying $x_{\min} \le x_1 < x_2 \le x_{\max}$. The corresponding weight can be obtained by minimizing the MISE over (x_1, x_2),

$$\mathrm{MISE}(p_{\pi(x_1,x_2)}(x,\hat{\boldsymbol{\theta}})) = \mathrm{E}\left[\int_{x_1}^{x_2}\{p_{\pi(x_1,x_2)}(x,\hat{\boldsymbol{\theta}}) - p(x)\}^2\mathrm{d}x\right].$$

For continuous outcomes, Mays et al. (2001) proposed another novel way to construct semiparametric estimates by mixing a parametric fit to the data with a nonparametric fit to the residuals from the parametric model. Their approach has the advantage that the resulting curve estimate may not always lie between the parametric and the nonparametric estimates. It would be interesting to extend their method to binary outcomes, which, however, becomes much more challenging because the residuals of a parametric fit (e.g., a probit or logit model) are neither normal nor binary. In addition, the minimizer of the MISE will not have a similar form as (3) and thus the asymptotic properties also need further investigation.

6. Supplementary Materials

Web Appendices A and B referenced in Section 2.1 are available under the Paper Information link at the *Biometrics* website `http://www.biometrics.tibs.org`.

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