Supplementary material to "Dynamic Calibration of Pharmacokinetic Parameters in Dose Finding Studies"

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Almost sure convergence to correct dose

The most practically useful tool for investigating operating characteristics is that of simulation. The methods are very easy to put into practice and the user can obtain a good idea on how things work by studying behaviour over a range of potential situations. Large sample properties are of lesser interest in view of the typically small to moderate sample sizes we usually deal with. Nonetheless, if large sample behaviour is erratic or unpredictable then the grounds for having confidence in finite sample behaviour becomes shaky.

It is important then to establish central statistical properties such as almost sure convergence of estimators for these models. We might feel that convergence in probability is not enough. On the other hand, almost sure convergence indicates that as sample size increases, we do better and better in some sense. Even so, both types of convergence, are large sample properties. We cannot appeal to the usual maximum likelihood theory since our models are usually miss-specified. First consider the situation when X takes continuous values and let (X, Y) be governed by the relation.

$$Y = \alpha + \beta X + \sigma\epsilon, \quad \alpha > 0, \beta > 0, X > 0. \tag{1}$$

In the extreme case where $\sigma = 0$, i.e., there are no errors, we can show that the next design value $\bar{x}_{n+1}$ lies strictly between $\bar{x}_n$ and ξ_0. If $\bar{x}_n > \xi_0$, then we can see that $\bar{x}_n - \xi_0$ is a decreasing sequence bounded below. It therefore has a limit and this limit can be seen to be 0. If $\bar{x}_n < \xi_0$, then we can see that $\bar{x}_n - \xi_0$ is an increasing sequence bounded above.

Again the sequence has a limit which can be seen to be 0. When $\sigma > 0$ we can refine this argument to show that $\bar{x}_n$ converges almost surely to ξ_0. Next, consider the situation when X takes only a finite number of values. This case is of more interest to us because, in practice, the design levels will often be restricted to a small finite range. Suppose these values are denoted by $d_1 <, \ldots, < d_k$. Let $(x_1, y_1), \ldots, (x_n, y_n)$ be the first n observations. After fitting an ordinary linear model without intercept to the data we can calculate $\theta/\hat{\beta}_n = \theta\bar{x}_n/\bar{y}_n$. The next design value x_{n+1} is chosen from $d_1 <, \ldots, < d_k$ so that it is the closest to $\theta\bar{x}_n/\bar{y}_n$. Consider an example in which the design variable X takes the following values: $1, 2, \ldots, 10$. The response variable Y is generated according to

$$Y = 2 + 0.5X + \sigma\epsilon.$$

Consider the case where $\sigma = 0$. Suppose that the target value for Y is taken as $\theta = 3$. Solving equation $3 = 2 + 0.5x$ gives $\xi_0 = 2$, the target level that we are trying to estimate. However, if we start with the wrong level $x_1 = 3$, which is one level above the target one, then we have $y_1 = 3.5$. The least squared estimate (without the intercept) of β is $\hat{\beta}_1 = 3.5/3 = 1.167$. To select the recommended level for the next experiment, we calculate $3/\hat{\beta}_1 = 3/1.167 = 2.564$. Therefore x_2 should be chosen as 3 instead of 2. It is easy to see that this process will continue and, at each step, level 3 will be the recommended level. Hence there will be no chance for the experiment to be carried out at the right level. A careful examination of the above model reveals that for this particular set of possible design values, the slope ($\beta = 0.5$) is too low or the regression line is too flat. Thus it is difficult to distinguish the effect of different levels in terms of their responses. Establishing consistency would require that the slope of the regression line be sufficiently large. This concept is now made precise but without loss of generality, we assume that the design values $d_1, \ldots, d_k$ satisfy: for some $\Delta > 0$, $d_{i+1} = d_i + \Delta, i = 2, \ldots, k$. Again, let ξ_0 be the target level, i.e., $\alpha + \beta\xi_0 = \theta$. Introduce the following condition:

$$\beta > \frac{\theta}{2d_1 + \Delta}. \tag{2}$$

When the condition is not met we would anticipate obtaining a level still close to the target but not necessarily the closest among those available. For instance, consider the case when $\beta \leq \theta/(2d_1 + \Delta)$, $d_2 = \xi_0 = d_1 + \Delta$ and the procedure stars with $x_1 = d_1$. We can even

assume that $\sigma = 0$. Then it is easy to show that

$$\frac{\theta d_1}{\alpha + \beta d_1} < d_1 + \frac{\Delta}{2},$$

which implies $x_2 = d_1$. Thus the procedure will stay at d_1 regardless of sample size. The design point converges to d_1 and not as we would hope to d_2. If we can assume the condition of Equation 2 then consistency will indeed follow as detailed below. The arguments lean on straightforward algebraic manipulation and are a little tedious. We first examine the extreme case when $\sigma = 0$, i.e., there is no error in the observations. The following lemma will be applied repeatedly.

Lemma 1 *Suppose that $\sigma = 0$ in (1). Assume that $(x_1, y_1), \ldots, (x_n, y_n)$ are generated according to (1) with $\sigma = 0$. Let $x_{n+1} = \theta \bar{x}_n / \bar{y}_n$ be the next design value.*
(i) If $\bar{x}_n > \xi_0$ then $\xi_0 < x_{n+1} < \bar{x}_n$, and therefore $\xi_0 < \bar{x}_{n+1} < \bar{x}_n$.
(ii) If $\bar{x}_n < \xi_0$ then $\bar{x}_n < x_{n+1} < \xi_0$, and consequently $\bar{x}_n < \bar{x}_{n+1} < \xi_0$.

Proof. We provide the proof for the first assertion only. The second assertion can be shown similarly. Note that when $\sigma = 0$, $\bar{y}_n = \alpha + \beta \bar{x}_n$. Thus $x_{n+1} \equiv \theta \bar{x}_n / (\alpha + \beta \bar{x}_n)$ is less than $\bar{x}_n$ if and only if $\alpha + \beta \bar{x}_n > \theta = \alpha + \beta \xi_0$, which follows from the assumption that $\bar{x}_n > \xi_0$ and that $\beta > 0$. This establishes the second inequality. The first inequality can be shown in the same way using the assumption that $\alpha > 0$. The implication of this lemma is that when $\sigma = 0$, the absolute value of $(\bar{x}_n - \xi_0)$ is decreasing and that all the $\bar{x}_n'$s stay at the same side of ξ_0 as does the starting value x_1. Without loss of generality, assume that $\bar{x}_n \geq \xi_0$ and $\bar{x}_n \downarrow \xi_1$. Then $\bar{y}_n \to \alpha + \beta \xi_1$. Since $x_{n+1} = \theta \bar{x}_n / \bar{y}_n$, we have $\xi_1 = \theta_0 \xi_1 / (\alpha + \beta \xi_1)$. Thus $\xi_1 = \xi_0$. In other words, $\bar{x}_n$ converges to ξ_0 when n tends to infinity. It is easy to see that this property is retained by x_n as well. Thus the consistency has been established for $\sigma = 0$. Next we consider the case that $\sigma > 0$.

Theorem 1 *Under the model $E(Y_j) = \phi(x_j) + \sigma \epsilon_j$ with $\sigma > 0$ and $\phi'(x) > 0$, let $x_1, \ldots, x_n$ be defined sequentially as above, then $x_n \to \xi_0$ almost surely.*

Proof. First, since $\phi'(x)$ exists and is positive, we replace, at x, the function $\phi(x)$ by $M(x)$. Define $\delta_n = n^{-1} \sum_{i=1}^n \epsilon_i$. Since $\epsilon_1, \ldots, \epsilon_n$ are i.i.d. samples with mean zero and a finite second moment, $\delta_n \to 0$ almost surely by the law of large numbers. Let A denote the subset of

the sample space, on which δ_n tends to zero. Then $P(A) = 1$. The following derivation is performed on the set A. Without loss of generality, we can assume that $\alpha + \delta_n > 0$ and $\delta_n/\beta << 1$. If $\bar{x}_n > \xi_0 - \delta_n/\beta$, then

$$\bar{y}_n = \alpha + \beta\bar{x}_n + \delta_n > \alpha + \beta(\xi_0 - \frac{\delta_n}{\beta}) + \delta_n = \alpha + \beta\xi_0 = \theta.$$

Thus $x_{n+1} \equiv \theta\bar{x}_n/(\alpha + \beta\bar{x}_n + \delta_n) < \bar{x}_n$. On the other hand, simple calculation reveals that:

$$\bar{x}_n \left\{ \alpha + \beta(\xi_0 - \frac{\delta_n}{\beta}) + \delta_n \right\} > (\xi_0 - \frac{\delta_n}{\beta})(\alpha + \beta\bar{x}_n + \delta_n)$$

by the assumption that $\alpha + \delta_n > 0$ and $\bar{x}_n > \xi_0 - \delta_n/\beta$. The above inequality reduces to

$$x_{n+1} = \frac{\theta\bar{x}_n}{\alpha + \beta\bar{x}_n + \delta_n} > \xi_0 - \frac{\delta_n}{\beta}.$$

Therefore

$$\xi_0 - \delta_n/\beta < \bar{x}_{n+1} < \bar{x}_n, \text{ when } \bar{x}_n > \xi_0 - \delta_n/\beta. \tag{3}$$

Similarly, it can be shown that

$$\bar{x}_n < \bar{x}_{n+1} \leq \xi_0 - \delta_n/\beta \quad \text{when } \bar{x}_n < \xi_0 - \delta_n/\beta. \tag{4}$$

Now suppose $\limsup_n \bar{x}_n = a$. Then $a \geq \xi_0$, or else there is a subsequence $\bar{x}_{n_k}$ which converges to $a < \xi_0$. Since $\delta_{n_k} \to 0$, $\bar{x}_{n_k} < \xi_0 - \delta_{n_k}/\beta$ for k sufficiently large, and thus $\bar{x}_{n_k+1} > \bar{x}_{n_k}$ by the above conclusion. Hence

$$a = \lim_k \bar{x}_{n_k} \leq \liminf_k \bar{x}_{n_k+1} \leq \limsup_k \bar{x}_{n_k+1} \leq \limsup_n \bar{x}_n = a.$$

This yields $\lim_k \bar{x}_{n_k+1} = a$. Since $\lim_k \bar{y}_{n_k} = \alpha + \beta a$, it then follows that $a = \lim_k \bar{x}_{n_k+1} = \theta a/(\alpha + \beta a)$, which implies that $a = \xi_0$, a contradiction. Thus we have shown that $a \geq \xi_0$. Next we shall establish that $a = \xi_0$. If $a > \xi_0$, define $\delta_0 = (a - \xi_0)/2 > 0$. There must exist N_0 such that for $n > N_0$, $|\delta_n| < \delta_0$. Therefore for $n_k > N_0$, $\bar{x}_{n_k} > \xi_0 + \delta_0 > \xi_0 - \delta_{n_k}/\beta$. By (3) again

$$\xi_0 - \frac{\delta_{n_k}}{\beta} < \bar{x}_{n_k+1} < \bar{x}_{n_k}.$$

If for each $i > 0$, $\bar{x}_{n_k+i} \geq a + \delta_0$ then

$$\bar{x}_{n_k+i} \geq \xi_0 - \frac{\delta_{n_k+i}}{\beta}, \text{ for all } i.$$

It follows that

$$\xi_0 - \frac{\delta_{n_k+1}}{\beta} < \bar{x}_{n_k+i+1} < \bar{x}_{n_k+i} \text{ for all } i > 0.$$

Therefore $\bar{x}_{n_k+1}$ is decreasing in i. Hence $\bar{x}_n$ is decreasing when $n > N_0$. Thus $\lim_n \bar{x}_n = a$ and it is easy to show that $a = \theta a/(\alpha + \beta a)$, which implies $a = \xi_0$, a contradiction. Hence there must exist an $i_0 > 0$ such that $\bar{x}_{n_k+i_0} < \xi_0 + \delta_0$. If $\bar{x}_{n_k+i_0} > \xi_0 - \delta_{n_k+i_0}/\beta$ then $\bar{x}_{n_k+i_0+1} < \bar{x}_{n_k+i_0} < \xi_0 + \delta_0$; if $\bar{x}_{n_k+i_0} \leq \xi_0 - \delta_{n_k+i_0}/\beta$ then

$$\bar{x}_{n_k+i_0} < \bar{x}_{n_k+i_0+1} \leq \xi_0 - \frac{\delta_{n_k+i_0}}{\beta} < \xi_0 + \delta_0.$$

In either case, $\bar{x}_{n_k+i_0+1} < \xi_0 + \delta_0$. In the same way, one can show that $\bar{x}_{n_k+i} < \xi_0 + \delta_0$ for all $i > i_0$. Letting $i = n_{k+1} - n_k$ yields $\bar{x}_{n_{k+1}} < \xi_0 + \delta_0$ which is again a contradiction. Thus we have shown that $a = \xi_0$. The same argument using (4) leads to $\liminf_n \bar{x}_n = \xi_0$. Similarly either or $\bar{x}_{n_k+2} < \xi_0 - \delta_{n_k+1}/\beta$, depending on whether $\bar{x}_{n_k+1} > \xi_0 - \delta_{n_k+1}/\beta$ or $\bar{x}_{n_k+1} < \xi_0 - \delta_{n_k+1}/\beta$. In either case, we have $\bar{x}_{n_k+2} < \xi_0 - \delta_0\beta$. Continuing this procedure, we conclude that for each i, $\bar{x}_{n_k+i} < \xi_0 - \delta_0/\beta$. This is impossible because, when $i = n_{k+1} - n_k$ it leads to $\bar{x}_{n_{k+1}} < \xi_0 - \delta_0/\beta$, violating the assumption that $\lim_k \bar{x}_{n_k} = a > \xi_0$. Therefore we have shown that $a = \xi_0$. Thus it follows that $\lim_n \bar{x}_n = \xi_0$ and hence $\lim_n \bar{y}_n = \theta$ and $\lim_n x_n = \xi_0$. Next we have:

Theorem 2 *Assume that the data are generated according to Model (1). Under condition (2), x_n is consistent.*

Proof. Define $\delta_n = n^{-1} \sum_i^n \epsilon_i$, which tends to zero almost surely. We first consider the situation where $d_1 \leq d_i \leq \bar{x}_n < d_{i+1} \leq \xi_0$ for some i. Write $\bar{x}_n = d_{i+1} - \delta_0$ where $\delta_0 > 0$. We would like to establish

$$\frac{\theta \bar{x}_n}{\alpha + \beta \bar{x}_n} - d_{i+1} > -\frac{\Delta}{2}, \tag{5}$$

because the above inequality would ensure that $x_{n+1} = d_{i+1}$ for n sufficiently large. Note that $\alpha + \beta \bar{x}_n = \alpha + \beta d_{i+1} - \beta \delta_0$. Since $\alpha + \beta d_{i+1} < \theta$, (5) would follow if

$$\theta(d_{i+1} - \delta_0) > (d_{i+1} - \frac{\Delta}{2})(\theta - \beta\delta_0),$$

which holds if and only if

$$\beta > \frac{\delta_0 - \frac{\Delta}{2}}{\delta_0} \frac{\theta}{d_{i+1} - \frac{\Delta}{2}} = \frac{2\delta_0 - \Delta}{\delta_0} \frac{\theta}{2d_{i+1} - \Delta}. \tag{6}$$

Note that $-\infty < (2\delta_0 - \Delta)/\delta_0 < 2 - \Delta/\delta_0 < 1$ and $d_{i+1} - \frac{\Delta}{2} > d_1$. Thus

$$\frac{2\delta_0 - \Delta}{\delta_0} \frac{\theta}{2d_{i+1} - \Delta} < \frac{\theta}{2d_1} < \beta.$$

Hence (6) and (5) hold. Since δ_n tends to zero almost surely, it follows from (5) that

$$\frac{\theta \bar{x}_n}{\bar{y}_n} = \frac{\theta \bar{x}_n}{\alpha + \beta \bar{x}_n + \delta_n} - d_{i+1} \geq -\frac{\Delta}{2},$$

which implies that $x_{n+1} = d_{i+1}$. Now we consider the situation in which $\bar{x}_n > \xi_0$. Suppose $\xi_0 \leq d_i \leq \bar{x}_n < d_{i+1}$, let $\Delta_1 = \bar{x}_n - d_i > 0$. It can be seen from (2) that

$$\beta > \frac{\theta}{2d_i + \Delta_1} > \frac{\Delta_1}{\Delta} \times \frac{\theta}{2d_i + \Delta_1}.$$

The above inequality leads to

$$\theta \bar{x}_n < (\theta + \beta\Delta_1)(d_i + \frac{\Delta_1}{2}) \leq (\alpha + \beta d_i + \beta\Delta_1)(d_i + \frac{\Delta_1}{2}) = (\alpha + \beta \bar{x}_n)(d_i + \frac{\Delta_1}{2}).$$

By the definition of Δ_1 and a simple calculation we conclude that when n becomes large enough,

$$\frac{\theta \bar{x}_n}{\alpha + \beta \bar{x}_n + \delta_n} < d_i + \frac{\Delta_1}{2} \leq d_i + \frac{\Delta}{2}.$$

Therefore if $\bar{x}_n$ is one level above $\xi_0 + \Delta$, then x_{n+1} must be at least one level lower than $\bar{x}_n$ if n is sufficiently large. Thus we have established that x_n converges to ξ_0 almost surely.

Simulated examples

The four pairs of figures (Figures 1 to 4) show four different situations corresponding to four different and arbitrary choices of the association between pharmacokinetic response and dose. In each case the targeted average pharmacokinetic response that is sought is 8.0. For illustration, a completely random sample of observations is shown in the left-hand panel. The dynamic calibration sampling described in this current work, targeting the value 8.0, is shown in the right hand figure. The initial value chosen for the log-dose is in all cases equal to 1.0 and the steps taken between dose increments, or decrements, cannot exceed the value 0.25.

A phenomenon, already observed in the more classical CRM setting (O'Quigley 2001), is that the more incorrect the initial guess of dose turns out to be, the better the algorithm

performs. At first this is puzzling but is easily explained. The method very quickly can detect that we are far below or far above the level we aim to be sampling at. Once we are sampling in the vicinity of the correct dose level, then it is much more difficult to "fine tune" the procedure since the natural variation that we are dealing with can often mask these smaller differences. Nonetheless, all the figures show that the sampling algorithm will quickly concentrate observations at and around the target level. Of course it would be difficult not to do better than simple random sampling and this is only presented for the purposes of illustration. The studies here worked with a fixed sample size. It ought be possible to introduce, if wished, some early stopping rule. For a fixed finite number of doses we could use the early stopping rule described in O'Quigley and Reiner (1998). For the situation of a continuum it might be possible to derive analogous rules based on the construction of intervals within which the responses are deemed to be approximately equivalent. This has yet to be studied.

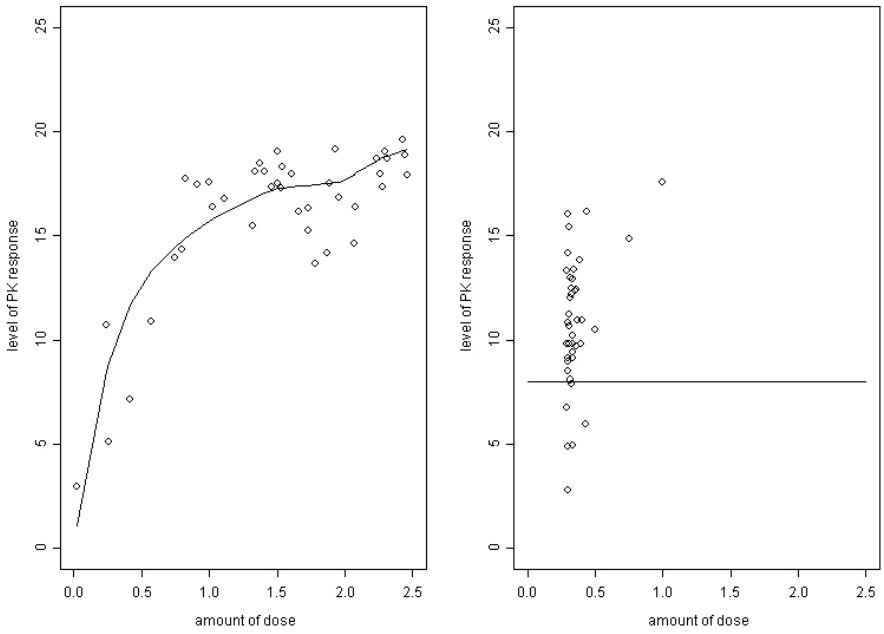

Figure 1: Left hand figure shows the true dose-response curve and random sampling of size 40. Right hand figure illustrates dynamic calibration targeting the value 8.0. The starting dose is 1.0 and step sizes constrained to be no greater than 0.25.

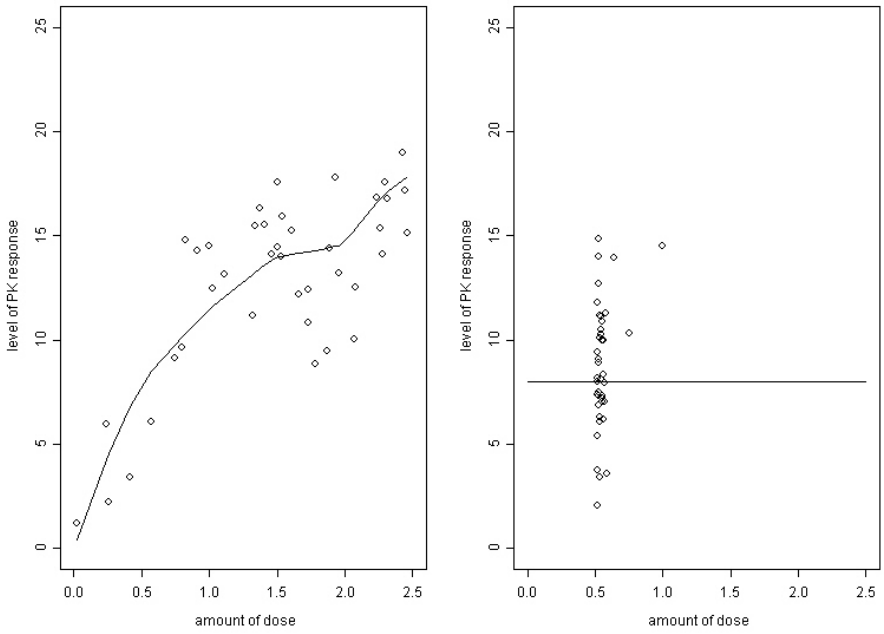

Figure 2: Left hand figure shows the true dose-response curve and random sampling of size 40. Right hand figure illustrates dynamic calibration targeting the value 8.0. The starting dose is 1.0 and step sizes constrained to be no greater than 0.25.

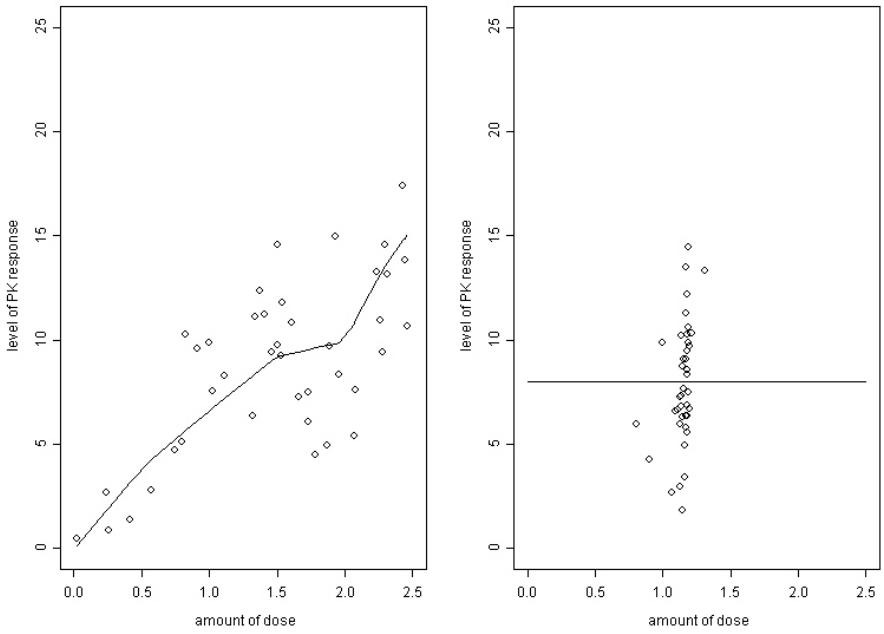

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Figure 3: Left hand figure shows the true dose-response curve and random sampling of size 40. Right hand figure illustrates dynamic calibration targeting the value 8.0. The starting dose is 1.0 and step sizes constrained to be no greater than 0.25.

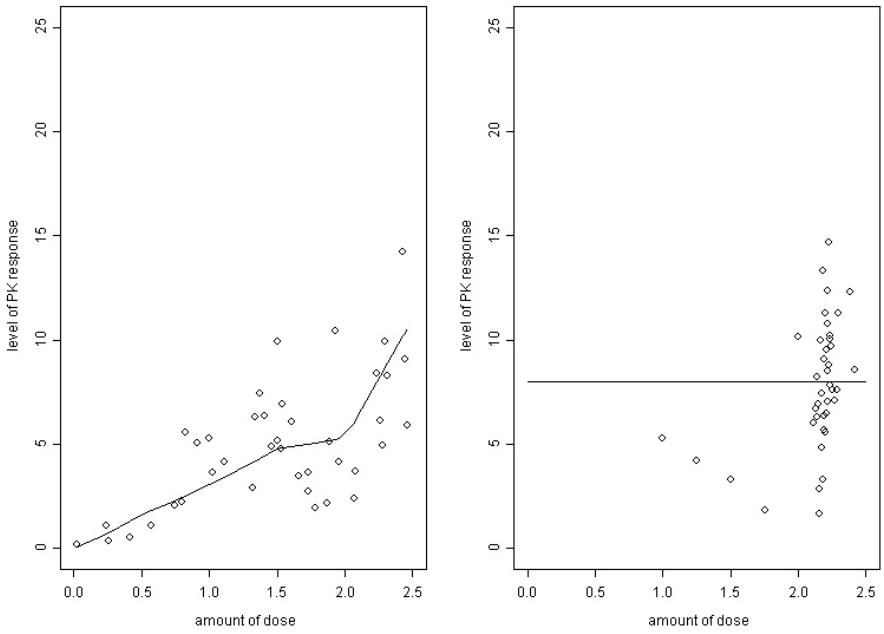

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Figure 4: Left hand figure shows the true dose-response curve and random sampling of size 40. Right hand figure illustrates dynamic calibration targeting the value 8.0. The starting dose is 1.0 and step sizes constrained to be no greater than 0.25.