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CONSISTENCY AND ASYMPTOTIC NORMALITY OF A MODIFIED LIKELIHOOD APPROACH CONTINUAL REASSESSMENT METHOD†

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ABSTRACT

The continual reassessment method (CRM) provides a Bayesian estimation of the maximum tolerated dose (MTD) in phase I clinical trials. The CRM has been proposed as an alternative design of the standard design. The CRM has been modified to improve practical feasibility and, recently, the likelihood approach CRM has been proposed. In this paper we investigate the consistency and asymptotic normality of the modified likelihood approach CRM in which the maximum likelihood estimate is used instead of the posterior mean. Small-sample properties of the consistency is examined using complete enumeration. Both the asymptotic results and their small-sample properties show that the modified CRML outperforms the standard design.

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1. INTRODUCTION

Phase I studies are experiments whose aim is to determine rapidly the maximum tolerated dose (MTD) of a new drug for use in a subsequent phase II trials. In the field of haematology and oncology, the studies are characterized by the high potential toxicity of a new drug at any dose required to be effective, so that they are conducted in patients. From ethical reason the number of patients should be minimized. Although the standard design is widely used in practice, much of the recent literature reports that the standard design has very poor operating characteristics compared with the continual reassessment method (Faries,

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1994; O'Quigley and Chevret, 1991; O'Quigley *et al.*, 1990; Goodman *et al.*, 1995; Moller, 1995; Ahn, 1998). One problem with the standard design is that many patients are treated at low dose levels. Another problem is the large variability of the estimated MTD around the true MTD. The major criticism of the standard design is that it has no interpretation as an estimate of the dose level which yields a specified toxicity rate. In particular, Kang and Ahn (2001) investigated this criticism extensively. They computed the expected toxicity rate at the MTD in the standard design by assuming three families of dose-toxicity functions (the logistic, hyperbolic tangent and power functions). They cautiously argued that the expected toxicity rate at the MTD in the standard design is between 17% and 21% if the dose-toxicity curve is S-shaped and the toxicity rates is very small in low dose levels. Their results shows inflexibility of the standard design well.

O'Quigley *et al.* (1990) proposed the continual reassessment method (CRM), in which reduces the number of patients treated with possibly ineffective dose levels. The starting dose of the CRM is selected to be the prior estimate of the MTD. When toxicity outcomes are known for successive patients, the dose-toxicity curve is updated and used to determine the dose at which to treat the next patient. A main advantage of the CRM is that, for a given target toxicity rate $0 < \theta < 1$, the toxicity rate at the MTD obtained from the CRM converges to θ as the sample size increases.

Although the CRM outperforms the standard design, the original CRM has some difficulties to be implemented in real practice. One of them is that it takes too long to complete the trial, because the CRM treat one patient at a time. Goodman *et al.* (1995) proposed the modified CRM that assigns more than one patient at a time to each dose level and limits the dose escalation one level. Another modification is that the starting dose of the modified CRM is the lowest dose level, not the prior estimate of the MTD. This modification makes clinicians more comfortable, probably because undertreating is viewed less seriously than overtreating. They showed that the modified CRM reduces the duration of the trial by 50–67 percent, reduces a toxicity incidence by 20–35 percent, and lowers toxicity severity from the original CRM.

Although the original and modified CRM have nice statistical properties, the two CRM are not widely used by clinicians, because clinicians are not familar with a Bayesian approach. O'Quigley and Shen (1996) proposed a new version of CRM, called likelihood approach CRM (CRML), in which the maximum likelihood estimate is used instead of the posterior mean. In this paper, we will introduce the modified CRML and investigate the consistency and asymptotic normality for the

maximum likelihood estimates in the modified CRML. In phase I clinical trials small-sample properties of a statistical procedure is very important, because the number of patients used in phase I clinical trials hardly exceeds 20. In this paper, especially, we investigate if the expected toxicity rate at the MTD converges to the target toxicity well in small-samples using complete enumeration. Since simulation has been used to investigate small-sample properties in phase I clinical trials, complete enumeration is a new research tool. With complete enumeration 150 hyperbolic tangent dose-toxicity functions are examined extensively.

2. Review

We review the modified likelihood approach CRM (CRML) with group inclusion which will be investigated in this paper. Let $x_1, x_2, \ldots, x_k$ denote the dose levels chosen for experiment. Let θ be the probability of toxic response corresponding to the aimed target dose level. Each cohort consists of three patients and let $\boldsymbol{Y_i}=(Y_{i1}, Y_{i2}, Y_{i3})$ $(i = 1, \ldots, n)$ be a random vector for the response of the i^{th} cohort. The binary random variable Y_{il}, $l = 1, 2, 3$, takes on 1 for toxic response and 0 for non-toxic response.

Let X take values $x_1, \ldots, x_k$ and stands for the dose level used for an experiment. We denote Y_{il} by Y for simplicity. We assume that the true dose-toxicity function generating the data is given by

$$P(Y = 1|X = x) = R(x).$$

In particular, let $R_j = P(Y = 1|X = x_j)$, $(j = 1, \ldots, k)$. We are interested in estimating the dose level x_0 at which $R(x_0)$ equals a target probability θ. However, $R(x_0)$ does not have to be equal to θ_0 exactly. It will be enough to find the dose level among $x_1, \ldots, x_k$ at which the toxicity probability is the closet to θ_0.

Consider some simple dose-response function for $E(Y)$ and denote this by $\Psi(x(i), a)$ where $x(i)$ denote the dose level chosen for the i^{th} cohort of three patient and a is an unknown parameter. The modified CRML is performed as follows.

1. A mathematical model $\Psi(x(i), a)$ for dose-toxicity is proposed (or assumed). The hyperbolic tangent has been employed in many studies (Faries, 1994; O'Quigley and Chevret, 1991; O'Quigley *et al.*, 1990; Goodman *et al.*, 1995;

Moller, 1995; Ahn, 1998).

$$\Psi(x(i), a) = \left(\frac{\tanh(x(i)) + 1}{2}\right)^a.$$

2. Define θ, aimed target toxicity level.

3. Assign the first cohort in the lowest dose level.

4. The likelihood will only have solutions at $a = 0$ or $a = \infty$ when all responses are either toxicities or nontoxicities. So we perform the standard design until we have a small set of heterogeneous responses. The standard design is described as follows. Three patients are assigned at the first dose. We proceed to the next higher dose level with a cohort of three patients until at least one patient experiences the toxicity. If we observe three toxicities at the first dose, we stop the trial, because in real practice dose levels are lowered for adjustment and a new trial is conducted.

   Suppose that we obtain heterogeneous responses in the m^{th} cohort.

5. The maximum likelihood estimate $\hat{a}_m$ of a is obtained using

$$(x(1), \ldots, x(m), \mathbf{Y_1}, \ldots, \mathbf{Y_m}).$$

6. Find a dose level which is closet to θ, *i.e.*,

$$\left\{x_l : |\Psi(x_l, \hat{a}_m) - \theta| = \min_{1 \le j \le k} |\Psi(x_j, \hat{a}_m) - \theta|\right\}.$$

   We take $x(m+1) = x_l$ in the original CRM. It sometimes allows the possibility of escalating more than one dose level after having treated a few patient at some low dose levels. This raises concern about whether patients will be treated at too toxic dose levels. In the modified CRML, a conservative approach is employed. Dosages can not increase by more than one level at a time, although there are no restrictions on dosage decreases. In other words,

$$x(m+1) = \begin{cases} x_{l^*+1}, & \text{if } l > l^* + 1, \\ x_l, & \text{if } l \le l^* + 1, \end{cases}$$

   where $x_{l^*} = x(m)$.

7. Assign the next cohort to the dose level $x(m+1)$ and observe $\boldsymbol{Y_{m+1}}$ and the likelihood is updated.

8. We repeat step 4, 5 and 6 until we reach a predetermined fixed sample size $3n$ (*i.e.*, n cohorts). The recommended dose is the dose which is determined in the step 6 of the last cohort.

To perform the above modified CRML, first, we need to obtain the likelihood. After we observe the n^{th} cohort, the likelihood is given as follows. Since the modified CRML is a sequential design, $x(2), x(3), \ldots, x(n)$ and $\boldsymbol{Y_1}$, $\boldsymbol{Y_2}$, $\ldots$, $\boldsymbol{Y_n}$ are random. $x(1)$ is constant, because $x(1)$ is the lowest dose level. Since X_i conditional on $(\boldsymbol{Y_1}, \ldots, \boldsymbol{Y_{i-1}}, x(1), \ldots, x(i-1))$ is deterministic and $\boldsymbol{Y_i}$ depends only on $x(i)$, not on previous outcomes or doses, we have

$$
\begin{aligned}
& P\left(\prod_{j=1}^{n} \boldsymbol{Y_j}, \prod_{j=1}^{n} x(j)\right) \\
&= P\left(\boldsymbol{Y_n} \,\middle|\, \prod_{j=1}^{n-1} \boldsymbol{Y_j}, \prod_{j=1}^{n} x(j)\right) \times P\left(x(n) \,\middle|\, \prod_{j=1}^{n-1} \boldsymbol{Y_j}, \prod_{j=1}^{n-1} x(j)\right) \times P\left(\prod_{j=1}^{n-1} \boldsymbol{Y_j}, \prod_{j=1}^{n-1} x(j)\right) \\
&= P\Big(\boldsymbol{Y_1}, x(1)\Big) \prod_{i=2}^{n} \left\{ P\left(\boldsymbol{Y_i} \,\middle|\, \prod_{j=1}^{i-1} \boldsymbol{Y_j}, \prod_{j=1}^{i} x(j)\right) \times P\left(x(i) \,\middle|\, \prod_{j=1}^{i-1} \boldsymbol{Y_j}, \prod_{j=1}^{i-1} x(j)\right) \right\} \\
&= P\Big(\boldsymbol{Y_1}, x(1)\Big) \prod_{i=2}^{n} P\left(\boldsymbol{Y_i} \,\middle|\, \prod_{j=1}^{i-1} \boldsymbol{Y_j}, \prod_{j=1}^{n} x(j)\right) \\
&= \prod_{i=1}^{n} P\Big(\boldsymbol{Y_i} \,\Big|\, x(i)\Big) \\
&= \prod_{i=1}^{n} \frac{3!}{y_i!(3-y_i)!} \Psi(x(i), a)^{y_i} \left\{1 - \Psi(x(i), a)\right\}^{3-y_i}
\end{aligned}
$$

where $y_i = \sum_{l=1}^{3} Y_{il}$.

3. Result

The modified CRML begins once we have observed some heterogeneity in the response. Define

$$
n_0 = \inf\left\{k : 0 < \sum_{i=1}^{k} y_i < 3k\right\}.
$$

Then n_0 is the first time that both toxicities and nontoxicities are observed and therefore the maximum likelihood estimate can be calculated.

Let

$$\Psi'(x,a) = \frac{\partial}{\partial a}\Psi(x,a).$$

For $k > n_0$, the maximum likelihood estimate $\hat{a}_k$ solves the equation

$$\sum_{i=1}^{k}\left\{y_i\frac{\Psi'}{\Psi}(x(i),a) + (3-y_i)\frac{-\Psi}{1-\Psi}(x(i),a)\right\} = 0.$$

We will show that $\hat{a}_k$ will converge to a_0 in the modified CRML where $\Psi(x_0,a_0) = \theta$.

For asymptotic results we need the following assumptions.

(C 1) For each a, function $\Psi(\cdot,a)$ is strictly increasing.

(C 2) Function $\Psi(x,\cdot)$ is continuous and is strictly monotone in a in the same direction for all x.

(C 3) For each $0 < t < 3$ and each x, the function

$$s(t,x,a) = t\frac{\Psi'}{\Psi}(x,a) + (3-t)\frac{-\Psi}{1-\Psi}(x,a)$$

is continuous and is strictly in a.

(C 4) The parameter a belongs to a finite interval $[A,B]$.

(C 5) The target dose level is x_0, that is, $R(x_0) = \theta$.

(C 6) The probabilities of toxicities at $x_1,\ldots,x_k$ satisfy $0 < R_1 < \cdots < R_k < 1$.

LEMMA 3.1. *If (C 6) holds, then* $P(n_0 < \infty) = 1$.

PROOF. Let $S_k = \sum_{i=1}^{k}\{y_i - 3R(x(i))\}$. Then S_k is a martingale from $E(y_i) = 3R(x(i))$. Since $y_i - 3R(x(i))$ is bounded, the limit theorem for martingale shows that $k^{-1}S_k$ tends to zero almost surely. From (C 6),

$$0 < \min_{1\le i\le k} 3R_i \le k^{-1}\sum_{i=1}^{k} 3R(x(i)) \le \max_{1\le i\le k} 3R_i < 3.$$

If we replace $k^{-1}\sum_{i=1}^{k} 3R(x(i))$ by $k^{-1}\sum_{i=1}^{k} y_i$, $1 \le \sum y_i \le 3(k-1)$ for sufficiently large n. It then follows that $P(n_0 < \infty) = 1$. □

The above lemma guarantees that it is possible to calculate the maximum likelihood estimate after a certain point.

We model the unknown true dose-toxicity function $R(x)$ with $\Psi(x, a)$. Since $R(x_0) = \theta$, x_0 is the dose level that we would like to find. Note that, from $\Psi(x_0, a_0) = \theta$, a_0 is the value of the parameter a with which $\Psi(x_0, a)$ produces the target toxic probability θ. Therefore, when $a = a_0$, ideally, we hope that $\Psi(x_i, a_0) = R_i$ for $i = 1, \ldots, k$. But, it is very unlikely for this to be true in real situation. In order to establish the asymptotic consistency, we need to require that the unknown true dose-toxicity function $R(x)$ is not too different from the assumed model $\Psi(x, a)$. We introduce the following set to characterize the difference

$$S = \{a : |\Psi(x_0, a) - R(x_0)| < |\Psi(x_i, a) - R(x_0)|, \text{ for all } x_i \neq x_0\}.$$

From (C 1)~(C 7), S is an open interval. We need the following extra condition to establish the asymptotic consistency.

(C 7) For $i = 1, \ldots, k$, $a_i \in S$.

THEOREM 3.1. *Under (C 1) to (C 7), for sufficiently large n, we have $\hat{a}_n \to a_0$ and $x(n+1) \to x_0$ almost surely, where $\hat{a}_n$ is the maximum likelihood estimate of the parameter a, and $x(n+1)$ is the recommended dose level for the next experiment when n patients finish experiments.*

PROOF. We assume that the first n experiments are conducted at $x(1)$, $x(2), \ldots, x(n)$ and the responses are $y_1, y_2, \ldots, y_n$. Let $I_n(a)$ be the loglikelihood.

$$I_n(a) = n^{-1} \sum_{i=1}^{n} \left\{ y_i \frac{\Psi'}{\Psi}(x(i), a) + (3 - y_i) \frac{-\Psi'}{1 - \Psi}(x(i), a) \right\}.$$

We will show that

$$\sup_{a \in [A,B]} |I_n(a) - \tilde{I}_n(a)| \to 0 \quad \text{as } n \to \infty \tag{3.1}$$

where

$$\tilde{I}_n(a) = n^{-1} \sum_{i=1}^{n} \left[3R(x(i)) \frac{\Psi'}{\Psi}(x(i), a) + \{3 - 3R(x(i))\} \frac{-\Psi'}{1 - \Psi}(x(i), a) \right].$$

Since for each dose level x_j, $(\Psi'/\Psi)(x_j, \cdot)$ and $[\Psi'/(1 - \Psi)](x_j, \cdot)$ are bounded and continuous in a over the finite interval $[A, B]$, the two functions are uniformly

continuous in a over $[A, B]$. Then for given $\epsilon > 0$ and for each x_j, we can take a partition $A = t_0 < t_1 < \cdots < t_k = B$ such that, for any $a \in [t_l, t_{l+1})$,

$$\left| \frac{\Psi'}{\Psi}(x_j, a) - \frac{\Psi'}{\Psi}(x_j, t_l) \right| < \epsilon, \qquad l = 0, 1, \ldots, k-1, \tag{3.2}$$

$$\left| \frac{\Psi'}{1-\Psi}(x_j, a) - \frac{\Psi'}{1-\Psi}(x_j, t_l) \right| < \epsilon, \qquad l = 0, 1, \ldots, k-1. \tag{3.3}$$

Since there are only m possible dose levels, we can take the partition such that (3.2) and (3.3) are valid for all x_j. We decompose $I_n(a) - \tilde{I}_n(a)$ into the sum of three pieces: $I_{n1}(a), I_{n2}$ and $I_{n3}(a)$, where

$$I_{n1}(a) = I_n(a) - \frac{1}{n} \sum_{i=1}^{n} \left\{ y_i \frac{\Psi'}{\Psi}(x(i), t_l) + (3 - y_i) \frac{-\Psi'}{1-\Psi}(x(i), t_l) \right\},$$

$$I_{n2} = \frac{1}{n} \sum_{i=1}^{n} \{ y_i - 3R(x(i)) \} \left\{ \frac{\Psi'}{\Psi}(x(i), t_l) + \frac{-\Psi'}{1-\Psi}(x(i), t_l) \right\},$$

$$\begin{aligned} I_{n3}(a) = \frac{1}{n} \sum_{i=1}^{n} \Bigg[& 3R(x(i)) \left\{ \frac{\Psi'}{\Psi}(x(i), t_l) - \frac{\Psi'}{\Psi}(x(i), a) \right\} \\ & + \{ 3 - 3R(x(i)) \} \left\{ \frac{-\Psi'}{1-\Psi}(x(i), t_l) - \frac{-\Psi'}{1-\Psi}(x(i), a) \right\} \Bigg]. \end{aligned}$$

From Eq. (3.2) and (3.3),

$$\begin{aligned} \sup_{a \in [A,B]} |I_{n1}(a)| &= \sup_{a \in [t_r, t_r+1)} |I_{n1}(a)| \qquad \text{for some } [t_r, t_r + 1) \text{ in the partition} \\ &\leq \frac{1}{n} \sum_{i=1}^{n} \{ y_i \epsilon + (3 - y_i) \epsilon \} = 3\epsilon. \end{aligned}$$

Similarly,

$$\sup_{a \in [A,B]} |I_{n3}(a)| \leq 3\epsilon.$$

For fixed t_l, $\{ n I_{n2} : n \geq 1 \}$ is a martingale. Since the terms in I_{n2} are bounded, I_{n2} converges to 0 almost surely from the limit theorem for martingales. Hence, we obtain (3.1).

Let S_1 denote the finite interval $[\min\{a_1, \ldots, a_k\}, \max\{a_1, \ldots, a_k\}]$. From (C 7), $S_1 \subset S$. Rewrite $\tilde{I}_n(a)$ as follows.

$$\tilde{I}_n(a) = \sum_{i=1}^{k} \frac{w_i}{n} \left\{ 3R(x_i) \frac{\Psi'}{\Psi}(x_i, a) + (3 - 3R(x_i)) \frac{-\Psi'}{1-\Psi}(x_i, a) \right\} \tag{3.4}$$

where $0 \leq w_i \leq n$ is the frequency that the level x_i has been used by the first n experiments. Since $\Psi(x_i, a_i) = R_i$, for each $1 \leq i \leq k$, (C 3) implies that

$$3R(x_i) \frac{\Psi'}{\Psi}(x_i, a_i) + (3 - 3R(x_i)) \frac{-\Psi'}{1-\Psi}(x_i, a_i) = 0. \tag{3.5}$$

Let $\tilde{a}_n$ be the solution to equation $\tilde{I}_n(a) = 0$. Since $\tilde{I}_n(\tilde{a}_n) = 0$ can be regarded as an weighted average of (3.5), from (C 2), $\tilde{a}_n$ must fall into the interval S_1. Since $S_1 \subset S$ and $\hat{a}_n$ solves $I_n(a) = 0$, (3.1) implies that $\hat{a}_n \in S$ almost surely for sufficiently large n. Then, $\hat{a}_n$ satisfies

$$|\Psi(x_0, \hat{a}_n) - \theta| < |\Psi(x_i, \hat{a}_n) - \theta|, \quad \text{for } i = 1, \ldots, k, \quad x_i \neq x_0.$$

Hence, $x(n+1) = x_0$ for sufficiently large n. Note that the change of deciding the next recommended dose level in finite sample does not influence on the asymptotic results. Hence, we start with the experiments with the ordinary CRM. That is, the next recommended dose level is the dose such that $(x_i - \Psi_{\hat{a}_n}^{-1})^2$ is minimized. After sufficiently large n, we add the constraint that dosages can not increase by more than one level at a time. However, this constraint does not change the asymptotic results, because $x(n+1) = x_0$ for sufficiently large n. So, $x(n+1) \to x_0$ as $n \to \infty$ in the modified likelihood approach CRM.

All w_i/n in (3.4) tends to zero as n goes to infinity, except one level which is the same as x_0. Thus, $\tilde{a}_n$, being the solution for (3.4), will converge to the solution of the following equation:

$$3R(x_0) \frac{\Psi'}{\Psi}(x_0, a) + (3 - 3R(x_0)) \frac{-\Psi'}{1-\Psi}(x_0, a) = 0.$$

Since a_0 is the solution of the above equation, $\hat{a}_n \to a_0$ as $n \to \infty$ from (3.1). This finishes the proof. □

THEOREM 3.2. *Under the conditions of Theorem 3.1,*

$$\sqrt{n}(\hat{a}_n - a_0) \xrightarrow{d} N(0, \sigma^2)$$

where $\sigma^2 = (\Psi'(x_0, a_0))^2 \theta_0(1-\theta_0)/3$ *and* $\hat{a}_n$ *is the maximum likelihood estimate of* a.

PROOF. Since there is only a finite number of dose levels, $x(n) = x_0$ for sufficiently large n. Thus the asymptotic distribution of $\hat{a}_n$ is the same as that of the solution of

$$\sum_{i=1}^{n} \left\{ y_i \frac{\Psi'}{\Psi}(x_0, a) + (3 - y_i) \frac{-\Psi'}{1 - \Psi}(x_0, a) \right\} = 0.$$

The asymptotic normality of $\hat{a}_n$ follows from standard theory of maximum likelihood estimators, because $(x_0, y_1), \ldots, (x_0, y_n)$ are independent and identically distributed. The asymptotic variance is given by

$$\begin{aligned}
\sigma^2 &= \left[\int \left\{ y \frac{\Psi'}{\Psi}(x_0, a_0) + (3 - y) \frac{-\Psi'}{1 - \Psi}(x_0, a_0) \right\}^2 dP \right]^{-1} \\
&= \left[\int \left\{ y \frac{\Psi'(x_0, a_0)}{\theta_0} + (3 - y) \frac{-\Psi'(x_0, a_0)}{1 - \theta_0} \right\}^2 dP \right]^{-1} \\
&= \left\{ \left(\frac{\Psi'(x_0, a_0)}{\theta_0} \right)^2 E(y^2) + \left(\frac{-\Psi'(x_0, a_0)}{1 - \theta_0} \right)^2 E(3 - y)^2 \right. \\
&\quad \left. + 2 \left(\frac{\Psi'(x_0, a_0)}{\theta_0} \right) \left(\frac{-\Psi'(x_0, a_0)}{1 - \theta_0} \right) E(3y - y^2) \right\}^{-1} \\
&= \frac{(\Psi'(x_0, a_0))^2 \theta_0 (1 - \theta_0)}{3} \qquad \text{from } y \sim B(3, \theta_0).
\end{aligned}$$

□

4. SMALL-SAMPLE PROPERTIES

First, we investigate $P(n_0 < \infty) = 1$. When R_i is the probability of toxicity at the dose level x_i, let $p_i = P(y_i = 1, 2 | R_i)$ and $q_i = P(y_i = 0, 3 | R_i)$. The probability of observing first heterogeneous responses in the i^{th} cohort is given by

$$p_i^* = \prod_{j=1}^{i-1} q_j p_i.$$

The probability that heterogeneous responses are observed among the first r cohorts in the standard design, that is, $\sum_{i=1}^{r} p_i^*$, is investigated by assuming the hyperbolic tangent function as the true dose-toxicity curve. Table 4.1 shows the results. As the number of cohort increases, the probability converges to 1 rapidly.

We investigate the expected toxicity rate at the MTD in the modified CRML, because it reflects the small-sample behavior of consistency. In most previous studies on CRM a few dose-toxicity curves were chosen and investigations were done by simulations. However, in this paper we employ an exact method based on complete enumeration. The exact method does not produce any sampling error which usually exists in simulation studies. Furthermore, since the computing time is saved with the exact method, hundreds of dose-toxicity curves that belong to the same family of increasing functions can be investigated within a few seconds. The maximum likelihood estimate $\hat{a}_k$'s are computed using IMSL. In this paper the hyperbolic tangent dose-toxicity functions are investigated, because the functions have been popular models in the investigation of CRM. The 20% and 30% toxicity rates are chosen. The number of cohort is restricted by 7, because $7 \times 3 = 21$ patients would be large enough for practical phase I cancer clinical trials. After we obtain the exact distribution of MTD based on complete enumeration, we compute the expected toxicity rate at the MTD and investigate how the expected toxicity rate at the MTD is close to the target toxicity rate. Since the number of cohort is restricted by 7, there are 4^7 all possible cases. It is straightforward to generate 4^7 all possible cases on computer and compute the maximum likelihood estimates and the next dose level.

The hyperbolic tangent and the logistic functions have been used frequently in studies of phase I clinical trials. Since the performance of the continual reassessment method in these two family of functions are similar in other studies (Kang and Ahn, 2001; Kang, 2002), in this paper we assume the hyperbolic tangent functions as the true dose-toxicity functions which are given by

$$\Psi(x_i, a) = \left(\frac{\tanh(x_i) + 1}{2}\right)^a$$

where $x_i = -1.4 + 0.25(i - 1)$, $1 \leq i \leq 7$, and a is the unknown parameter. The toxicity rates in each dose level are displayed in Table 4.2 when $a = 0.5, 0.75, 1.0, 1.5$ and 2.0. When $a = 0.5, 0.75, 1.0, 1.5$ and 2.0, the curves are plotted in the left corner of Figure 4.1. The curves have the almost identical shapes and are just shifted to the right as the value of a increases. The case of $a = 0.5$ represents a case of either toxicity that is too high even at low dose levels, or a dose level that is too high as an initial dose level. The case of $a = 2.0$ represents quite a steep dose-toxicity curve, but its toxicity rates never exceed those of $a = 0.5$. It is thought that the hyperbolic tangent dose-toxicity functions in the range of $0.05 \leq a \leq 2.0$ are large enough to cover most practical unknown dose-toxicity functions. The exact distribution of the MTD when $a = 0.5, 0.75, 1.0, 1.5$

and 2.0 are computed and presented in Table 4.3. The expected toxicity rate at the MTD is calculated for each value of $0.5 \leq a \leq 2.0$ with the increment of 0.01 and plotted in right corner of Figure 4.1. The broken and the solid lines correspond to 30% and 20% toxicity rate, respectively. As the value of a changes in the range of $0.5 \leq a \leq 2.0$, we can see that the expected toxicity rates at the MTD are pretty close to either 30% or 20%, respectively. From these results we can conclude that consistency of MLE in the modified CRML is well preserved in small samples.

TABLE 4.1 *The probabilities of heterogeneous responses*

number of	a				
cohorts	0.5	0.75	1.0	1.5	2.0
1	0.54	0.31	0.16	0.04	0.01
2	0.87	0.68	0.47	0.19	0.07
3	0.97	0.91	0.81	0.53	0.31
4	0.99	0.97	0.95	0.87	0.75
5	0.99	0.98	0.98	0.96	0.93
6	0.99	0.99	0.98	0.97	0.96
7	0.99	0.99	0.99	0.97	0.97

TABLE 4.2 *Toxicity rates of hyperbolic tangent functions*

$$\Psi(x_i; a) = \{(\tanh(x_i) + 1)/2\}^a$$

		a				
dose	x_i	0.5	0.75	1.0	1.5	2.0
1	−1.40	23.9	11.7	5.7	1.4	0.3
2	−0.90	37.7	23.1	14.2	5.3	2.0
3	−0.40	55.7	41.5	31.0	17.3	9.6
4	0.10	74.2	63.9	55.0	40.8	30.2
5	0.60	87.7	82.1	76.9	67.4	59.1
6	1.10	94.9	92.4	90.0	85.4	81.0
7	1.60	98.0	97.0	96.1	94.2	92.3

The major criticism of the standard design is that it has no interpretation as an estimate of the dose level which yields a specified toxicity rate. The results in this paper show that the toxicity rate at the MTD decided by the modified CRML converges to the predetermined toxicity rate as the sample size increases. Furthermore, the property holds well even in small samples. These results show clearly that the modified CRML outperform the standard design.

TABLE 4.3 *Exact distribution of MTD (hyperbolic tangent functions)*($\theta = 0.3$)

$$\Psi(x_i; a) = \{(\tanh(x_i) + 1)/2\}^a$$

		a				
dose	x_i	0.5	0.75	1.0	1.5	2.0
1	−1.40	45.8	6.8	0.1	0.0	0.0
2	−0.90	44.5	45.5	18.1	0.1	0.0
3	−0.40	9.4	43.5	63.4	36.1	10.7
4	0.10	0.3	4.2	18.3	59.4	73.8
5	0.60	0.0	0.0	0.1	4.3	15.4
6	1.10	0.0	0.0	0.0	0.1	0.1
7	1.60	0.0	0.0	0.0	0.0	0.0

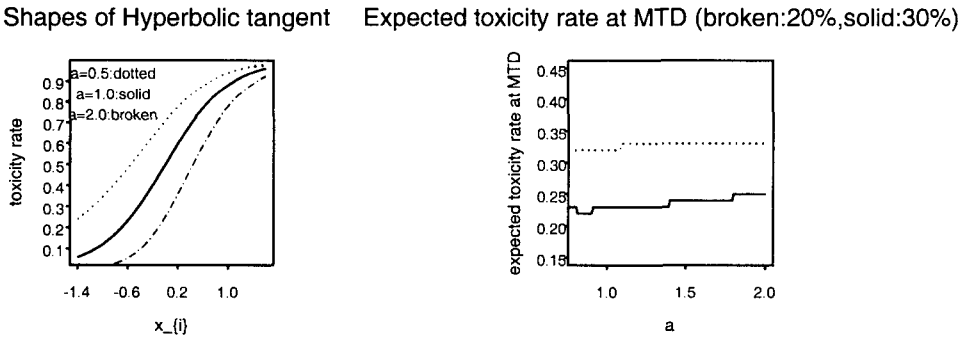

FIGURE 4.1 *Shapes of hyperbolic tangent functions and expected toxicity rate at MTD*

In the continual reassessment method there are two main approaches. One is the Bayesian approach to use the posterior mean and the other is the likelihood approach to use the maximum likelihood estimate. Small-sample properties are good for the two approaches as shown in this paper and Kang (2002). It has not been studied yet which approach is better. In my opinion at this moment it is a personal choice depending on whether the investigator perfers either Bayesian approach or frequentist approach. It could be an interesting future study to compare the Bayesian approach and the likelihood approach.

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