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Boundary Crossing Random Walks, Clinical Trials and Multinomial Sequential Estimation.

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Abstract: A sufficient condition for the uniqueness of multinomial sequential unbiased estimators is provided generalizing a classical result for binomial samples. Unbiased estimators are applied to infer the parameters of multidimensional or multinomial Random Walks which are observed until they reach a boundary. Clinical trials are shown to be representable within this scheme and an application to the estimation of the multinomial probabilities following multinomial clinical trials is presented.

Keywords: Absorbed random walks; Clinical trials; Killed random walks; Sequential multinomial estimation; Unbiased estimates.

Subject Classifications: 62L12; 62M05

1. INTRODUCTION

Stochastic processes are often used to model the behavior of some phenomena which is observed up to the first crossing of a threshold level. It is the case of neuronal modeling, population dynamics, ruin probabilities... (just to mention a few). Sequential parametric inference is needed to calibrate such models in order to obtain good fits with experimental data and specific maximum likelihood methods have been recently presented (Bibbona and Ditlevsen 2010) when the underlying process is a discretely observed diffusion. In many cases Random Walks (RWs) might be used as toy models for such phenomena and estimation methods that accounts for the presence of barriers can be of help. Moreover, as we shall see, data from a clinical trial can be interpreted as a trajectory of a suitable RW that came with a stopping boundary and such estimation methods can be applied. If the increments of the RW are independent Bernoulli random variables, then a classical result in binomial sequential estimation (Girshick, Mosteller, and Savage 1946) may be applied to find an unbiased estimator. In Savage (1947) (updating other references quoted therein) a sufficient condition for the uniqueness of the unbiased estimator is found. To a RW on a higher dimensional lattice or any other RW whose increments have k possible outcomes with probabilities $p_1 \cdots p_k$, a generalization of the above result still applies. Indeed in Koike (1993) and Kremers (1990) unbiased

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sequential estimation is extended to the multinomial context, but a sufficient condition for the uniqueness of the unbiased estimators is no longer available. The present paper fills this gap and presents a few examples where unbiased estimation is applied to multidimensional or multinomial boundary crossing RWs. An application of sequential estimation of the multinomial probabilities that deserve a special attention is that following a phase II multistage clinical trial (Zee, Melnychuk, Dancey, and Eisenhauer 1999) where patients are classified according to their response to a treatment. Group sequential multinomial designs recently attracted a lot of attention for application in cancer research (Zee et al. 1999, Kocherginsky, Cohen, and Karrison 2009, Freidlin, Dancey, Korn, Zee, and Eisenhauer 2002, Dent, Zee, Dancey, Hanauske, Wanders, and Eisenhauer 2001, Goffin, Pond, and Tu 2011). Their use has been recommended by the Task Force on Methodology for the Development of Innovative Cancer Therapies of the the NDDO Research Foundation (Booth, Calvert, Giaccone, Lobbezoo, Eisenhauer, and Seymour 2008). A short account on how multinomial unbiased estimation can be used in such setting concludes the paper and the explicit expression of the estimators is derived for a specific design. Further relevant results related to the main topic can be found in Bhat and Kulkarni (1966) regarding efficient multinomial sampling plans, in Sinha and Sinha (1992) for a review of the binomial case and in Sinha, Das, and Mukhoti (2008) for generalizations to the quasi-binomial context.

2. UNBIASED MULTINOMIAL SEQUENTIAL ESTIMATION

We consider a repeated experiment having k possible outcomes occurring with probabilities $p_1 \cdots p_k$. Denote by $X_n = (x_n^1, \dots, x_n^k)$ the process whose components $x_n^i \in \mathbb{N}$ count how many occurrences of events of type i we had at the n -th (independent) repetition. The process X_n lives in the hyper-plane where the sum of the coordinates is n . Denoting by $S_n \subset \mathbb{R}^k$ the portion of such plane where all the coordinates are positive or null (cf. Figure 1) and $S_n^{\mathbb{N}}$ the set of points in S_n with natural coordinates, for any n we have $X_n \in S_n^{\mathbb{N}}$.

Let X_n be observed until it reaches the boundary B of an accessible region $R \subset \mathbb{N}^k$ (we mean those points which are not in R but that might be reached in one step starting from R).

For every point $y \in B$ with coordinates (y_1, \dots, y_k) let us denote by $k(y)$ the number of paths in R that start at the origin and end in y and by $k_i^*(y)$ the number of those that end in y but start in the point whose i -th coordinate is 1 and the others are 0. The probability that the first hitting to the boundary occurs in y is

$$\mathbb{P}(y) = k(y) p_1^{y_1} \cdots p_k^{y_k}. \quad (1)$$

The region R is defined to be *closed* if $\sum_{y \in B} \mathbb{P}(y) = 1$.

Theorem 2.1 ((Koike 1993)). *For any closed region R , the ratios*

$$\hat{p}_i(y) = \frac{k_i^*(y)}{k(y)} \quad (2)$$

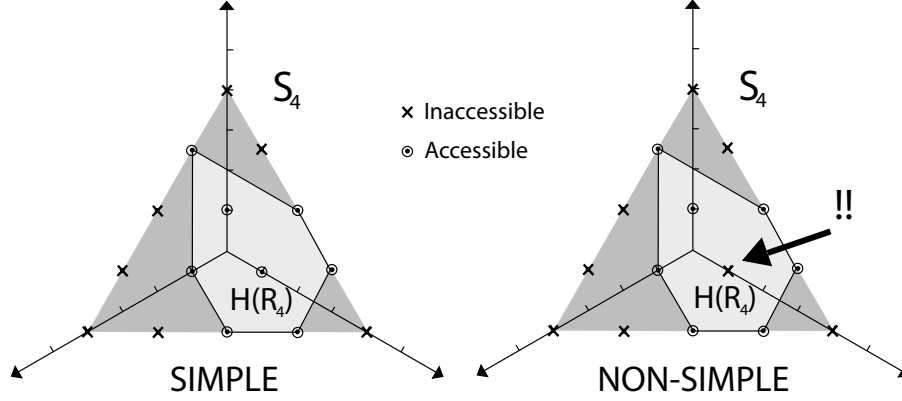


Figure 1: The triangle S_4 is illustrated in grey and accessible and inaccessible points of two different regions are plotted with different markers. The convex hull of the accessible points of order 4 is colored in a lighter gray. In the right plot it contains an inaccessible point, thus the corresponding accessible region is not simple

are unbiased estimators for the probabilities p_i .

A necessary and sufficient condition on the region R for the estimator (2) to be the unique bounded unbiased estimator for the binomial ($k=2$) probability is given in Savage (1947). We are going to generalize the sufficient condition to the multinomial context. For any n the region $R \in \mathbb{N}^k$ and its boundary B project onto $S_n^{\mathbb{N}}$ defining the accessible points of order n , $R_n = R \cap S_n^{\mathbb{N}}$, the inaccessible points $S_n^{\mathbb{N}} - R_n$ and (among them) the boundary points $B_n = B \cap S_n^{\mathbb{N}}$. R is said to be a *simple* region if for any n the convex hull $H(R_n)$ of R_n does not contain inaccessible points. In Figure 1 the definition of a simple region is illustrated.

Theorem 2.2. *If the region $R \subset \mathbb{N}^k$ is simple and closed, the estimators (2) are the unique bounded unbiased estimators of the parameters p_i .*

We adapt the method in Savage (1947), but we need the following Lemma (obvious when $k = 2$) that will be proved after the main theorem.

Lemma 2.3. *Let R be a simple region, and n an order such that in $S_n^{\mathbb{N}}$ there are both accessible and boundary points. Among any collection of boundary points $C_n \subset B_n$ it is always possible to choose a $\bar{y} \in C_n$ and a $(k-2)$ -hyperplane $\pi_{\bar{y}}$ lying in the $(k-1)$ -hyperplane that contains S_n such that*

1. $\bar{y} \in \pi_{\bar{y}}$
2. $\pi_{\bar{y}}$ is identified by two linear equations

$$\begin{cases} L(x) = m_1x_1 + \dots + m_kx_k = b \\ x_1 + \dots + x_n = n \end{cases} \quad (3)$$

where $m_i \in \mathbb{N}$, one vanishing and at least one non-vanishing, and $b \in \mathbb{N}$.

3. on R_n we have $L(x) \geq b + 1$

4. at any other boundary point $y \in C_n$, we have $L(y) \geq b + 1$

Proof of Theorem 2.2. If the theorem were false we would have another unbiased estimator \hat{U} of p_i and the difference $\Delta = \hat{p}_i - \hat{U}$ would be a non-identically vanishing unbiased estimate of zero. Since the first boundary point y hit by the process is a sufficient statistics (Ferguson 1967, Section 7.3, Lemma 1), we restrict to those estimators that are function of it and $\mathbb{E}(\Delta) = \sum_{y \in B} \Delta(y) \mathbb{P}(y) = 0$. Let m be the smallest integer such that Δ is not vanishing at one element of B_m . If $R_m = \emptyset$ for such m then the region R is finite and the thesis follows from Theorem 4 in Kremers (1990). If instead $S_m^{\mathbb{N}}$ contains accessible points we apply Lemma 2.3 to the collection C_m of boundary points $y \in B_m$ such that $\Delta(y) \neq 0$ and find a point \bar{y} and a linear combination $L(x) = m_2 x_2 + \dots + m_k x_k$ (for notational convenience we stipulate that the vanishing coefficient is the first one) with $m_i \in \mathbb{N}$ such that $L(\bar{y}) = b$ and that for any $z \in C_m \cup R_m$ we have $L(z) \geq b + 1$. A fortiori $L(y) \geq b + 1$ at any y in any B_n with $n > m$ since any such a y may only be reached evolving from an $x \in R_m$. For some positive Δ^* we have

$$|\Delta(\bar{y})| k(\bar{y}) p_1^{\bar{y}_1} \dots p_k^{\bar{y}_k} = \left| \sum_{y: \begin{cases} L(y) \geq b+1 \\ \Delta(y) \neq 0 \end{cases}} \Delta(y) \mathbb{P}(y) \right| \leq \Delta^* \sum_{y: \begin{cases} L(y) \geq b+1 \\ \Delta(y) \neq 0 \end{cases}} \mathbb{P}(y). \quad (4)$$

We are going to show that there are values of the parameters at which such inequality cannot hold. By construction any path from the origin to an $y \in B$ such that $\Delta(y) \neq 0$ and $L(y) \geq b + 1$ either ends in C_m or crosses R_m . In $R_m \cup C_m$ we have a finite number F of points $z^1 \dots z^F$ and there $L(z^i) \geq b + 1$. For any $y \in B$ such that $\Delta(y) \neq 0$ and $L(y) \geq b + 1$ we have

$$\mathbb{P}(y) = \mathbb{P}(y | R_m \cup C_m) \mathbb{P}(R_m \cup C_m) = \mathbb{P}(y | R_m \cup C_m) \sum_{s=1}^F k(z^s) p_1^{z_1^s} \dots p_k^{z_k^s} \quad (5)$$

Let us now choose the parameters $p_2 \dots p_k$ in such a way that for some common factor $0 < p < 1$ we have $p_i = p^{m_i}$ for any $i = 2 \dots k$. We get

$$\mathbb{P}(y) \leq \mathbb{P}(y | R_m \cup C_m) p^{b+1} \sum_{s=1}^F k(z^s)$$

and inequality (4) becomes

$$p^b |\Delta(\bar{y})| k(\bar{y}) p_1^{\bar{y}_1} \leq \Delta^* p^{b+1} \sum_{s=1}^F k(z^s) \cdot \sum_{y: \begin{cases} L(y) \geq b+1 \\ \Delta(y) \neq 0 \end{cases}} \mathbb{P}(y | R_m \cup C_m) \leq \Delta^* p^{b+1} \sum_{s=1}^F k(z^s)$$

that is always violated when p is small enough. \square

Proof of Lemma 2.3. Existence of an y' and of a $\pi_{y'}$ satisfying conditions 1. and 3. with rational coefficients in (3) is ensured by the Separating Hyperplane theorem (Ferguson 1967, Sec. 2.7), and the density of \mathbb{Q} in \mathbb{R} . To get natural coefficients in (3) it is then sufficient to multiply the first equation by a suitable integer and to add to it the second equation a sufficient number of times. Let us denote by $L'(x) = b'$ the new equation of $\pi_{y'}$ meeting the first three conditions. Condition 4. may still not be fulfilled by $\pi_{y'}$. Let us denote by $c \leq b'$ the minimum value taken by L' on C_n and let us consider the plane π_c with first equation $L'(x) = c$. If it intersects C_n in one and only one point we have found both the point and the plane satisfying condition 4. If $C_n \cap \pi_c$ contains more than one point, let us select one with the following algorithm. Start with the last coordinate x_n and select the points in $C_n \cap \pi_c$ where x_k is largest. Among them choose those at which x_{k-1} is largest and continue until the choice of the largest j -th coordinate singles out one and only one point \bar{y} of $C_n \cap \pi_c$. Now consider the plane $\pi_{\bar{y},r}$ with first equation

$$L_r(x) = L'(x) - \frac{1}{r}x_1 - \frac{1}{r^2}x_2 - \cdots - \frac{1}{r^k}x_k = c - \frac{1}{r}\bar{y}_1 - \frac{1}{r^2}\bar{y}_2 - \cdots - \frac{1}{r^k}\bar{y}_k = b_r. \quad (6)$$

Of course $\pi_{\bar{y},r}$ still passes through \bar{y} , and equation (6), once multiplied by r^k , has integer coefficients. Moreover, since R_n is finite and since $L(x) - b > 0$ for any $x \in R_n$, we can take r large enough to ensure both that $L_r(x) - b_r > 0$ for every $x \in R_n$ and that the coefficients are natural. The same argument applies to the points in $C_n - \pi_c$. Moreover for any $y \in C_n \cap \pi_c$ we have

$$L_r(y) - b_r = \frac{1}{r}(\bar{y}_1 - y_1) + \frac{1}{r^2}(\bar{y}_2 - y_2) + \cdots + \frac{1}{r^k}(\bar{y}_k - y_k)$$

which is certainly positive due to the algorithm we used to select \bar{y} . \square

3. EXAMPLES

In the following examples we derive the unbiased estimators for some multidimensional or multinomial RWs observed up to the crossing of a boundary.

3.1. RWs on a bidimensional lattice

Let W_i be a RW on \mathbb{Z}^2 such that $W_0 = 0$ and $W_i = W_{i-1} + I_i$ where the increments I_i take the values (0,1), (1,0), (0,-1) and (-1,0) with probabilities p_1, p_2, p_3 and $1 - \sum_{i=1}^3 p_i$. Let W_i be observed up to the first time its second component equals $b > 0$. The process $X_n = (x_n^1, \dots, x_n^4)$ whose components x_n^i count how many occurrences of increments of type i we had at the n -th step of the RW is of the kind described in Section 2. and it is observed until it hits $B = \{x \in \mathbb{N}^4 : x_1 - x_3 = b\}$. The accessible region is closed whenever $p_1 \geq p_3 > 0$ and simple. The maximum likelihood (ML) estimators of the p_i are X_N^i/N , while the unique unbiased estimators (2) are

$$\hat{p}_1 = \frac{b-1}{b} \cdot \frac{X_N^1}{N-1}, \quad \hat{p}_2 = \frac{X_N^2}{N-1}, \quad \hat{p}_3 = \frac{b+1}{b} \cdot \frac{X_N^3}{N-1}$$

	ML estimators			Unbiased estimators		
	mean	sd	m.s.e.	mean	std	m.s.e.
$p_1 = 0.4$	0.436	0.081	0.0078	0.400	0.080	0.0063
$p_2 = 0.15$	0.148	0.045	0.0020	0.150	0.046	0.0020
$p_3 = 0.3$	0.268	0.078	0.007	0.200	0.087	0.008
$p_1 = 0.7$	0.727	0.123	0.016	0.701	0.130	0.017
$p_2 = 0.1$	0.095	0.072	0.005	0.101	0.077	0.006
$p_3 = 0.1$	0.084	0.085	0.007	0.098	0.098	0.010

Table 1: Results of inference on a simulated sample of RWs on a bidimensional lattice stopped as soon as their second component reaches the threshold value $b = 10$.

The trajectory count is based on the reflection principle (Feller 1971).

The results of a simulation study performed on 10.000 paths are shown in Table 1. The performances of the two methods are not much different and the best choice depends on the parameter range. When p_1 is close to p_3 some of the unbiased estimators have a smaller mean square error than the corresponding ML, while when p_1 is higher ML estimates are better. Let us remark that the estimates of parameters p_2 and p_4 , in the direction on which the RW is not constrained, are estimated much better than the other two.

3.2. A simple RW allowing for null steps

Let W_i be a RW on \mathbb{Z} such that $W_0 = 0$ and $W_i = W_{i-1} + I_i$ where the increments I_i are 1, 0 or -1 with probabilities p_1, p_2 and $1 - \sum_{i=1}^2 p_i$. Still we count the increments by $X_n = (x_n^1, \dots, x_n^3)$. W_i is observed up to the first time it equals $b > 0$ and X_i until $X_1 - X_3 = b$. The accessible region is simple and whenever $p_1 \geq p_3 > 0$ also closed. ML estimators are again the sample proportions, and the unbiased ones are

$$\hat{p}_1 = \frac{b-1}{b} \cdot \frac{X_N^1}{N-1} \quad \hat{p}_2 = \frac{X_N^2}{N-1}.$$

4. SEQUENTIAL MULTINOMIAL ESTIMATION AND CLINICAL TRIALS

In a classical binomial multistage phase II clinical trial (Jennison and Turnbull 2000, Chapter 12) a group of patients is treated with a new drug and classified into *responders* vs. *non-responders*. If the number of responders is high enough, the drug is considered as potentially active and phase III studies are started. If instead the number of responders is too low, the trial is stopped and the drug is no longer considered. In the intermediate case when the number of respondent patients lies between the thresholds, a further group of patients is enrolled to accumulate more data and a new stopping rule is applied to the second stage. When the trial is terminated a further analysis of the data is often carried on: point (or interval) estimation of the response probability is of interest, for ex-

ample, for an initial comparison with that of other treatments and in order to optimize the design of phase III studies (Jennison and Turnbull 2000, Chapters 8 and 12). In Jung and Kim (2004) the estimation of the response probability after a multistage binomial phase II clinical trial is directly addressed. Maximum likelihood estimators are shown to be biased and an unbiased estimator is derived which is nothing but the explicit expression of (2) once the design is specified. The efficiency of the two methods are compared showing that for some values of the parameter maximum likelihood outperform unbiased estimation, in other ranges the opposite is true. This is in perfect agreement with our results of Section 3.

Recently multinomial phase II clinical trials attracted a lot of attention for their application in cancer research (Zee et al. 1999, Kocherginsky et al. 2009, Freidlin et al. 2002, Dent et al. 2001, Goffin et al. 2011) and their use has been recommended by the Task Force on Methodology for the Development of Innovative Cancer Therapies of the the NDDO Research Foundation (Booth et al. 2008). In this setting, indeed, a finer classification of the responses is needed since even when the cancer is not reduced but its dimension is kept stationary it might indicate that the drug is active (it has a cytostatic effect). After a first group of patients are treated with the new therapy, they are classified as *responders* if tumor shrinkage is more than 50%, *non-responders* if it is less and *early progressions* if they undergo a progress in the disease. The design proposed in Zee et al. (1999) is the following. Let K be the maximum number of stages allowed and n_s for $s = 1 \cdots K$ the number of patients enrolled in each stage. We denote by $N_s = \sum_{i \leq s} n_i$ the number of patients involved up to the s -th stage. The process $X_j = (r_j, j - r_j - e_j, e_j)$ counts the number of respondent, non-respondent and early progressions among the first j patients. For any $j \neq N_s$ the trial is continued, but when $j = N_s$ for some $s < K$ there are three options:

1. the trial is stopped and the therapy considered *promising* if $r_{N_s} \geq \rho_s^P$ and $e_{N_s} \leq \epsilon_s^P$ and such stopping region is denoted by $B_{N_s}^P$
2. the trial is stopped and the therapy considered *ineffective* if $r_{N_s} \leq \rho_s^I$ and $e_{N_s} \geq \epsilon_s^I$ and such stopping region is denoted by $B_{N_s}^I$
3. the trial is continued to stage $s + 1$ in any other case and the continuation region is denoted by R_{N_s} .

The stopping regions involved in such multinomial design are illustrated in Figure 2.

Estimation of the probability of response and early progressions after such trials is again of interest, but it has not been addressed yet. It is our aim to make available a couple of unbiased estimator that render formula (2) explicit for such a design. Let us fix the following notation: the trial ends at a random stage $S \leq K$ with a final observation $X_{N_S} = (r, N_S - r - e, e)$. Estimators (2)

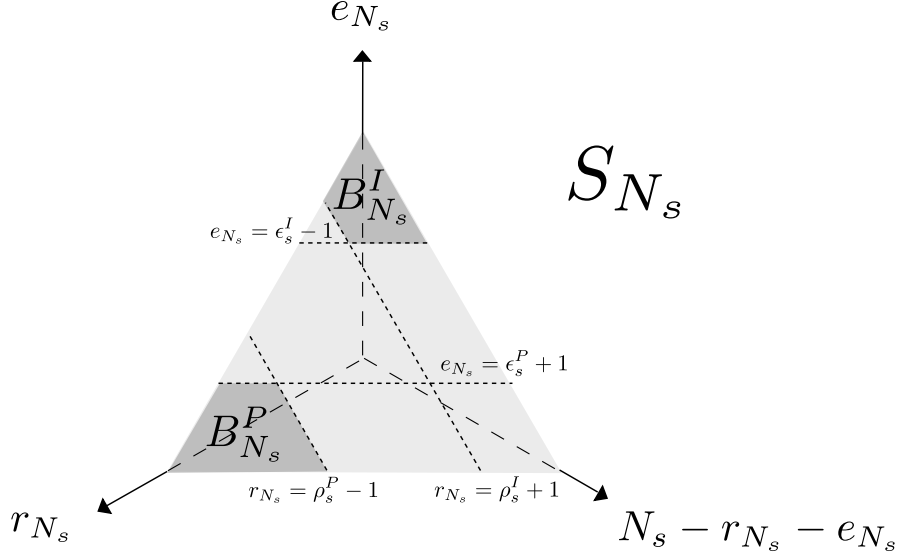


Figure 2: At every step N_s when the s -th stage is ended the trial is stopped for futility at the region $B_{N_s}^I$ while it is stopped for activity in $B_{N_s}^P$. The light grey region is the convex hull of the continuation region, that in general is not a simple region.

are

$$\hat{p}_1(r, N_S - r - e, e) = \frac{\sum_{R_{N_1}} \sum_{R_{N_2}} \cdots \sum_{R_{N_{S-1}}} \binom{n_1-1}{r_{N_1}-1, y_1, e_{N_1}} \binom{n_2}{r_{N_2}, y_2, e_{N_2}} \cdots \binom{n_S}{r_{N_S}, y_S, e_{N_S}}}{\sum_{R_{N_1}} \sum_{R_{N_2}} \cdots \sum_{R_{N_{S-1}}} \binom{n_1}{r_{N_1}, y_1, e_{N_1}} \binom{n_2}{r_{N_2}, y_2, e_{N_2}} \cdots \binom{n_S}{r_{N_S}, y_S, e_{N_S}}}$$

$$\hat{p}_3(r, N_S - r - e, e) = \frac{\sum_{R_{N_1}} \sum_{R_{N_2}} \cdots \sum_{R_{N_{S-1}}} \binom{n_1-1}{r_{N_1}, y_1, e_{N_1}-1} \binom{n_2}{r_{N_2}, y_2, e_{N_2}} \cdots \binom{n_S}{r_{N_S}, y_S, e_{N_S}}}{\sum_{R_{N_1}} \sum_{R_{N_2}} \cdots \sum_{R_{N_{S-1}}} \binom{n_1}{r_{N_1}, y_1, e_{N_1}} \binom{n_2}{r_{N_2}, y_2, e_{N_2}} \cdots \binom{n_S}{r_{N_S}, y_S, e_{N_S}}}$$

where $\binom{n}{r, y, e}$ denotes the multinomial coefficient $\frac{n!}{r!y!e!}$ and the sums are performed over the triples (r_{N_i}, y_i, e_{N_i}) belonging to the continuation regions R_{N_i} with $i < S$. Let us remark that the continuation region is in general not a simple one (cf. Figure 2) and estimators (2) might not be the unique bounded unbiased estimators for the multinomial probabilities, nevertheless they are unbiased.

5. CONCLUSIONS

The main mathematical result of the paper is to prove that simplicity of the accessible region R is a sufficient condition to ensure the uniqueness of the unbiased estimators (2). Of course the availability (and the uniqueness) of unbiased estimators does not mean that they are the best way to estimate the parameters and the simulation study performed on RWs in Sec. 3. shows that

there are both parameter ranges where the unbiased estimators are superior than ML and vice-versa. The bias of the ML estimators, moreover, can be reduced as in Whitehead (1986) or by bootstrapping and the best method to be used needs to be decided case by case. Multinomial clinical trials provide an important application of the method presented.

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