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Power and sample size determination for a stepwise test procedure for finding the maximum safe dose

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Abstract

This paper addresses the problem of power and sample size calculation for a stepwise multiple test procedure (SD2PC) proposed in Tamhane et al. [2001. Multiple test procedures for identifying the maximum safe dose. J. Amer. Statist. Assoc. 96, 835–843] to identify the maximum safe dose of a compound. A general expression for the power of this procedure is derived. It is used to find the minimum overall power and minimum power under the constraint that the dose response function is bounded from below by a linear response function. It is shown that the two minima are attained under step and linear response functions, respectively. The sample sizes necessary on the zero dose control and each of the positive doses to guarantee a specified power requirement are calculated under these two least favorable configurations. A technique involving a continuous approximation to the sample sizes is used to reduce the number of quantities that need to be tabled, and to derive the asymptotically optimal allocation of the total sample size between the zero dose and the positive doses. An example is given to illustrate use of the tables. Extensions of the basic formulation are noted.

MSC: 62J15; 62K99

Keywords: Design of dose–response experiments; Multiple testing; Multivariate normal distribution; Toxicology

1. Introduction

In Tamhane et al. (2001) (referred to as TDGW hereafter) we proposed three step-down (SD) multiple test procedures (labeled there as SD1PC, SD2PC and SD1HC) to find the maximum safe

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dose (MAXSD) of a compound in relation to a zero dose control. These procedures control the type I familywise error rate (FWE), which is the probability of declaring *any* unsafe dose as safe, at a specified level α. In TDGW we investigated the power properties of the proposed procedures via simulation. In this paper we derive analytical expressions for the power of SD2PC (which is a preferred procedure for the reasons explained in the sequel). We use these expressions to calculate the sample sizes necessary to guarantee a specified power requirement.

Practical applications of the MAXSD approach were described in TDGW. This problem arises in toxicology experiments to evaluate safety of agricultural compounds where efficacy is not a concern. The MAXSD approach was motivated in the first author's collaborations with scientists from DuPont.

The outline of the paper is as follows. In Section 2, we define the notation and formulate the problem. The SD2PC procedure is briefly reviewed in Section 3. An expression for its power is derived in Section 4. This expression is used to find the minimum overall power and minimum power under the constraint that the dose response function is bounded from below by a linear response function. It is shown that the two minima are attained under step and linear response functions, respectively. The exact discrete optimization problem of finding the smallest total sample size under these two least favorable configurations to guarantee a specified power requirement is stated and solved in Section 5. A continuous approximation to this problem for the minimum overall power is stated and solved in Section 6. The solution from the continuous approximate problem is used as an initial solution for the numerical search of the corresponding exact discrete optimum. The continuous problem is also useful for deriving asymptotically optimal allocation of the sample sizes between the zero dose control and positive doses. An example is given in Section 7. Finally, some extensions of the basic formulation are noted in Section 8. An evaluation of the derivative of the power function needed in the continuous optimization problem is given in the Appendix.

2. Problem formulation

We assume the usual homoscedastic normal theory one-way layout model with increasing doses denoted by $0, 1, \ldots, k$, where 0 is the zero dose (control). The unknown dose means are denoted by μ_i and the unknown common error variance by σ^2. A smaller μ_i (e.g., a lower yield of a crop contaminated by a herbicide) is assumed to represent a more toxic response. The case where a larger μ_i represents a more toxic response can be handled analogously.

We take n_i observations, y_{ij} $(1 \leqslant j \leqslant n_i)$, on dose i and compute the sample means $\overline{y}_i$ and the pooled sample variance s^2 based on $\nu = \sum_{i=0}^{k} n_i - (k+1)$ degrees of freedom (df). The corresponding random variables $\overline{Y}_i$ and S^2 are distributed independently as $\mathrm{N}(\mu_i, \sigma^2/n_i)$ and $\sigma^2\chi^2_\nu/\nu$, respectively.

We regard a dose as *unsafe* if it causes a decrease in mean yield below a specified percentage (say, 10%) of the mean yield μ_0 at the zero dose level. More generally, we regard the ith dose as *unsafe* if $\mu_i \leqslant \lambda\mu_0$ and as *safe* if $\mu_i > \lambda\mu_0$ where $\lambda < 1$ is specified, e.g., $\lambda = 0.90$ for a 10% decrease in the mean yield compared to μ_0. The maximum safe dose (MAXSD) for specified λ is defined as

$$\mathrm{MAXSD} = \max\{i : \mu_j > \lambda\mu_0 \ \forall j \leqslant i\}. \tag{2.1}$$

If a larger μ_i represents a more toxic response then $\lambda > 1$. In that case, doses with $\mu_i \geqslant \lambda\mu_0$ are regarded as unsafe and those with $\mu_i < \lambda\mu_0$ are regarded as safe. The MAXSD is defined as

$\text{MAXSD} = \max\{i : \mu_j < \lambda\mu_0 \ \forall j \leqslant i\}$. Note that the above definition assumes that μ_0 is > 0. This is a reasonable assumption in most practical problems as the measurements are positive. If necessary, a preliminary test could be performed to check it.

We want to guarantee that the probability that *any* unsafe dose is declared safe is no more than a specified constant α. If $\widehat{\text{MAXSD}}$ denotes the estimated MAXSD then this requirement translates to

$$P\{\widehat{\text{MAXSD}} > \text{MAXSD}\} \leqslant \alpha. \tag{2.2}$$

Now consider the family of hypothesis testing problems

$$\text{H}_{0i} : \mu_i \leqslant \lambda\mu_0 \quad \text{vs.} \quad \text{H}_{1i} : \mu_i > \lambda\mu_0 \quad (1 \leqslant i \leqslant k). \tag{2.3}$$

Here H_{0i} states that the ith dose is unsafe and H_{1i} states that the ith dose is safe. After testing the hypotheses we set $\widehat{\text{MAXSD}} = \max\{i : \text{H}_{0j} \text{ is rejected } \forall j \leqslant i\}$. The error probability requirement (2.2) is satisfied if we control the type I FWE at level α:

$$\text{FWE} = P\{\text{Any true } \text{H}_{0i} \text{ is rejected}\} \leqslant \alpha \tag{2.4}$$

for the family of hypotheses (2.3).

It was shown in Section 8 of TDGW that this requirement is satisfied if the null hypotheses in (2.3) are tested in a step-down (SD) manner beginning with H_{01}; if it is rejected then test H_{02} and so on, each at level α, which is what SD2PC does. On the other hand, SD1PC and SD1HC test $\bigcap_{j=i}^{k} \text{H}_{0j} \subseteq \text{H}_{0i}$ in a step-down manner, each at level α. Under the assumption of monotonicity, $\mu_0 \geqslant \mu_1 \geqslant \cdots \geqslant \mu_k$, we have $\text{H}_{0i} = \bigcap_{j=i}^{k} \text{H}_{0j}$. Therefore, SD1PC and SD1HC procedures also control (2.2). However, if the means are not monotone then only SD2PC controls this requirement as shown by Bauer (1997).

In the present paper we restrict attention to the SD2PC procedure because (i) as noted above, it is valid even if the dose–response function is non-monotone, (ii) simulation studies reported in TDGW showed that SD2PC generally has high power, especially under the linear dose–response function, although its power can be very low under the step response function when the MAXSD is high, (iii) it is very easy to apply and explain to a practitioner, and (iv) it can be readily extended to non-normal setups, where statistics such as Mann–Whitney may be used for comparing each dose with the zero dose control.

Specification of the power requirement for the hypothesis testing problem (2.3) entails specification of two constants, δ $(0 < \delta < 1 - \lambda)$ and $1 - \beta$ $(\alpha < 1 - \beta < 1)$. In analogy with definition (2.1) of MAXSD, we specify the power requirement as follows:

$$P\left\{\text{Reject all false } \text{H}_{0i} \text{ with } \min_{j \leqslant i} \mu_j \geqslant (\lambda + \delta)\mu_0\right\} \geqslant 1 - \beta. \tag{2.5}$$

Under monotonicity, this is equivalent to a more stringent requirement in which $\min_{j \leqslant i} \mu_j$ is replaced by μ_i. As an example, suppose $\lambda = 0.90$, $\delta = 0.05$ and $1 - \beta = 0.80$. Then any dose with mean $\mu_i > 0.90\mu_0$ is safe, but we want to guarantee that all consecutive doses with means $\mu_i \geqslant 0.95\mu_0$ are declared safe with probability at least 0.80.

We note that Horn and Vollandt (2002) have done sample size calculations for a similar setting but for a formulation that uses an additive threshold constant in contrast to our multiplicative constant λ.

3. SD2PC procedure

The SD2PC procedure is a SD testing procedure based on pairwise contrasts, $\overline{y}_i - \lambda\overline{y}_0$ $(1 \leqslant i \leqslant k)$. The corresponding t-statistics are

$$t_i = \frac{\overline{y}_i - \lambda\overline{y}_0}{s\sqrt{1/n_i + \lambda^2/n_0}} \quad (1 \leqslant i \leqslant k).$$

SD2PC uses an α-level t-test at each step, beginning with the test of H_{01}. Thus it rejects H_{01} if $t_1 > t_{\nu,\alpha}$, where $t_{\nu,\alpha}$ is the upper α critical point of Student's t with ν df, and goes on to test H_{02}. If H_{01} is not rejected then testing stops and it is concluded that $\widehat{\text{MAXSD}} < 1$, i.e., dose 1 itself is not proven safe. In general, if $H_{01}, H_{02}, \ldots, H_{0i}$ have been tested and rejected and if $i < k$ then $H_{0,i+1}$ is tested next and rejected if $t_{i+1} > t_{\nu,\alpha}$; otherwise testing stops and it is concluded that $\widehat{\text{MAXSD}} = i$.

4. Power of SD2PC procedure

Suppose that $\mu_i \geqslant (\lambda + \delta)\mu_0$ for $1 \leqslant i \leqslant m$ and $\mu_i < (\lambda + \delta)\mu_0$ for $i > m$, so that effectively m is the MAXSD as far as the power requirement (2.5) is concerned, which is then

$$P\{\text{Reject } H_{0i} \text{ for } i = 1, 2, \ldots, m\} \geqslant 1 - \beta. \tag{4.1}$$

To write the power expression, introduce the following notation:

$$Z_i = \frac{\overline{Y}_i - \lambda\overline{Y}_0 - (\mu_i - \lambda\mu_0)}{\sigma\sqrt{1/n_i + \lambda^2/n_0}} \quad (1 \leqslant i \leqslant k) \quad \text{and} \quad U = \frac{S}{\sigma}.$$

Further let

$$\lambda_i = \frac{\mu_i}{\mu_0} \quad \text{and} \quad r_i = \frac{n_0}{n_i} \quad (1 \leqslant i \leqslant k).$$

Then $Z_1, Z_2, \ldots, Z_k$ have a k-variate standard normal distribution with correlations

$$\rho_{ij} = \text{Corr}(Z_i, Z_j) = \frac{\lambda^2}{\sqrt{(r_i + \lambda^2)(r_j + \lambda^2)}} = \tau_i\tau_j \quad (1 \leqslant i \neq j \leqslant k), \tag{4.2}$$

where

$$\tau_i = \frac{\lambda}{\sqrt{r_i + \lambda^2}} \quad (1 \leqslant i \leqslant k),$$

and $U = S/\sigma \sim \sqrt{\chi^2_\nu/\nu}$ independent of the Z_i's. In other words, $T_i = Z_i/U$ $(1 \leqslant i \leqslant k)$ have a central k-variate t-distribution with the above correlation structure and ν df. Then, for fixed

m $(1 \leqslant m \leqslant k)$, the power expression (4.1) is given by

$$
\begin{aligned}
& P\left\{\frac{\overline{Y}_i - \lambda \overline{Y}_0}{S\sqrt{1/n_i + \lambda^2/n_0}} > t_{\nu,\alpha}\ (1 \leqslant i \leqslant m)\right\} \\
&= P\left\{\frac{Z_i}{U} > t_{\nu,\alpha} - \frac{\mu_i - \lambda\mu_0}{S\sqrt{1/n_i + \lambda^2/n_0}}\ (1 \leqslant i \leqslant m)\right\} \\
&= P\left\{Z_i > t_{\nu,\alpha} U - \frac{(\lambda_i - \lambda)(\mu_0/\sigma)}{\sqrt{1/n_i + \lambda^2/n_0}}\ (1 \leqslant i \leqslant m)\right\} \\
&= \int_0^\infty P\left\{-Z_i \leqslant -t_{\nu,\alpha} u + \frac{(\lambda_i - \lambda)(\mu_0/\sigma)}{\sqrt{1/n_i + \lambda^2/n_0}}\ (1 \leqslant i \leqslant m)\right\} h_\nu(u)\,\mathrm{d}u, \qquad (4.3)
\end{aligned}
$$

where

$$
h_\nu(u) = \frac{2(\nu/2)^{\nu/2}}{\Gamma(\nu/2)} u^{\nu-1} \exp(-\nu u^2/2), \quad u \geqslant 0
$$

denotes the p.d.f. of $U \sim \sqrt{\chi^2_\nu/\nu}$. Put

$$
c_i(u) = -t_{\nu,\alpha} u + \frac{(\lambda_i - \lambda)(\mu_0/\sigma)}{\sqrt{1/n_i + \lambda^2/n_0}} \quad (1 \leqslant i \leqslant m).
$$

Then noting that the $-Z_i$'s have the same joint distribution as the Z_i's, and by exploiting the product correlation structure in (4.2), we can express the m-variate normal probability in the last step of (4.3) as a univariate iterated integral (see Eq. (1.1a) in Appendix 3 of Hochberg and Tamhane (1987)) leading to the following expression for power:

$$
\int_0^\infty \left\{\int_{-\infty}^\infty \prod_{i=1}^m \Phi\left[\frac{\tau_i z + c_i(u)}{\sqrt{1-\tau_i^2}}\right] \phi(z)\,\mathrm{d}z\right\} h_\nu(u)\,\mathrm{d}u, \qquad (4.4)
$$

where $\Phi(\cdot)$ and $\phi(\cdot)$ are, respectively, the c.d.f. and the p.d.f. of the standard normal distribution.

4.1. Minimum overall power

From symmetry considerations, we will assume that the experiment is designed with $n_1 = n_2 = \cdots = n_k = n$ (say). Let $n_0/n = r$. Suppose that the dose response function satisfies

$$
\mu_i \geqslant (\lambda + \delta)\mu_0, \quad 1 \leqslant i \leqslant m \quad \text{and} \quad \mu_{m+1} < (\lambda + \delta)\mu_0.
$$

Then, since (4.4) is increasing in the λ_i, its minimum for fixed m $(1 \leqslant m \leqslant k)$ is attained when $\mu_i = (\lambda + \delta)\mu_0$ for $i = 1, \ldots, m$. Thus the step response function is least favorable. Furthermore,

the minimum over m is attained when $m = k$ and it depends on δ and μ_0/σ only through their product, denoted by $\eta = \delta(\mu_0/\sigma)$. This minimum power is given by

$$P_k(n_0, n, \lambda, \eta) = \int_0^\infty \left\{ \int_{-\infty}^\infty \Phi^k \left[\frac{\tau z + c(u)}{\sqrt{1-\tau^2}} \right] \phi(z)\, \mathrm{d}z \right\} h_\nu(u)\, \mathrm{d}u, \tag{4.5}$$

where we have put

$$c(u) = -t_{\nu,\alpha} u + \frac{\eta}{\sqrt{1/n + \lambda^2/n_0}} \quad \text{and} \quad \tau = \frac{\lambda}{\sqrt{r+\lambda^2}}. \tag{4.6}$$

4.2. Minimum power under linear lower bound on the dose response function

Suppose that the dose response function is bounded below by a linear function:

$$\mu_i \geqslant \mu_0 - i\xi \quad (1 \leqslant i \leqslant k)$$

for some $\xi > 0$. For fixed $m (1 \leqslant m \leqslant k)$ consider the restricted parameter space $\Omega = \bigcup_{m=1}^k \Omega_m$, where

$$\begin{aligned} \Omega_m = \{ \boldsymbol{\mu} = (\mu_0, \mu_1, \ldots, \mu_k) : \mu_i &\geqslant \mu_0 - i\xi \geqslant (\lambda+\delta)\mu_0 \ (1 \leqslant i \leqslant m), \\ \mu_{m+1} &< (\lambda+\delta)\mu_0 \}. \end{aligned}$$

It is readily seen that for $\boldsymbol{\mu} \in \Omega_m$, power (4.3) is minimized when $\mu_i = \mu_0 - i\xi$ and ξ is as large as possible, i.e.,

$$\xi = \frac{\{1 - (\lambda+\delta)\}\mu_0}{m}.$$

(The values of μ_i for $i > m$ are irrelevant.) Thus the linear response function is least favorable in this case. Then the power expression becomes

$$\begin{aligned} &P\left\{ -Z_i \leqslant -t_{\nu,\alpha} U + \frac{\{(1-\lambda) - [1-(\lambda+\delta)](i/m)\}(\mu_0/\sigma)}{\sqrt{1/n + \lambda^2/n_0}} \ (1 \leqslant i \leqslant m) \right\} \\ &\quad = \int_0^\infty \left\{ \int_{-\infty}^\infty \prod_{i=1}^m \Phi[b_{i,m}(z,u)] \phi(z)\, \mathrm{d}z \right\} h_\nu(u)\, \mathrm{d}u, \end{aligned} \tag{4.7}$$

where

$$b_{i,m}(z,u) = \frac{\tau z + c_{i,m}(u)}{\sqrt{1-\tau^2}} \quad (1 \leqslant i \leqslant m)$$

and

$$c_{i,m}(u) = -t_{\nu,\alpha} u + \frac{\{(1-\lambda) - [1-(\lambda+\delta)](i/m)\}(\mu_0/\sigma)}{\sqrt{1/n + \lambda^2/n_0}} \quad (1 \leqslant i \leqslant m).$$

Since $i/m \leqslant (i+1)/(m+1)$, it follows that for every fixed (z, u), $b_{i,m}(z,u) \geqslant b_{i+1,m+1}(z,u)$. Hence

$$\prod_{i=1}^{m} \Phi[b_{i,m}(z,u)] \geqslant \prod_{i=1}^{m} \Phi[b_{i+1,m+1}(z,u)] = \prod_{i=2}^{m+1} \Phi[b_{i,m+1}(z,u)] \geqslant \prod_{i=1}^{m+1} \Phi[b_{i,m+1}(z,u)].$$

Thus (4.7) is minimized when $m = k$. The final minimum power expression for the linear response function depends on both δ and (μ_0/σ), and is given by

$$P_k(n_0, n, \lambda, \delta, \mu_0/\sigma) = \int_0^{\infty} \left\{ \int_{-\infty}^{\infty} \prod_{i=1}^{k} \Phi\left[\frac{\tau z + c_{i,k}(u)}{\sqrt{1-\tau^2}} \right] \phi(z)\, \mathrm{d}z \right\} h_\nu(u)\, \mathrm{d}u, \tag{4.8}$$

where τ is as defined in (4.6) and

$$c_{i,k}(u) = -t_{\nu,\alpha} u + \frac{\{(1-\lambda) - [1-(\lambda+\delta)](i/k)\}(\mu_0/\sigma)}{\sqrt{1/n + \lambda^2/n_0}} \quad (1 \leqslant i \leqslant k).$$

To evaluate (4.8), the quantity μ_0/σ, which is the inverse of the coefficient of variation for the zero dose, needs to be specified or at least a lower bound on it. (To evaluate (4.5), only the product $\eta = \delta(\mu_0/\sigma)$ needs to be specified.) The larger the coefficient of variation, the smaller the power and hence the larger the sample size needed to guarantee a specified power requirement.

5. Exact discrete optimization problem

The exact optimization problem to be solved is the following: For given k and specified λ, δ, (μ_0/σ), α and $1-\beta$,

$$\text{Minimize } N = n_0 + kn \text{ subject to (4.5) or (4.8)} \geqslant 1-\beta.$$

As noted before, in case of the overall minimum power given by (4.5), one need not specify δ and (μ_0/σ) separately, but only $\eta = \delta(\mu_0/\sigma)$. One can use numerical search to solve this optimization problem. However, it can be very time consuming and laborious. Numerical search can be accelerated if we know the optimum value of the ratio $r = n_0/n$ because then we only need to find the smallest N so that the expression (4.5) or (4.8) is $\geqslant 1-\beta$. This is an easy trial and error exercise because the minimum power is a strictly increasing function of N.

In the next section we find the optimum value of r by solving an approximate continuous problem for the overall minimum power case. (The constrained minimum under a linear response lower bound case could be studied analogously, but it is analytically far more involved.) This continuous approximation also has the advantage that it obviates the need to compute N (and associated n_0 and n) for each specified value of $\eta = \delta(\mu_0/\sigma)$; rather it is only necessary to compute a quantity γ defined in (6.1) and the associated r. We are also able to study the asymptotic behavior of optimum r and show that $r \to \lambda\sqrt{k}$ (which is a simple extension of Dunnett's (1955) square root allocation rule) as $\gamma \to \infty$. The optimum r found by solving the approximate continuous problem is used as a starting solution for numerical search to find the exact discrete optimum solution to the optimization problem. The corresponding optimum sample sizes are given in Tables 1 and 2

Table 1
Exact (discrete) optimum sample sizes for step response ($\alpha = 0.05$)

k	$1-\beta$	η	λ	N	n_0	n	r
3	0.70	0.25	0.75	762	210	184	1.141
			0.80	790	229	187	1.225
			0.85	819	246	191	1.288
			0.90	848	263	195	1.349
		0.50	0.75	192	54	46	1.174
			0.80	199	58	47	1.234
			0.85	206	62	48	1.292
			0.90	213	66	49	1.347
	0.80	0.25	0.75	917	260	219	1.187
			0.80	952	283	223	1.269
			0.85	987	303	228	1.329
			0.90	1023	327	232	1.409
		0.50	0.75	231	66	55	1.200
			0.80	240	72	56	1.286
			0.85	248	77	57	1.351
			0.90	258	84	58	1.448
	0.90	0.25	0.75	1159	337	274	1.230
			0.80	1204	367	279	1.315
			0.85	1249	394	285	1.382
			0.90	1296	426	290	1.469
		0.50	0.75	292	85	69	1.232
			0.80	303	93	70	1.329
			0.85	315	99	72	1.375
			0.90	326	107	73	1.466
4	0.70	0.25	0.75	1038	250	197	1.269
			0.80	1072	268	201	1.333
			0.85	1106	290	204	1.422
			0.90	1141	309	208	1.486
		0.50	0.75	261	65	49	1.327
			0.80	269	69	50	1.380
			0.85	278	74	51	1.451
			0.90	287	79	52	1.519
	0.80	0.25	0.75	1230	306	231	1.325
			0.80	1272	332	235	1.413
			0.85	1314	358	239	1.498
			0.90	1357	385	243	1.584
		0.50	0.75	309	77	58	1.328
			0.80	320	84	59	1.424
			0.85	330	90	60	1.500
			0.90	341	97	61	1.590
	0.90	0.25	0.75	1528	396	283	1.399
			0.80	1581	429	288	1.490
			0.85	1635	463	293	1.580
			0.90	1690	498	298	1.671

Table 1 (*continued*)

k	$1-\beta$	η	λ	N	n_0	n	r
		0.50	0.75	384	100	71	1.408
			0.80	397	109	72	1.514
			0.85	411	119	73	1.630
			0.90	425	125	75	1.667
5	0.70	0.25	0.75	1318	283	207	1.367
			0.80	1357	302	211	1.431
			0.85	1397	327	214	1.528
			0.90	1437	347	218	1.592
		0.50	0.75	331	71	52	1.365
			0.80	341	76	53	1.434
			0.85	351	81	54	1.500
			0.90	361	91	54	1.685
	0.80	0.25	0.75	1545	350	239	1.464
			0.80	1592	377	243	1.551
			0.85	1640	405	247	1.640
			0.90	1689	434	251	1.729
		0.50	0.75	388	88	60	1.467
			0.80	400	95	61	1.557
			0.85	412	102	62	1.645
			0.90	425	110	63	1.746
	0.90	0.25	0.75	1896	451	289	1.561
			0.80	1957	487	294	1.656
			0.85	2018	523	299	1.749
			0.90	2081	561	304	1.845
		0.50	0.75	476	116	72	1.611
			0.80	491	121	74	1.635
			0.85	507	132	75	1.760
			0.90	522	142	76	1.868
6	0.70	0.25	0.75	1603	307	216	1.498
			0.80	1647	333	219	1.521
			0.85	1692	354	223	1.587
			0.90	1736	380	226	1.681
		0.50	0.75	403	79	54	1.463
			0.80	414	84	55	1.527
			0.85	425	89	56	1.589
			0.90	437	95	57	1.667
	0.80	0.25	0.75	1862	386	246	1.569
			0.80	1916	416	250	1.664
			0.85	1970	446	254	1.756
			0.90	2024	476	258	1.845
		0.50	0.75	468	102	61	1.672
			0.80	481	109	62	1.758
			0.85	495	111	64	1.734
			0.90	509	119	65	1.831

Table 1 (*continued*)

k	$1-\beta$	η	λ	N	n_0	n	r
	0.90	0.25	0.75	2267	503	294	1.711
			0.80	2335	541	299	1.809
			0.85	2404	580	304	1.908
			0.90	2474	620	309	2.006
		0.50	0.75	569	125	74	1.689
			0.80	586	136	75	1.813
			0.85	603	247	76	1.914
			0.90	620	158	77	2.052

for $k = 3, 4, 5, 6$, $1-\beta = 0.70, 0.80, 0.90$, $\mu_0/\sigma = 5, 10$, $\lambda = 0.75, 0.80, 0.85, 0.90$, $\delta = 0.05$ (which corresponds to $\eta = 0.25, 0.50$) and $\alpha = 0.05$. These tables are self-explanatory. Their use is illustrated in Section 7.

6. Approximate continuous optimization problem

To simplify the optimization problem we will assume $v = \infty$ so that the power expression (4.5) for step response reduces to a single integral. Furthermore, we define the quantity

$$\gamma = \eta\sqrt{N} = \left(\frac{\delta\mu_0}{\sigma}\right)\sqrt{N}, \tag{6.1}$$

which we treat as a continuous variable along with r. Thus the optimization problem for the step response case can be stated as: For given k and specified λ, α and $1-\beta$, find the smallest value of γ and the associated value of r so that

$$\int_{-\infty}^{\infty} \Phi^k\left[\frac{\tau z + c}{\sqrt{1-\tau^2}}\right]\phi(z)\,\mathrm{d}z = 1-\beta \tag{6.2}$$

where

$$c = -z_\alpha + \frac{\gamma\sqrt{r}}{\sqrt{(k+r)(r+\lambda^2)}} \quad \text{and} \quad \tau = \frac{\lambda}{\sqrt{r+\lambda^2}};$$

here $z_\alpha = t_{\infty,\alpha}$ is the upper α critical point of the standard normal distribution.

To solve this problem, first fix r and solve (6.2) for c or equivalently γ. An explicit solution for c can be obtained as follows. Note that the integral in (6.2) equals $P\{Z_1 \leqslant c, Z_2 \leqslant c, \ldots, Z_k \leqslant c\}$, where $Z_1, Z_2, \ldots, Z_k$ have a k-variate standard normal distribution with common correlation $\tau^2 = \lambda^2/(r+\lambda^2)$. Therefore c is the upper β critical point of $\max_{1\leqslant i\leqslant k} Z_i$; we denote this critical point by $z_{k,\tau^2,\beta}$. Dunnetts (1989) program can be used to calculate $c = z_{k,\tau^2,\beta}$. Then

$$\gamma = \eta\sqrt{N} = (z_\alpha + z_{k,\tau^2,\beta})\sqrt{\frac{(k+r)(r+\lambda^2)}{r}},$$

Table 2
Exact (discrete) optimum sample sizes for linear response ($\delta = 0.05$, $\alpha = 0.05$)

k	$1-\beta$	η	λ	N	n_0	n	r
3	0.70	0.25	0.75	465	129	112	1.152
			0.80	489	141	116	1.216
			0.85	516	156	120	1.300
			0.90	587	182	135	1.348
		0.50	0.75	118	34	28	1.214
			0.80	123	36	29	1.241
			0.85	130	40	30	1.333
			0.90	146	47	33	1.424
	0.80	0.25	0.75	614	176	146	1.205
			0.80	639	189	150	1.260
			0.85	668	206	154	1.338
			0.90	733	235	166	1.416
		0.50	0.75	155	44	37	1.189
			0.80	161	50	37	1.351
			0.85	168	54	38	1.421
			0.90	184	61	41	1.488
	0.90	0.25	0.75	849	246	201	1.224
			0.80	884	269	205	1.312
			0.85	919	292	209	1.397
			0.90	978	321	219	1.466
		0.50	0.75	214	64	50	1.280
			0.80	222	69	51	1.353
			0.85	231	75	52	1.442
			0.90	246	81	55	1.473
4	0.70	0.25	0.75	580	140	110	1.273
			0.80	607	155	113	1.372
			0.85	655	171	121	1.413
			0.90	761	209	138	1.514
		0.50	0.75	145	37	27	1.370
			0.80	152	40	28	1.429
			0.85	165	45	30	1.500
			0.90	191	55	34	1.618
	0.80	0.25	0.75	755	191	141	1.355
			0.80	786	206	145	1.421
			0.85	832	228	151	1.510
			0.90	936	268	167	1.605
		0.50	0.75	190	50	35	1.429
			0.80	198	54	36	1.500
			0.85	209	57	38	1.500
			0.90	235	67	42	1.595
	0.90	0.25	0.75	1043	271	193	1.404
			0.80	1081	293	197	1.487
			0.85	1127	319	202	1.579
			0.90	1223	359	216	1.662

Table 2 (*continued*)

k	$1-\beta$	η	λ	N	n_0	n	r
		0.50	0.75	262	70	48	1.458
			0.80	272	76	49	1.551
			0.85	284	80	51	1.569
			0.90	308	92	54	1.704
5	0.70	0.25	0.75	692	147	109	1.349
			0.80	733	163	114	1.430
			0.85	798	188	122	1.541
			0.90	939	229	142	1.613
		0.50	0.75	173	38	27	1.407
			0.80	183	43	28	1.536
			0.85	200	50	30	1.667
			0.90	235	60	35	1.714
	0.80	0.25	0.75	895	205	138	1.486
			0.80	936	221	143	1.545
			0.85	1000	250	150	1.667
			0.90	1141	296	169	1.751
		0.50	0.75	224	54	34	1.588
			0.80	234	59	35	1.686
			0.85	252	62	38	1.632
			0.90	286	76	42	1.810
	0.90	0.25	0.75	1232	292	188	1.553
			0.80	1277	317	192	1.651
			0.85	1338	348	198	1.758
			0.90	1472	397	215	1.847
		0.50	0.75	310	75	47	1.596
			0.80	321	81	48	1.688
			0.85	336	91	49	1.857
			0.90	370	100	54	1.852
6	0.70	0.25	0.75	806	158	108	1.463
			0.80	860	176	114	1.544
			0.85	945	201	124	1.621
			0.90	1121	245	146	1.678
		0.50	0.75	202	40	27	1.481
			0.80	215	47	28	1.679
			0.85	237	51	31	1.645
			0.90	281	65	36	1.806
	0.80	0.25	0.75	1033	217	136	1.596
			0.80	1085	239	141	1.695
			0.85	1171	265	151	1.755
			0.90	1347	321	171	1.877
		0.50	0.75	259	55	34	1.618
			0.80	272	62	35	1.771
			0.85	294	72	37	1.946
			0.90	339	81	43	1.884

Table 2 (*continued*)

k	$1-\beta$	η	λ	N	n_0	n	r
	0.90	0.25	0.75	1415	311	184	1.690
			0.80	1469	341	188	1.814
			0.85	1549	273	196	1.903
			0.90	1721	431	215	2.005
		0.50	0.75	356	80	46	1.739
			0.80	369	87	47	1.851
			0.85	389	95	49	1.939
			0.90	433	109	54	2.019

and the integral in (6.2) is a function of r alone. We denote it by $\psi(r)$, and find the optimum value of r by setting

$$\psi'(r) = \frac{\mathrm{d}\psi(r)}{\mathrm{d}r} = 0.$$

In Appendix we show, using the same methods as in Bechhofer (1969), that

$$\begin{aligned}\psi'(r) = & -\frac{\lambda k(k-1)\tau(1-\tau^2)r^{-3/2}}{\sqrt{8\pi(1+\tau^2)}}\phi\left(c\sqrt{\frac{2}{1+\tau^2}}\right)\\ & \times \Phi_{k-2}\left(c\sqrt{\frac{1-\tau^2}{(1+\tau^2)(1+2\tau^2)}}\,\middle|\,\frac{\tau^2}{1+2\tau^2}\right)+\frac{k\sqrt{1-\tau^2}}{2\tau}\\ & \times [\tau d-\lambda c(1-\tau^2)r^{-3/2}]\phi(c)\Phi_{k-1}\left(c\sqrt{\frac{1-\tau^2}{1+\tau^2}}\,\middle|\,\frac{\tau^2}{1+\tau^2}\right),\end{aligned} \tag{6.3}$$

where $\Phi_k(x|\rho)$ denotes the equicoordinate c.d.f. at point x of a k-variate standard normal distribution with common correlation ρ, and

$$d = \frac{\lambda c r^{-3/2}}{\tau} + z_\alpha\frac{\lambda^2}{r^2}\left(1+\frac{\lambda^2}{r}\right)^{-1/2} - \gamma(k+r)^{-3/2}. \tag{6.4}$$

The solution to the equation $\psi'(r)=0$ is substituted in $\tau=\lambda/\sqrt{r+\lambda^2}$ to find a new value of $c=z_{k,\tau^2,\beta}$ and the process is iterated until convergence is reached. The solutions to the continuous optimization problem are given in Table 3 for the same values of k, λ, $1-\beta$ and α as in Tables 1 and 2. Use of this table is illustrated in Section 7.

It may be noted from Table 3 that as $\gamma=\eta\sqrt{N}$ increases, r approaches $\lambda\sqrt{k}$. This fact can be shown analytically as follows. As γ and $c\to\infty$, the first term in the expression for $\psi'(r)$ goes to zero faster than the second term because $c\sqrt{2/(1+\tau^2)}<c$ and hence $\phi(c\sqrt{2/(1+\tau^2)})>\phi(c)$. As a result, the second term is the dominant one. Therefore, for large c, the solution to the equation $\psi'(r)=0$ can be approximated by the solution to the equation

$$\tau d-\lambda c(1-\tau^2)r^{-3/2}=0, \tag{6.5}$$

Table 3
Approximate (continuous) optimum sample sizes for step response case ($\alpha = 0.05$)

k	$1-\beta$	λ	γ	r
3	0.70	0.75	6.883	1.137
		0.80	7.009	1.210
		0.85	7.135	1.282
		0.90	7.260	1.354
	0.80	0.75	7.556	1.182
		0.80	7.698	1.258
		0.85	7.840	1.334
		0.90	7.982	1.409
	0.90	0.75	8.498	1.228
		0.80	8.662	1.307
		0.85	8.826	1.386
		0.90	8.990	1.465
4	0.70	0.75	8.032	1.257
		0.80	8.162	1.336
		0.85	8.292	1.414
		0.90	8.422	1.492
	0.80	0.75	8.747	1.330
		0.80	8.894	1.415
		0.85	9.041	1.498
		0.90	9.187	1.581
	0.90	0.75	9.752	1.400
		0.80	9.921	1.490
		0.85	10.090	1.579
		0.90	10.259	1.668
5	0.70	0.75	9.056	1.347
		0.80	9.190	1.429
		0.85	9.323	1.510
		0.90	9.456	1.590
	0.80	0.75	9.807	1.454
		0.80	9.957	1.544
		0.85	10.108	1.634
		0.90	10.258	1.722
	0.90	0.75	10.866	1.552
		0.80	11.039	1.650
		0.85	11.212	1.748
		0.90	11.384	1.845
6	0.70	0.75	9.992	1.414
		0.80	10.129	1.497
		0.85	10.266	1.579
		0.90	10.402	1.661
	0.80	0.75	10.774	1.561
		0.80	10.927	1.656
		0.85	11.080	1.750
		0.90	11.233	1.843

Table 3 (*continued*)

k	$1-\beta$	λ	γ	r
	0.90	0.75	11.881	1.687
		0.80	12.057	1.793
		0.85	12.232	1.898
		0.90	12.407	2.003

where d is given by (6.4). Now for large c and hence large γ,

$$d \approx \frac{\lambda c r^{-3/2}}{\tau} - \gamma(k+r)^{-3/2} \quad \text{and} \quad c \approx \frac{\gamma\sqrt{r}}{\sqrt{(k+r)(r+\lambda^2)}}.$$

Substituting these approximations and $\tau = \lambda/\sqrt{r+\lambda^2}$ in (6.5), we obtain

$$\begin{aligned}
&\frac{\lambda\gamma}{r\sqrt{(k+r)(r+\lambda^2)}} - \frac{\lambda\gamma(k+r)^{-3/2}}{\sqrt{r+\lambda^2}} - \frac{\lambda\gamma}{\sqrt{(k+r)(r+\lambda^2)^3}} \\
&\quad = \frac{\lambda\gamma}{\sqrt{(k+r)(r+\lambda^2)}}\left[\frac{1}{r} - \frac{1}{k+r} - \frac{1}{\lambda^2+r}\right] \\
&\quad = 0,
\end{aligned}$$

the solution to which can be easily checked to be $r = \lambda\sqrt{k}$.

This approximately optimum value of r can be shown to minimize

$$\mathrm{Var}(\overline{Y}_i - \lambda\overline{Y}_0) = \sigma^2\left(\frac{1}{n} + \frac{\lambda^2}{n_0}\right).$$

Putting $n_0 = rn$ and hence $n = N/(k+r)$, we see that, for fixed total sample size N, we need to minimize $(k+r)(1+\lambda^2/r)$, and the minimizing value is $r = \lambda\sqrt{k}$.

7. Example

Suppose that $k = 5$ doses are to be compared to a zero dose control to find the MAXSD. We do not assume any knowledge of the shape of the response function, and therefore use the step response as the least favorable configuration. The following quantities are specified: $\lambda = 0.80$, $\delta = 0.05$, $\alpha = 0.05$, $1-\beta = 0.70$ and $\mu_0/\sigma = 10$, so $\eta = (0.05)(10) = 0.50$. Then from Table 1, the exact discrete optimum sample sizes are found to be $n_0 = 76$, $n = 53$ and $N = 341$. Here $n_0/n = 1.434$, which is not very close to the asymptotically optimal allocation $\lambda\sqrt{k} = 1.789$.

Let us see how these sample sizes compare with those computed from Table 3. For $k = 5$, $\lambda = 0.80$, $\alpha = 0.05$, $1-\beta = 0.70$, we find that $\gamma = 9.190$ and $r = 1.429$. Therefore

$$N = \left(\frac{\gamma}{\eta}\right)^2 = \left(\frac{9.190}{0.50}\right)^2 = 338,$$

which gives

$$n = \frac{N}{k+r} = \frac{338}{5+1.429} = 53 \quad \text{and} \quad n_0 = N - kn = 73.$$

We see that these sample sizes are quite close to those obtained from Table 1, but are slightly smaller. This will generally be the case because the continuous approximation assumes that σ is known which results in slightly smaller sample sizes. However, the differences are not appreciable especially if N is large.

For the linear response case, from Table 2 we find that $n_0 = 43$, $n = 28$ and $N = 183$. Note that the sample sizes are much smaller in this case.

8. Extensions

In Section 4.2 we assumed that $\mu_i \geqslant \mu_0 - i\xi$. This linear lower bound implicitly assumes that the doses d_i are equispaced. A more general approach might be to incorporate the actual dose values in this lower bound, e.g., assume that

$$\mu_i \geqslant \mu_0 - (d_i - d_0)\xi \quad (1 \leqslant i \leqslant k),$$

where $\xi > 0$. We refer to this lower bound as the *generalized linear response*. Alternatively, one could assume an *exponential response* lower bound:

$$\mu_i \geqslant \mu_0(1/\xi)^{d_i - d_0} \iff \ln \mu_i \geqslant \ln \mu_0 - (d_i - d_0) \ln \xi \quad (1 \leqslant i \leqslant k),$$

where $\xi \geqslant 1$.

First consider the generalized linear response case. The definitions of Ω_m and Ω can be modified in an obvious manner. Then for $\boldsymbol{\mu} \in \Omega_m$, the power is minimized when

$$\xi = \frac{[1 - (\lambda + \delta)]\mu_0}{d_m - d_0}.$$

If the sequence $\{d_i - d_0,\ i = 1, 2, \ldots, k\}$ is log-concave, i.e., if $(d_i - d_0)/(d_{i+1} - d_0)$ is increasing in i, then the minimum power is given by (4.7), where i/k in the definition of $c_{i,k}(u)$ must be replaced by $(d_i - d_0)/(d_k - d_0)$.

For the exponential case, Ω_m is given by

$$\Omega_m = \{(\mu_0, \mu_1, \ldots, \mu_k) : \mu_i \geqslant \mu_0(1/\xi)^{d_i - d_0}\ (1 \leqslant i \leqslant m),\ \mu_{m+1} < (\lambda + \delta)\mu_0\}.$$

The power can be shown to be minimized when $1/\xi = (\lambda + \delta)^{1/(d_m - d_0)}$. Again, if the sequence $\{d_i - d_0,\ i = 1, 2, \ldots, k\}$ is log-concave then the minimum power is given by (4.7) with

$$c_{i,k}(u) = -t_{\nu,\alpha} + \{[(\lambda + \delta)^{\frac{d_i - d_0}{d_k - d_0}} - \lambda](\mu_0/\sigma)\}/\sqrt{1/n + \lambda^2/n_0}.$$

Power and sample size calculations can be done under these dose response functions by simple modifications in our computer programs. We can provide the programs to anyone interested.

This paper has given a method to compute the sample size for the SD2PC step-down multiple test procedure for finding the maximum safe dose of a compound. The method is based on the least favorable configuration approach. Therefore the resulting sample sizes may be too conservative for practical applications. To resolve this problem, a Bayesian approach can be adopted by putting prior distributions on the unknown parameters. However, this approach faces analytical difficulties

as well as the fact that adequate previous knowledge is often lacking to specify full priors. A way out of both these difficulties is to specify a discrete prior distribution on the MAXSD itself, i.e., one could specify prior probabilities $p_1, p_2, \ldots, p_k$, where p_m is the probability that the mth dose is MAXSD ($1 \leqslant m \leqslant k$). Then instead of using the power expressions (4.5) or (4.7), which use MAXSD $= k$ as the LFC, we will obtain the weighted averages of the corresponding expressions for different values of MAXSD. The simplest prior is the uniform prior: $p_1 = p_2 = \cdots = p_k = 1/k$. We plan to use this uniform prior to compute the required sample sizes and compare them with the sample sizes reported here using the LFC approach. These calculations will be reported in a future paper.

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Appendix A. Evaluation of the derivative $\psi'(r)$

For $v = \infty$ the minimum power expression, $\psi(r)$, for the step response function is given by (6.2). Taking its derivative with respect to r, we get

$$\psi'(r) = k \int_{-\infty}^{\infty} \Phi^{k-1}\left[\frac{\tau z + c}{\sqrt{1-\tau^2}}\right]\left[\frac{\mathrm{d}}{\mathrm{d}r}\left(\frac{\tau z + c}{\sqrt{1-\tau^2}}\right)\right]\phi\left(\frac{\tau z + c}{\sqrt{1-\tau^2}}\right)\phi(z)\,\mathrm{d}z.$$

First calculate,

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}r}\left(\frac{\tau z + c}{\sqrt{1-\tau^2}}\right) &= \frac{\mathrm{d}}{\mathrm{d}r}\left(\frac{\lambda z/\sqrt{r+\lambda^2} - z_\alpha + \gamma\sqrt{r/(k+r)(r+\lambda^2)}}{\sqrt{1-\lambda^2/(r+\lambda^2)}}\right)\\
&= \frac{\mathrm{d}}{\mathrm{d}r}\left(\frac{\lambda z - z_\alpha\sqrt{r+\lambda^2} + \gamma\sqrt{r/(k+r)}}{\sqrt{r}}\right)\\
&= \frac{\mathrm{d}}{\mathrm{d}r}\left(\frac{\lambda z}{\sqrt{r}} - z_\alpha\sqrt{1+\frac{\lambda^2}{r}} + \frac{\gamma}{\sqrt{k+r}}\right)\\
&= -\frac{1}{2}\lambda z r^{-3/2} + \frac{1}{2}z_\alpha\left(1+\frac{\lambda^2}{r}\right)^{-1/2}\frac{\lambda^2}{r^2} - \frac{1}{2}\gamma(k+r)^{-3/2}.
\end{aligned}$$

Put

$$y = \frac{\tau z + c}{\sqrt{1-\tau^2}}.$$

Then the above expression becomes

$$\frac{\mathrm{d}}{\mathrm{d}r}\left(\frac{\tau z+c}{\sqrt{1-\tau^2}}\right) = -\frac{\lambda r^{-3/2}\sqrt{1-\tau^2}}{2\tau}y + \frac{\lambda c r^{-3/2}}{2\tau} + \frac{1}{2}z_\alpha\left(1+\frac{\lambda^2}{r}\right)^{-1/2}\frac{\lambda^2}{r^2} - \frac{1}{2}\gamma(k+r)^{-3/2}.$$

Substitute this expression in $\psi'(r)$ to obtain

$$\begin{aligned}\psi'(r) &= k\int_{-\infty}^{\infty}\Phi^{k-1}(y)\phi(y)\phi^*(y)\frac{\sqrt{1-\tau^2}}{\tau} \\ &\quad\times\left[-\frac{\lambda r^{-3/2}\sqrt{1-\tau^2}}{2\tau}y + \frac{\lambda c r^{-3/2}}{2\tau}\right. \\ &\quad\left.+\frac{1}{2}z_\alpha\left(1+\frac{\lambda^2}{r}\right)^{-1/2}\frac{\lambda^2}{r^2} - \frac{1}{2}\gamma(k+r)^{-3/2}\right]\mathrm{d}y \\ &= -\frac{\lambda k r^{-3/2}(1-\tau^2)}{2\tau^2}A \\ &\quad+\frac{k\sqrt{1-\tau^2}}{2\tau}\left\{\frac{\lambda c r^{-3/2}}{\tau} + z_\alpha\left(1+\frac{\lambda^2}{r}\right)^{-1/2}\frac{\lambda^2}{r^2} - \gamma(k+r)^{-3/2}\right\}B,\end{aligned}$$

where

$$\phi^*(y) = \phi\left(\frac{y\sqrt{1-\tau^2}-c}{\tau}\right), \quad A = \int_{-\infty}^{\infty} y\Phi^{k-1}(y)\phi(y)\phi^*(y)\,\mathrm{d}y \quad \text{and}$$

$$B = \int_{-\infty}^{\infty}\Phi^{k-1}(y)\phi(y)\phi^*(y)\,\mathrm{d}y.$$

We now evaluate A and B. Integrating by parts in A with $u = \Phi^{k-1}(y)\phi^*(y)$ and $\mathrm{d}v = y\phi(y)\,\mathrm{d}y$, we find that

$$A = -\frac{1-\tau^2}{\tau^2}A + \frac{c\sqrt{1-\tau^2}}{\tau^2}B + (k-1)C,$$

where

$$C = \int_{-\infty}^{\infty}\Phi^{k-2}(y)\phi^2(y)\phi^*(y)\,\mathrm{d}y.$$

So,

$$A = c\sqrt{1-\tau^2}B + \tau^2(k-1)C.$$

Notice that

$$\begin{aligned}\phi(y)\phi^*(y) &= \frac{1}{\sqrt{2\pi}}\mathrm{e}^{-y^2/2}\frac{1}{\sqrt{2\pi}}\mathrm{e}^{-(y\sqrt{1-\tau^2}-c)^2/2\tau^2} \\ &= \phi(c)\phi\left(\frac{y-c\sqrt{1-\tau^2}}{\tau}\right)\end{aligned}$$

and

$$\phi^2(y)\phi^*(y) = \frac{1}{\sqrt{2\pi}}\phi\left(c\sqrt{\frac{2}{1+\tau^2}}\right)\phi\left(\frac{\sqrt{1+\tau^2}}{\tau}y - \frac{c}{\tau}\sqrt{\frac{1-\tau^2}{1+\tau^2}}\right).$$

Using the above relations we get

$$B = \phi(c)\int_{-\infty}^{\infty} \Phi^{k-1}(y)\phi\left(\frac{y - c\sqrt{1-\tau^2}}{\tau}\right)\mathrm{d}y.$$

Let

$$x = \frac{y - c\sqrt{1-\tau^2}}{\tau} \Rightarrow y = \tau x + c\sqrt{1-\tau^2} \quad \text{and} \quad \mathrm{d}y = \tau\,\mathrm{d}x.$$

Then

$$\begin{aligned} B &= \phi(c)\tau\int_{-\infty}^{\infty} \Phi^{k-1}\left(\tau x + c\sqrt{1-\tau^2}\right)\phi(x)\,\mathrm{d}x \\ &= \phi(c)\tau\Phi_{k-1}\left(c\sqrt{\frac{1-\tau^2}{1+\tau^2}}\,\middle|\,\frac{\tau^2}{1+\tau^2}\right) \end{aligned}$$

and

$$C = \frac{1}{\sqrt{2\pi}}\phi\left(c\sqrt{\frac{2}{1+\tau^2}}\right)\frac{\tau}{\sqrt{1+\tau^2}}\Phi_{k-2}\left(c\sqrt{\frac{1-\tau^2}{(1+\tau^2)(1+2\tau^2)}}\,\middle|\,\frac{\tau^2}{1+2\tau^2}\right).$$

Combining the expressions for A, B and C, and substituting them in the last expression for $\psi'(r)$ we get the final expression (6.3).

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