A NOTE ON AN INDIVIDUAL BIOEQUIVALENCE SETTING

C. SURULESCU & N. SURULESCU

ABSTRACT. We give a new simpler proof along with a generalization for the inequality of Yao and Iyer [YaIy99] arising in bioequivalence studies and by using a nonparametric approach we also discuss an extension of the individual bioequivalence setting to the case where the data are not necessarily normally distributed.

1. INTRODUCTION

Bioequivalence testing is required when trying to get the approval for manufacturing and selling of a generic drug having mainly the same properties with a (more expensive) reference (brand-name) drug. Establishing bioequivalence prevents the generic drug manufacturer from performing expensive clinical trials to demonstrate the quality of his product. Two drugs are considered bioequivalent if they are absorbed into the blood and become active at about the same rate and concentration. Bioequivalent drugs are supposed to provide the same therapeutic effect.

For explaining the notions and notations we use, we recall the problem setting in [YaIy99] for the individual bioequivalence. Thus, the amount of the chemical absorbed by a patient's bloodstream when using a reference drug is a random variable X, which has mean μ_R and standard deviation σ_R. The corresponding variable for the same patient when using the generic drug has mean μ_T and standard deviation σ_T. The *therapeutic window* of a patient is defined to be the interval in which must lie the concentration of the chemical in the bloodstream, in order for the drug to be classified as beneficial for that

Date: March 21, 2005.
2000 *Mathematics Subject Classification.* 60E15, 62F03, 62P10.
Key words and phrases. bioequivalence, probabilistic inequalities.

patient. Usually, the therapeutic window is assumed to be an interval centered at the mean μ_R, namely the range $(\mu_R - z\sigma_R, \mu_R + z\sigma_R)$. The drug will be uneffective if the amount absorbed in the bloodstream is too low and it could cause severe side effects if too much of the chemical substance is absorbed.

Denoting by p_R and p_T the probabilities that the subject will have benefit from using drug R, respectively T, the regulatory agency might approve the marketing of drug T provided that $\frac{p_T}{p_R} \geq \gamma$, where γ is about 1 or even larger.

The therapeutic window of a patient is generally unknown, therefore a quantity of interest for the approval procedure will be $\inf_{z\geq 0} \frac{p_T}{p_R}$.

Usually, to derive this quantity the assumption that X and T have normal distributions is made, though it is well known that in practice this is rarely the case. Under this assumption, Yao and Iyer [YaIy99] have shown that

$$\inf_{z>0} \frac{p_T}{p_R} = \inf_{z>0} \frac{\Phi(\frac{\mu_R+z\sigma_R-\mu_T}{\sigma_T}) - \Phi(\frac{\mu_R-z\sigma_R-\mu_T}{\sigma_T})}{\Phi(z) - \Phi(-z)}$$

$$= \min\left\{1, \frac{\sigma_R\sqrt{2\pi}}{\sigma_T}\phi\Big(\frac{\mu_T-\mu_R}{\sigma_T}\Big)\right\}, \tag{1}$$

where ϕ and Φ are the probability density function, respectively the cummulative density function of a standard normal variable and $(\mu, \sigma^2) \neq (0, 1)$.

Thus, the approval of manufacturing the generic drug T may be granted if from the statistical analysis of experimental data it can be proven that

$$\frac{\sigma_R\sqrt{2\pi}}{\sigma_T}\phi\Big(\frac{\mu_T-\mu_R}{\sigma_T}\Big) \geq \gamma. \tag{2}$$

Alternatively to (2), a more flexible approval criterion can be used, namely one of the type

$$\ell(\mathcal{Z}_\gamma) \geq b_\gamma, \tag{3}$$

for some large enough given bound b_γ, where $\mathcal{Z}_\gamma := \{z > 0 \ : \ \frac{p_T}{p_R} > \gamma\}$ and ℓ is for instance the Lebesgue measure. We will discuss in the next sections sufficient conditions for (3) to be satisfied.

For more information about individual bioequivalence see [AnHa90], [Schal95], [ScLu93], [MaFr02], [Manl04], [MHPB03] and the references therein.

In this paper we give a simpler proof and a generalization of the inequality of Yao and Iyer and we also give a nonparametric extension of the above bioequivalence setting.

For the sake of clarity, we put all our proofs in the Appendix.

2. A generalization of the inequality of Yao and Iyer

The main result of Yao and Iyer in [YaIy99] was the proof of the following inequality:

$$\frac{\Phi(\frac{z-\mu}{\sigma}) - \Phi(\frac{-z-\mu}{\sigma})}{\Phi(z) - \Phi(-z)} > \min\Big\{1, \frac{\sqrt{2\pi}}{\sigma}\phi\Big(\frac{\mu}{\sigma}\Big)\Big\}, \tag{4}$$

for all $z > 0$, $\mu \in \mathbb{R}\backslash\{0\}$ and $\sigma \in (0,\infty)\backslash\{1\}$; this inequality comes from (1) after some changes of notations.

As in [YaIy99], observe that it is enough to treat the case $\mu \geq 0$. Here we will prove the following generalization:

Proposition 2.1. *In the above settings, we have:*

(i) If $\sigma > 1$, then

$$\begin{aligned}
\frac{\Phi(\frac{z-\mu}{\sigma}) - \Phi(\frac{-z-\mu}{\sigma})}{\Phi(z) - \Phi(-z)} &> e^{-\frac{\mu^2}{2\sigma^2}} \frac{\Phi(\frac{z}{\sigma}) - \Phi(\frac{-z}{\sigma})}{\Phi(z) - \Phi(-z)} \\
&> e^{-\frac{\mu^2}{2\sigma^2}} \frac{1}{\sigma}\Big[1 + \frac{1}{6}\Big(1 - \frac{1}{\sigma^2}\Big) \cdot z^2 e^{-\frac{z^2}{2}}\Big] \\
&> \frac{1}{\sigma} e^{-\frac{\mu^2}{2\sigma^2}} = \min\Big\{1, \frac{\sqrt{2\pi}}{\sigma}\phi\Big(\frac{\mu}{\sigma}\Big)\Big\}, \ \forall z > 0.
\end{aligned}$$

(ii) If $\sigma \in (0,1)$ then

$$\begin{aligned}
\frac{\Phi(\frac{z-\mu}{\sigma}) - \Phi(\frac{-z-\mu}{\sigma})}{\Phi(z) - \Phi(-z)} &\geq \min\Big\{1, \frac{\sqrt{2\pi}}{\sigma}\phi\Big(\frac{\mu}{\sigma}\Big)\Big\} \frac{\Phi(\frac{z-\mu(\sigma)}{\sigma}) - \Phi(\frac{-z-\mu(\sigma)}{\sigma})}{\Phi(z) - \Phi(-z)} \\
&> \min\Big\{1, \frac{\sqrt{2\pi}}{\sigma}\phi\Big(\frac{\mu}{\sigma}\Big)\Big\}, \ \forall z > 0, \ \forall \mu > 0,
\end{aligned} \tag{5}$$

where $\mu(\sigma) := \sigma\sqrt{2\ln\frac{1}{\sigma}}$.

This result is based on Lemma 2.1, generalising Lemma 3 in [YaIy99], (which was the most difficult part of the proof therein) and on Lemmas 2.2 and 2.3 below.

Lemma 2.1. *The function* $\sigma \mapsto F(\sigma) := \Phi(\frac{z-\mu(\sigma)}{\sigma}) - \Phi(\frac{-z-\mu(\sigma)}{\sigma})$ *is strictly decreasing on* $(0,1)$, *where* $\mu(\sigma) = \sigma\sqrt{2\ln\frac{1}{\sigma}}$.

Lemma 2.2. *For every* $\sigma > 0$, $\sigma \neq 1$, *we have:*

$$\begin{aligned}(6)\quad \frac{\Phi(\frac{z}{\sigma}) - \Phi(\frac{-z}{\sigma})}{\Phi(z) - \Phi(-z)} - \min\{1, \frac{1}{\sigma}\} \;&>\; \frac{1}{6\sigma}\Big(1 - \min\{1, \frac{1}{\sigma}\}^2\Big)\cdot z^2 e^{-\frac{z^2}{2}} \\ &+\; \Big(\frac{1}{\sigma} - \min\{1, \frac{1}{\sigma}\}\Big)e^{-\frac{z^2}{2\sigma^2}} > 0,\ \forall z > 0.\end{aligned}$$

The following lemma generalises Lemma 1 and Lemma 4 in [YaIy99]:

Lemma 2.3.

$$(7)\qquad \frac{\Phi(z-\mu_1) - \Phi(-z-\mu_1)}{\Phi(z-\mu_2) - \Phi(-z-\mu_2)} > \min\{1, e^{-\frac{1}{2}[(\mu_1)^2 - (\mu_2)^2]}\}$$

$\forall z > 0,\ \mu_1,\ \mu_2 \in \mathbb{R},\ \mu_1 \neq \mu_2$.

Remark 2.1. Replacing z with $\frac{z}{\sigma}$, μ_1 by $\frac{\mu_1}{\sigma}$ and μ_2 by $\frac{\mu_2}{\sigma}$ then

- for $\mu_1 > \mu_2 > 0$ one has
  $$\frac{\Phi(\frac{z-\mu_1}{\sigma}) - \Phi(\frac{-z-\mu_1}{\sigma})}{\Phi(\frac{z-\mu_2}{\sigma}) - \Phi(\frac{-z-\mu_2}{\sigma})} > \min\{1, e^{-\frac{1}{2}[(\frac{\mu_1}{\sigma})^2 - (\frac{\mu_2}{\sigma})^2]}\} = e^{-\frac{1}{2}[(\frac{\mu_1}{\sigma})^2 - (\frac{\mu_2}{\sigma})^2]},$$
  thus the function
  $$(0,\infty) \ni \mu \mapsto B_1(\mu) := e^{\frac{1}{2}(\frac{\mu}{\sigma})^2}[\Phi(\frac{z-\mu}{\sigma}) - \Phi(\frac{-z-\mu}{\sigma})]$$
  is increasing, i.e. Lemma 1 in [YaIy99] is obtained;
- for $\mu_2 > \mu_1 > 0$ one has
  $$\frac{\Phi(\frac{z-\mu_1}{\sigma}) - \Phi(\frac{-z-\mu_1}{\sigma})}{\Phi(\frac{z-\mu_2}{\sigma}) - \Phi(\frac{-z-\mu_2}{\sigma})} > 1,$$
  thus the function
  $$(0,\infty) \ni \mu \mapsto B_2(\mu) := \Phi(\frac{z-\mu}{\sigma}) - \Phi(\frac{-z-\mu}{\sigma})$$
  is proved to be decreasing, i.e. we obtained Lemma 4 in [YaIy99].

Remark 2.2. Sufficient conditions ensuring (3) to be satisfied can be easily derived upon using for $\sigma > 1$ the monotonicity of the function $z \mapsto z^2 e^{-\frac{z^2}{2}}$ (increasing on $(0, \sqrt{2})$, decreasing on $[\sqrt{2}, \infty)$) and for $0 < \sigma < 1$ the fact that

$$\begin{aligned} \frac{\Phi(\frac{z-\mu}{\sigma}) - \Phi(\frac{-z-\mu}{\sigma})}{\Phi(z) - \Phi(-z)} &> \min\Big\{1, \frac{\sqrt{2\pi}}{\sigma}\phi\Big(\frac{\mu}{\sigma}\Big)\Big\}\frac{\Phi(\frac{z-\mu(\sigma)}{\sigma}) - \Phi(\frac{-z-\mu(\sigma)}{\sigma})}{\Phi(z) - \Phi(-z)} \\ &\geq \sigma \min\Big\{1, \frac{\sqrt{2\pi}}{\sigma}\phi\Big(\frac{\mu}{\sigma}\Big)\Big\}\frac{\Phi(\frac{z}{\sigma}) - \Phi(\frac{-z}{\sigma})}{\Phi(z) - \Phi(-z)}, \ \forall z > 0 \end{aligned}$$

and this term can be minorated by applying Lemma 2.2.

3. A nonparametric approach for the bioequivalence setting

Consider now that the random variables X, T from the Introduction have continuous univariate distributions, with the densities f_X, respectively f_T, which are not necessarily Gaussian, and assume that we correspondingly have the independent observations: $x_1, \ldots, x_m$, respectively $t_1, \ldots, t_n$. Then f_X and f_T can be estimated by using the classical nonparametric estimators:

$$\hat{f}_X(x) = \frac{1}{mh_m^X} \cdot \sum_{i=1}^{m} K\Big(\frac{x - x_i}{h_m^X}\Big)$$

$$\hat{f}_T(t) = \frac{1}{nh_n^T} \cdot \sum_{i=1}^{n} K\Big(\frac{t - t_i}{h_n^T}\Big),$$

where K is a kernel, h_m^X and h_n^T are the bandwidths (with the usual properties: $h_m^X \to 0$, $h_n^T \to 0$ for $m, n \to \infty$; $mh_m^X \to 0$, $nh_n^T \to \infty$ for $m, n \to \infty$ and, of course, h_m^X and h_n^T have to be chosen in practice by a corresponding criterion).

With the above notations, the rapports of interest for bioequivalence studies are

$$\frac{p_T}{p_R} = R(z) := \frac{\int_{\mu_R - z\sigma_R}^{\mu_R + z\sigma_R} f_T(t)dt}{\int_{\mu_R - z\sigma_R}^{\mu_R + z\sigma_R} f_X(x)dx} \approx \hat{R}(z) := \frac{\int_{\mu_R - z\sigma_R}^{\mu_R + z\sigma_R} \hat{f}_T(t)dt}{\int_{\mu_R - z\sigma_R}^{\mu_R + z\sigma_R} \hat{f}_X(x)dx}, \quad z > 0, \tag{8}$$

and for the approval procedure it will be important to find the quantity of interest $\inf_{z>0} \hat{R}(z)$, but this is clearly more difficult then for the case presented

in the previous section and an analytic treatment is hardly possible. Even when considering the Gaussian kernel, the usual nonlinear optimization procedure implemented in Maple is surprisingly very much time consuming. However, a great (and also easy to implement) simplification can be achieved when using one of the following kernels (see e.g., [Scott92]):

- the rectangular kernel: $K(u) := \frac{1}{2}\chi_{(-1,1)}(u)$;
- the triangular kernel: $K(u) := (1-|u|)\chi_{(-1,1)}(u)$;
- the Epanechnikov kernel: $K(u) := \frac{3}{4}(1-u^2)\chi_{(-1,1)}(u)$;
- the triangle kernel: $K(u) := (1-|u|)\chi_{(-1,1)}(u)$;
- the double Epanechnikov kernel: $K(u) := 3|u|(1-|u|)\chi_{(-1,1)}(u)$.

Moreover, the procedure can also be used for finding the largest therapeutic window under which the rapport of interest exceeds some given positive constant γ.

Since all kernels above are supported on $(-1,1)$, then the global minimum can be found in the following way:

- construct $A_n^{T,+} := A_n^T \cap (0,\infty)$, where

$$A_n^T := \bigcup_{i=1}^{n}\{-\frac{t_i - h_n^T - \mu_R}{\sigma_R},\ \frac{t_i + h_n^T - \mu_R}{\sigma_R},\ \frac{t_i - h_n^T - \mu_R}{\sigma_R},\ -\frac{t_i + h_n^T - \mu_R}{\sigma_R}\};$$

- construct $A_m^{X,+} := A_m^X \cap (0,\infty)$, where

$$A_m^X := \bigcup_{j=1}^{m}\{-\frac{x_j - h_m^X - \mu_R}{\sigma_R},\ \frac{x_j + h_m^X - \mu_R}{\sigma_R},\ \frac{x_j - h_m^X - \mu_R}{\sigma_R},\ -\frac{x_j + h_m^X - \mu_R}{\sigma_R}\};$$

- if K is not the rectangular kernel, then construct $A_{T,deriv}^+$ as the set constituted by the critical points of $\hat{R}(z)$ on the union of the subintervals of $\mathbb{R}_+$ where $\hat{R}$ is differentiable (which in this case are roots of some polynomials, thus easy to be handled by the computer); if K is the rectangular kernel, set $A_{T,deriv}^+ = \emptyset$.
- denote $\mathfrak{A} := A_n^{T,+} \bigcup A_m^{X,+} \bigcup A_{T,deriv}^+$.

Then we have:

Proposition 3.1. *With the notations above and with K being one of the kernels enumerated before,*

$$\frac{\frac{1}{nh_n^T}\sum_{i=1}^{n}\int_{\mu_R-z\sigma_R}^{\mu_R+z\sigma_R}K\left(\frac{t-t_i}{h_n^T}\right)dt}{\frac{1}{mh_m^X}\sum_{i=1}^{m}\int_{\mu_R-z\sigma_R}^{\mu_R+z\sigma_R}K\left(\frac{x-x_i}{h_m^X}\right)dx}\geq\min\{\hat{R}(z_{max}),\lim_{z\to 0}\hat{R}(z),\hat{R}(\mathfrak{A})\},$$

where $z_{max}=\max\{|\zeta|\ :\ \zeta\in\mathfrak{A}\}$,

$$\lim_{z\to 0}\hat{R}(z)=\frac{mh_m^X}{nh_n^T}\frac{\sum_{i=1}^{n}K\left(\frac{\mu_R-t_i}{h_n^T}\right)}{\sum_{i=1}^{m}K\left(\frac{\mu_R-x_i}{h_m^X}\right)}\ \textit{for the continuous kernels above,}$$

and

$$\lim_{z\to 0}\hat{R}(z)=\frac{mh_m^X}{nh_n^T}\frac{\sum_{i=1}^{n}\left[K_+\left(\frac{\mu_R-t_i}{h_n^T}\right)+K_-\left(\frac{\mu_R-t_i}{h_n^T}\right)\right]}{\sum_{i=1}^{m}\left[K_+\left(\frac{\mu_R-x_i}{h_m^X}\right)+K_-\left(\frac{\mu_R-x_i}{h_m^X}\right)\right]}\ \textit{for the rectangular kernel,}$$

with the notations $K_+(\xi):=\lim_{t\searrow\xi}K(t)$, *respectively* $K_-(\xi):=\lim_{t\nearrow\xi}K(t)$.

Remark 3.1. If K is one of the kernels presented above, then for each $\gamma>0$ and using an algorithm similar to the one described above one can easily determine $\mathcal{Z}_\gamma$, in order to check the approval condition (3).

Simulation result: Figure 1 illustrates a simulation with $m=150$, $n=160$ for the case where X and T are normally distributed and the nonparametric estimators are constructed with the Epanechnikov kernel. The continuous lines represent $\hat{R}(z)$ and its minimum, which is 0.012; the lines of circles represent $R(z)$ and its minimum, which is 0.0088. This shows that the Gaussian case can be well recovered with this nonparametric procedure.

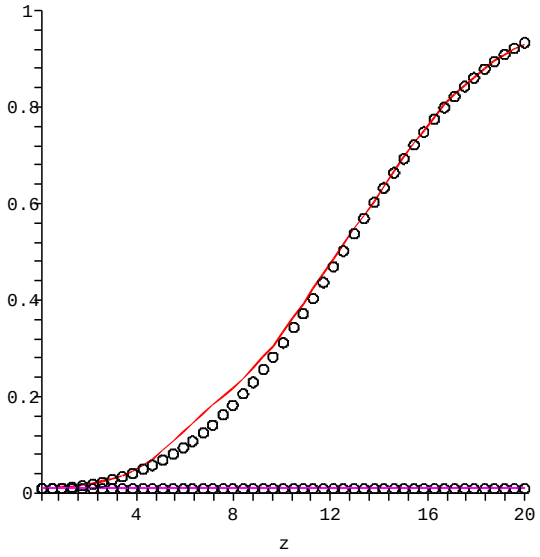

FIGURE 1. The continuous line is $\hat{R}(z)$; the line of circles is $R(z)$; the horizontal lines are the corresponding minimums

4. CONCLUSIONS

In this paper we gave a generalization and a simpler proof of the inequality of Yao and Iyer [YaIy99] concerning an individual bioequivalence setting when the data were supposed to be normally distributed. Our generalization can be used to develop a more flexible approval criterion (of the type (3)) for manufacturing and selling a drug which is supposed to be bioequivalent with a reference one. Finally, we extend these settings to the more general situation when the data are not necessarily normally distributed, upon using the nonparametric estimation technique. This idea can also be useful in the context of global nonlinear optimization problems.

Appendix A. Proofs

Proof. (of Lemma 2.1) Denoting $\theta := \frac{1}{\sigma} \in (1, \infty)$, we have

$$\Phi(\frac{z-\mu(\sigma)}{\sigma}) - \Phi(\frac{-z-\mu(\sigma)}{\sigma}) = \Phi(z\theta - \sqrt{2\ln\theta}) - \Phi(-z\theta - \sqrt{2\ln\theta}).$$

Consider $g : (1, \infty) \to \mathbb{R},\ g(\theta) := \Phi(z\theta - \sqrt{2\ln\theta}) - \Phi(-z\theta - \sqrt{2\ln\theta}),\ \forall\theta > 1$. Observe that

$$g'(\theta) = \Big(z + \frac{1}{\theta\sqrt{2\ln\theta}}\Big)\cdot\phi(z\theta - \sqrt{2\ln\theta})\Big[\frac{z\theta\sqrt{2\ln\theta}-1}{z\theta\sqrt{2\ln\theta}+1} + \exp(-2z\theta\sqrt{2\ln\theta})\Big] > 0,$$

for all $\theta > 1$, because $u := z\theta\sqrt{2\ln\theta} > 0$ and it is easy to see that

$$\frac{u-1}{u+1} + e^{-2u} > 0,\ \forall u > 0.$$

□

Proof. (of Lemma 2.2) If $\sigma > 1$, we can write

$$\begin{aligned}\Phi(\frac{z}{\sigma}) - \Phi(\frac{-z}{\sigma}) &= \frac{1}{\sigma\sqrt{2\pi}}\int_{-z}^{z} e^{-\frac{x^2}{2\sigma^2}}dx \\ &> \frac{1}{\sigma}\Big[\Phi(z) - \Phi(-z) + \frac{1}{\sqrt{2\pi}}\cdot\frac{1}{2}\Big(1-\frac{1}{\sigma^2}\Big)\int_{-z}^{z} x^2 e^{-\frac{x^2}{2}}dx\Big],\end{aligned}$$

since $e^{\frac{x^2}{2}\left(1-\frac{1}{\sigma^2}\right)} \geq 1 + \frac{x^2}{2}\Big(1-\frac{1}{\sigma^2}\Big),\ \forall x \in \mathbb{R}\backslash\{0\}$. Further, from the decreasing monotonicity of $x \mapsto e^{-\frac{x^2}{2}}$ on $[0, z]$ deduce that

$$\Phi(\frac{z}{\sigma}) - \Phi(\frac{-z}{\sigma}) \geq \frac{1}{\sigma}\Big[\Phi(z) - \Phi(-z) + \frac{1}{\sqrt{2\pi}}\Big(1-\frac{1}{\sigma^2}\Big)\cdot\frac{z^3}{3}e^{-\frac{z^2}{2}}\Big]$$

and

$$\Phi(z) - \Phi(-z) < z\sqrt{2/\pi},\quad \forall z > 0$$

and thus (6) is proved.

For the case where $\sigma \in (0,1)$ we have:

$$\begin{aligned}\frac{\Phi(\frac{z}{\sigma})-\Phi(\frac{-z}{\sigma})}{\Phi(z)-\Phi(-z)} &= 1+2\frac{\Phi(\frac{z}{\sigma})-\Phi(z)}{\Phi(z)-\Phi(-z)} = 1+2\frac{\int_z^{\frac{z}{\sigma}}\frac{1}{\sqrt{2\pi}}e^{-\frac{x^2}{2}}dx}{\Phi(z)-\Phi(-z)} \\ &> 1+2\frac{\frac{1}{\sqrt{2\pi}}e^{-\frac{z^2}{2\sigma^2}}\cdot z\Big(\frac{1}{\sigma}-1\Big)}{\Phi(z)-\Phi(-z)} > 1+\Big(\frac{1}{\sigma}-1\Big)e^{-\frac{z^2}{2\sigma^2}}, \forall z>0,\end{aligned}$$

upon using the same method as in the previous case. □

Proof. (of Lemma 2.3) Let

$$Q(z) := \Phi(z-\mu_1)-\Phi(-z-\mu_1)-e^{-\frac{1}{2}[(\mu_1)^2-(\mu_2)^2]}[\Phi(z-\mu_2)-\Phi(-z-\mu_2)],\ z>0.$$

Then

$$\begin{aligned}Q'(z) &= \frac{2}{\sqrt{2\pi}}e^{-\frac{1}{2}[(\mu_1)^2+z^2]}\Big[\frac{e^{z\mu_1}+e^{-z\mu_1}}{2}-\frac{e^{z\mu_2}+e^{-z\mu_2}}{2}\Big] \\ &= \frac{2}{\sqrt{2\pi}}e^{-\frac{1}{2}[(\mu_1)^2+z^2]}[\cosh(z|\mu_1|)-\cosh(z|\mu_2|)],\quad \forall z>0.\end{aligned}$$

Now using the fact that the hyperbolic cosine is an increasing function on $(0,\infty)$, we have that $Q'(z)>0$ if $|\mu_1|>|\mu_2|$ and $Q'(z)<0$ if $|\mu_1|<|\mu_2|$.

Thus, if $|\mu_1|>|\mu_2|$, then $Q(z)>0$, $\forall z>0$, i.e. inequality (7) is satisfied, since the minimum therein is $e^{-\frac{1}{2}[(\mu_1)^2-(\mu_2)^2]}$.

If $|\mu_1|<|\mu_2|$, then consider the function

$$G(\mu) := \Phi(z-\mu)-\Phi(-z-\mu)$$

and observe that it is decreasing on $(0,\infty)$, since its derivative is

$$G'(\mu) = -\frac{1}{\sqrt{2\pi}}e^{-(z^2+\mu^2)/2}[e^{z\mu}-e^{-z\mu}]<0,\ \forall z>0,\ \mu>0.$$

Observing that $G(\mu)=G(-\mu)$, $\forall \mu\in\mathbb{R}$, we have that $G(\mu_2)=G(|\mu_2|)<G(|\mu_1|)=G(\mu_1)$, which proves the inequality in this case. □

Proof. (of Proposition 2.1) In the case (i) observe that we can write

$$\frac{\Phi(\frac{z-\mu}{\sigma})-\Phi(\frac{-z-\mu}{\sigma})}{\Phi(z)-\Phi(-z)} = \frac{\Phi(\frac{z-\mu}{\sigma})-\Phi(\frac{-z-\mu}{\sigma})}{\Phi(\frac{z}{\sigma})-\Phi(\frac{-z}{\sigma})}\cdot\frac{\Phi(\frac{z}{\sigma})-\Phi(\frac{-z}{\sigma})}{\Phi(z)-\Phi(-z)}.$$

Now apply Lemma 2.3 for the first term in the right hand side and Lemma 2.2 for the other one.

In the case (ii), if $\mu \in (0, \mu(\sigma))$, then we have that $B_2(\mu) \geq B_2(\mu(\sigma))$ (see Lemma 2.3 and Remark 2.1). Further, use Lemma 2.1 to obtain the last inequality in (5).

If $\mu > \mu(\sigma)$, then $\sigma B_1(\mu) \geq \sigma B_1(\mu(\sigma))$ (see again Lemma 2.3 and Remark 2.1). Then Lemma 2.1 implies that

$$\frac{\sigma B_1(\mu(\sigma))}{\Phi(z) - \Phi(-z)} = \frac{F(\sigma)}{\Phi(z) - \Phi(-z)} > 1,$$

which completes the proof. □

Proof. (of Proposition 3.1)

The proof follows observing that for each of the kernels above $\hat{R}(z)$ becomes a rapport of polynomials on some finite intervals dictated by the points in $A_m^{X,+} \bigcup A_n^{T,+}$. Thus, the problem reduces to characterising the minimum of these fractional expressions on such corresponding finite intervals, which in this particular case means to find the roots of the polynomials at the numerator of the derivatives. It only remains to observe that $\lim_{z\to\infty} \hat{R}(z) = \hat{R}(z_{max})$. □

References

[AnHa90] S. Anderson, W.W. Hauck, *Consideration of individual bioequivalence*, J. of Parmacokinetics and Biopharmaceutics, vol. 18 (1990) 259-274.

[Grama97] I.G. Grama, *On moderate deviations for martingales*, The Annals of Probability, vol. 25, no.1 (1997) 152-183.

[JoKe03] B. Jones, M.G. Kenward, *Design and Analysis of Cross-Over Trials (2nd edition)*, Chapman & Hall, 2003.

[MaFr02] B.F.J. Manly, R.I.C.C. Francis, *Testing for mean and variance differences with samples from distributions that may be non-normal with unequal variances*, Journal of Statistical Computation and Simulation, vol. 72, no. 8 (2002) 633 - 646.

[Manl04] B.F.J. Manly, *One-Sided Tests of Bioequivalence With Nonnormal Distributions and Unequal Variances*, Journal of Agricultural, Biological and Environmental Statistics, vol.9, no.3 (2004) 270 - 283.

[MHPB03] L.L.McDonald, S. Howlin, J. Polyakova, C.J. Bilbrough, *Evaluation and Comparison of Hypothesis Testing Techniques for Bond Release Applications*, a project for the Abandoned Coal Mine Lands Research Program at the University of Wyoming, 2003.

[Schal95] R. Schall, Assessment of individual and population bioequivalence using the probability that bioavailabilities are similar, Biometrics, vol. 51 (1995) 615-626.

[ScLu93] R. Schall, H.G. Luus, *On population and individual bioequivalence*, Statistics in Medicine, vol. 12 (1993) 1109-1124.

[Scott92] D.W. Scott, *Multivariate Density Estimation. Theory, Practice, and Visualization*, John Wiley & Sons, 1992.

[YaIy99] Yi-Ching Yao, H. Iyer, *On an Inequality for the Normal Distribution Arising in Bioequivalence Studies*, J. Appl. Prob. 36 (1999) 279-286.

Institut für Angewandte Mathematik, INF 294, 69120 Heidelberg, Germany.
E-mail address: Christina.Surulescu@IWR.Uni-Heidelberg.De
E-mail address: Nicolae.Surulescu@iwr.uni-heidelberg.de