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**Re: MS#03-112**

Dear Dr. Albert,

Thank you for your speedy reply. Our responses to your comments follow:

## Larger concerns

*1. (Comparison with alternatives.) You need to explain more carefully what you mean by the "point estimate and error bar" plot. The naive thing to do is to just use*

*point estimate* $\pm$ *1.96 standard error*

*as your limits, but it seems that you are doing something else in the figures.*

**We have clarified that we are using likelihood-based intervals in Figure 6 ...**

*2. (Some more discussion for the Bayesians.) When plotting probability densities (posteriors), there are alternative displays that are commonly used. For example, it is common to display a boxplot that gives the median, quartiles and upper percentiles of the distribution. You should mention this alternative, but you don't need to show these boxplots.*

**We have added the following sentences to the Discussion: "An alternative is to use a boxplot-type display that shows the median, quartiles, and upper percentiles of a distribution. We contend that the HDR-raindrop is more informative."**

*3. (Interpretation.) A reader may criticize your plot since it violates the area principle – the area enclosed by the raindrop doesn't correspond to a probability (if it is a HDR raindrop) nor a likelihood. You should discuss this point. I think the primary advantages are the quadratic shape (under normality), the ability to reflect a variety of likelihood shapes, the tightness of the display, and (very last) the visual attractiveness. As I say later in my list of specific comments, it is not clear why it is desirable to reflect the curve to form*

*the raindrop.*

> **The area principle holds that the perceived size of a plot element should correspond to the magnitude of the value displayed. When confidence intervals (or Bayesian credible intervals or evidentialist support intervals) are displayed, the wider the interval, the less certainty we have about the estimate in question. Curiously, it is the most precise estimates that are shown with the least ink ...**

## Specific comments

*1. Page 4, line 5. Can you explicitly define $\theta_k^{MLE}$? This would help clarify your later comment that (1) is close to the MLE.*

> **We can write $\theta_k^{\mathbf{MLE}} = \mathbf{argmax}_{\theta_k} L_k(\theta_k)$.**

*2. Page 4, before equation (3). Add phrase – "1.92, this interval is equivalent to"*

> **Done.**

*3. Page 4, line 5 from bottom. Can you give the expression for the "95% confidence interval based on the normal approximation and the standard error"? I assume you mean*

*estimate $\pm$ 1.96 standard error*

> **We will rewrite this ...**

*4. Page 4, line 4 from bottom. "the likelihood-ratio based interval (3) is substantially different"*

> **We have inserted "(3)".**

*5. Page 5, after first paragraph. I understand you describe how to construct a raindrop plot in the caption of the figure. But I think you need to at least briefly describe this construction in the text.*

*6. Page 5, second paragraph. One alternative to reflecting the curve is just to have a horizontal line at the minimum value of the log likelihood. Is there any other reason for the reflection than to be "visually appealing"?*

> **Instead of justifying the reflection as producing a "visually appealing symmetry", we have changed this to say that it *avoids* a "visually distracting asymmetry" ...**

*7. Page 5. It would help to give the equation of the quadratic form of the log-likelihood when the likelihood is normal.*

> **Changed sentence to: "If $x$ is the realization of a normal random variable $X$ with known variance $\sigma^2$, the log likelihood for the mean of $X$ has a particularly simple form: $\ell_k(\theta_k) \approx -(x-\theta_k)^2/(2\sigma^2)$."**

*Related comment (page 4) – since you will be using different probability contents, you should define the likelihood interval corresponding to an arbitrary confidence value gamma.*

**Done.**

*8. Section 3. Since you've already described how to construct the plot, the section title is not right. Actually, the S code for the plot is best placed in an appendix – you can mention in Section 2 that code for the plot is in the appendix.*

**Done.**

*9. Section 4. Before you discuss Figure 3, you need to describe the two raindrops (95 and 99 display) that you will be plotting. The second paragraph on page 7 should go at the beginning of Section 4 so the reader will understand what is being plotted.*

*In fact, Figure 4 and the discussion should be placed before the examples. The densities curves and the accompanying raindrops are helpful to get the reader oriented on what the raindrops look like.*

**Will do.**

*10. Page 7, first paragraph. One nice feature of your plots is that they can display posterior distributions. So I would place this paragraph describing the HDR-raindrop in Section 2.*

**Will do.**

*11. Page 8, line 8 from bottom. You should define what the profile likelihood is in this case.*

**Done.**

*12. Page 9. Since the horizontal variable in your plot is log alpha, I think you should refer to values of log alpha (instead of alpha) in your discussion.*

Ram, what do you think? $\alpha$ **has a direct biological interpretation, but does it matter here?**

*13. Page 9, line 8 from bottom. Is it necessary to assume that the mixed model mean has an asymptotic normal distribution?*

**General asymptotic results have not yet been obtained for nonlinear mixed effects models. To clarify this point, we have changed the wording to the following: "The 'mixed model mean (with CI)' is represented by a quadratic raindrop based on the point estimate and standard error obtained using the method of Lindstrom and Bates (1990)."** Ram, I had previously said that the mixed model mean had an asymptotic normal distribution, which has not been shown yet. What do you think of this change?

*14. Page 10, second paragraph from bottom. One advantage of the raindrop plot is that, by using the log scale, you get tighter displays (on the vertical scale), and so you can display many on the same page.*

**Will put this in.**

*15. Figure 4. I think you need a couple of labels over the two sets of plots (say raindrop and density). Also I think it would be more standard to call your densities beta(3, 3) instead of using the Greek beta.*

**Will make both of these changes.**

*16. Figure 6. Likewise, you need two labels to describe your two types of plots.*

**Unfortunately this might make the plot a bit cluttered because the scale for $\alpha$ is on the top of the figure.** Ram, what do you think?