A Segmented Measurement Error Model for Modeling and Analysis of Method Comparison Data

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Abstract

Method comparison studies are concerned with estimating relationship between two clinical measurement methods. The methods often exhibit a structural change in the relationship over the measurement range. Ignoring this change would lead to an inaccurate estimate of the relationship. Motivated by a study of two digoxin assays where such a change occurs, this article develops a statistical methodology for appropriately analyzing such studies. Specifically, it proposes a segmented extension of the classical measurement error model to allow a piecewise linear relationship between the methods. The changepoint at which the transition takes place is treated as an unknown parameter in the model. An expectation-maximization type algorithm is developed to fit the model and appropriate extensions of existing measures are proposed for segment-specific evaluation of similarity and agreement. Bootstrapping and large-sample theory of maximum likelihood estimators are employed to perform the relevant inferences. The proposed methodology is evaluated by simulation and is illustrated by analyzing the digoxin data.

Keywords: agreement; bootstrap; changepoint; concordance correlation; ECM algorithm; total deviation index.

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1 Introduction

Method comparison studies are generally concerned with estimation of relationship between two clinical measurement methods to determine if they can be used interchangeably [1, 2]. The variable being measured is continuous. The methods are assumed to have the same unit of measurement and none of them is considered error-free. Such studies are common in biomedical literature. For example, the article [3] that proposed the *limits of agreement* approach for analysis of method comparison data has over 25,000 citations.

The motivation for this article comes from a study comparing two assays, labelled 1 and 2, for measuring concentration of digoxin [4], a medication for treating certain heart conditions such as atrial fibrillation and heart failure. The data consist of natural logarithm of concentrations (ng/ml) of digoxin measured by the assays on $n = 134$ specimens. Figure 1 presents a scatterplot of measurements of assay 2 (Y_2) against those of assay 1 (Y_1). A plot of difference ($D = Y_2 - Y_1$) against the average of these measurements — popularly known as the *Bland-Altman plot* [3] — is also presented in Figure 2. The scatterplot shows that the underlying trend is piecewise linear. The initial linear trend appears to undergo a change in slope around $y_1 = -0.5$. The assays behave quite differently in the left and right segments formed by this *changepoint*. For example, they have higher correlation and higher agreement in the right segment than the left segment. The change in behavior can be seen more clearly in the Bland-Altman plot where a downward linear trend is followed by a flattening of the trend, with points on the right centered near zero. In [4], it is concluded from this plot that "the two assays are not comparable at low analyte levels" but "may be equivalent above some cut-off level."

The digoxin data are an example of paired method comparison data. Such data are often analyzed by modeling them using the classical *measurement error model* — also known as *errors-in-variables* model — or its variants, see, e.g., [1, 4–7]. The literature on measurement error models, especially in the context of regression analysis, is vast and the books [8–10] may be consulted for an introduction to this topic. The readers specifically interested in measurement error models for method comparison studies may begin with [1]. The classical measurement error model assumes a linear trend over the entire measurement range. However, it is clear from Figure 1 that this model must be extended to allow incorporating the change of slope that is observed in the digoxin data. What is necessary is a *segmented* measurement error model that allows a piecewise linear trend over two segments of the measurement range and treats the changepoint at which the trend lines join as an unknown parameter in the model. Studying this extension is the goal of this article.

Segmented models, also known as *multiphase* or *piecewise* models, for linear regression where the regression function either has different forms or involves different parameters over different segments of the covariate domain have been studied at least since [11], with early contributions including [12, 13]. These articles studied inference for piecewise simple linear regression model over two segments. The changepoint, also known as *join point*, *break point*, or *knot*, represents a value of the covariate at which the regression functions join and it may be known or unknown. The overall regression function may be continuous or discontinuous at the changepoint. A survey of the early literature on segmented regression models can be found in [14, Chapter 9]. More recently, segmented models in the context of logistic and other regressions have been studied by [15–19]. See [20–23] for segmented models for longitudinal data.

When the covariate in regression is measured with error, giving rise to segmented measurement error models, the changepoint represents a value of the error-free covariate. An early article on this topic is [24]. It considered a *threshold model* — a special case of a segmented model where it is assumed that the exposure has no relation with the response up to a threshold — and focussed on estimation of the threshold (i.e., the changepoint) in the context of linear and logistic regression. It found that ignoring the measurement error led to asymptotically biased estimator of the threshold. Moreover, the standard methods for correcting for such bias in classical measurement error models, namely, regression calibration, simulation extrapolation, and maximum likelihood (ML), behaved quite differently when the model is segmented. In particular, if the assumed model was plausible, the ML estimator outperformed the other two estimators in terms of bias and variance. Other articles on segmented measurement error models include [25–27]. They respectively considered probit regression with mixture of normals as the error distribution, logistic regression from a Bayesian perspective, and making use of external and internal validation data in addition to the main data. Bias of the estimated changepoint was a primary focus of these articles.

To our knowledge, none of the existing segmented measurement error models allows the kind of piecewise linear trend that is needed for digoxin data. Such a model is also simple enough to allow closed-form expressions for the likelihood function. In addition to studying this model, another novel contribution of this work is that we apply the proposed model to analyze method comparison data. The eventual goal in the analysis of these data is not just to perform inference regarding regression coefficients or the changepoint, which is typically the case in regression, but to evaluate similarity and agreement of the measurement methods [2, Chapters 1 and 2]. Evaluation of similarity refers to a comparison of marginal characteristics of the methods such as their biases and precisions. Whereas, evaluation of agreement essentially refers to an examination of how close the bivariate distribution of the methods is to being degenerate on the 45^o line. In this case, the methods have perfect agreement because their measurements are identical, or equivalently, their difference is zero with probability one, making them interchangeable. Agreement is evaluated by performing inference on agreement measures such as concordance correlation coefficient [28] and total deviation index [29, 30](see Section 4). These measures are functions of parameters of the model. In case of a segmented model, the evaluation of similarity and agreement has to be performed separately in each segment because the relationship between the methods may be different in the two segments. This is exemplified by the digoxin data in Figures 1 and 2.

The rest of this article is organized as follows. In Section 2, we present the classical measurement model for method comparison data and propose its segmented extension. Section 3 considers an expectation-maximization (EM) type algorithm [31] for fitting the proposed model and discusses tests for changepoint. Section 4 considers segment-specific evaluation of similarity and agreement under the new model. A simulation study is presented in Section 5. The digoxin data are analyzed in Section 6. Section 7 concludes with a discussion. Appendix A presents some necessary distributional results under the new model. The statistical package R [32] has been used for all the computations in this article.

2 Segmented modeling of method comparison data

Let (Y_{i1}, Y_{i2}), $i = 1, \ldots, n$ denote paired measurements data collected in a method comparison study. These data are assumed to be a random sample from the distribution of (Y_1, Y_2), where Y_j represents the measurement by the jth method, $j = 1, 2$, on a randomly selected subject from the underlying population. Here method 1 is assumed to be the standard method that serves as a reference and method 2 is the test method in the comparison.

2.1 Classical measurement error model

The classical measurement error model for paired measurements (Y_1, Y_2) from a method comparison study is [1, 4]

$$Y_1 = b + e_1, \ Y_2 = \beta_0 + \beta_1 b + e_2, \tag{1}$$

where β_0 and β_1 are fixed regression coefficients, b is a random quantity representing the underlying true unobservable measurement, and e_1 and e_2 are random errors associated with the two measurement methods. The true value b is measured with error by method 1 as Y_1 and by method 2 as Y_2. The conditional means of the two methods — $E(Y_1|b) = b$

and $E(Y_2|b) = \beta_0 + \beta_1 b$ — represent their error-free values. These are linearly related. It is assumed that $b \sim N(\mu_b, \sigma_b^2)$, $e_1 \sim N(0, \sigma_{e1}^2)$, and $e_2 \sim N(0, \sigma_{e2}^2)$; and b, e_1, and e_2 are mutually independent. It follows that (Y_1, Y_2) has a bivariate normal distribution with parameters

$$E(Y_1) = \mu_b, \mathrm{var}(Y_1) = \sigma_b^2 + \sigma_{e1}^2, E(Y_2) = \beta_0 + \beta_1 \mu_b, \mathrm{var}(Y_2) = \beta_1^2 \sigma_b^2 + \sigma_{e2}^2, \mathrm{cov}(Y_1, Y_2) = \beta_1 \sigma_b^2.$$

By design, method 1 is assumed to have no bias in that its error-free value equals the true value b. The intercept β_0 and the slope β_1 are respectively known as the *fixed bias* and *proportional bias* of method 2 [2, Chapter 1]. If $\beta_1 = 1$, the methods are said to have the same *scale*. If the methods have unequal scales, their precisions are measured by their *squared sensitivity* — $1/\sigma_{e1}^2$ for method 1 and β_1^2/σ_{e2}^2 for method 2 [33]. The sensitivities are compared using the *squared sensitivity ratio*, $\beta_1^2(\sigma_{e1}^2/\sigma_{e2}^2)$ [2, Chapter 1]. If $(\beta_0, \beta_1) = (0, 1)$, the two methods have the same fixed and proportional biases and hence the same mean. If $(\beta_1, \sigma_{e1}^2/\sigma_{e2}^2) = (1, 1)$, they have the same precision.

It follows from (1) that the model for the observed data (Y_{i1}, Y_{i2}), $i = 1, \ldots, n$ is

$$Y_{i1} = b_i + e_{i1}, \; Y_{i2} = \beta_0 + \beta_1 b_i + e_{i2}, \tag{2}$$

where b_i, e_{i1}, and e_{i2} are mutually independent draws from the respective distributions of b, e_1, and e_2. This model is not identifiable on the basis of paired measurements data and one constraint must be imposed on its parameters to make it identifiable. Although a number of possibilities exist, see, e.g., [9, Chapter 1], three are common in method comparison studies. One is $\beta_1 = 1$, in which case the model becomes a mixed-effects model and is often known as the *Grubbs' model* after [34]. Another is $\sigma_{e1}^2 = \sigma_{e2}^2$, see, e.g., [4] and [8, Chapter 1]. The third is that the ratio $\sigma_{e1}^2/\sigma_{e2}^2$ is known, in which case *Deming regression* is a widely known procedure to fit the model; see, e.g., [6]. See also [1, Chapter 3] and [4] for a discussion of relative merits and demerits of the three approaches. In this article, just as in [4], we work under the equal error variance assumption and denote the common value by σ_e^2.

2.2 Segmented measurement error model

The proposed extension of the classical measurement error model (1) for (Y_1, Y_2) is a segmented model,

$$Y_1 = b + e_1, \quad Y_2 = \beta_0 + \beta_1 b + \beta_2 (b - \psi)_+ + e_2, \tag{3}$$

where $(b - \psi)_+ = \max\{0, b - \psi\}$. We can write $(b - \psi)_+ = (b - \psi) I(b > \psi)$, with $I(A)$ denoting the indicator function of A. Here ψ is the changepoint. It follows from (3) that the conditional mean $E(Y_2|b)$ of method 2, which represents its error-free value, follows the piecewise linear model,

$$E(Y_2|b) = \begin{cases} \beta_0 + \beta_1 b, & b \leq \psi, \\ (\beta_0 - \beta_2 \psi) + (\beta_1 + \beta_2) b, & b > \psi. \end{cases} \tag{4}$$

Thus, $E(Y_2|b)$ undergoes a change in slope from β_2 to $\beta_1 + \beta_2$ at the changepoint $b = \psi$ and it is continuous in b at the changepoint. The latter necessitates a change in intercept also — from β_0 to $\beta_0 - \beta_2 \psi$ at the changepoint. For the distributions of the random terms in (3), we assume as in (1) that

$$b \sim N(\mu_b, \sigma_b^2), \; e_1 \sim N(0, \sigma_e^2), \; e_2 \sim N(0, \sigma_e^2), \tag{5}$$

and b, e_1, and e_2 are mutually independent. Thus, the segmented model for the observed data is

$$Y_{i1} = b_i + e_{i1}, \; Y_{i2} = \beta_0 + \beta_1 b_i + \beta_2 (b_i - \psi)_+ + e_{i2}, \; i = 1, \ldots, n, \tag{6}$$

where b_i, e_{i1}, and e_{i2} are mutually independent draws from the respective distributions of b, e_1, and e_2 given by (5). The classical model (2) becomes a special case of the segmented model (6) when $\beta_2 = 0$ or in the limit as $\psi \to \infty$. Appendix A presents some distributional results under the segmented model (3) that are needed in this article for development of the proposed methodology.

3 Fitting the segmented model

The segmented model (6) has 7 unknown parameters, $(\mu_b, \beta_0, \beta_1, \beta_2, \sigma_b^2, \sigma_e^2, \psi)$. Let $\boldsymbol{\theta}$ be the 7×1 vector of these parameters. Its log-likelihood function can be written as

$$L(\boldsymbol{\theta}) = \sum_{i=1}^{n} \log\{f(y_{i1}, y_{i2}|\boldsymbol{\theta})\}, \tag{7}$$

where the density f is given by (A.4) in Proposition A.3 in Appendix A. The parameter vector $\boldsymbol{\theta}$ is now explicitly included as an argument of f. We may numerically maximize $L(\boldsymbol{\theta})$ by a Newton-Raphson type algorithm to get ML estimate $\hat{\boldsymbol{\theta}}$ of $\boldsymbol{\theta}$. However, in our experience, a direct maximization of this function is sensitive to starting points and often leads to unstable estimates. Therefore, we consider an alternative approach. It is a variant of the EM algorithm, specifically the ECM algorithm [31], in which the M-step of EM is replaced by a sequence of computationally simpler constrained maximization (CM) steps. Each iteration of ECM increases the likelihood function and the algorithm often converges to a maxima [35, Chapter 5].

The ECM algorithm is presented in Appendix B. As is true with any EM-type algorithm, one needs to try a number of starting points to have some assurance that the algorithm converges to a global maxima $\hat{\boldsymbol{\theta}}$. Next, let $\mathbf{I} = -\partial^2 \log\{L(\boldsymbol{\theta})\}/\partial\boldsymbol{\theta}^2|_{\boldsymbol{\theta}=\hat{\boldsymbol{\theta}}}$ denote the Hessian matrix of $-L(\boldsymbol{\theta})$ evaluated at the MLE. This matrix is also known as the *observed information matrix*. It can be computed by numerical differentiation. Analytical expressions for the elements of this matrix are also available in [36, Chapter 3]. However, we avoid presenting them here as they are rather tedious. When n is large, it follows from the large-sample theory of ML estimators [37, Chapter 7] that the distribution of $\hat{\boldsymbol{\theta}}$ can be approximated by a $N(\boldsymbol{\theta}, \mathbf{I}^{-1})$ distribution. This result can be used to perform inference on $\boldsymbol{\theta}$.

Once the model (6) is fit to the data, we can replace the unknown parameters in the expression (A.11) for the best linear predictor of b_i with their ML estimates to get the estimated predictor $\hat{b}_i$. Then, the fitted values can be computed as

$$\hat{Y}_{i1} = \hat{b}_i,\ \hat{Y}_{i2} = \hat{\beta}_0 + \hat{\beta}_1 \hat{b}_i + \hat{\beta}_2 (\hat{b}_i - \hat{\psi})_+, \quad i = 1, \ldots, n.$$

3.1 Testing for changepoint

In the segmented model (6), we are particularly interested in checking whether or not there is a need to include the changepoint. Without the changepoint, the model reduces to the classical model (2). Thus, the null hypothesis H_0 of interest is that the data follow (2) against the alternative H_1 that the data follow (6). We consider a likelihood ratio test for this. The test statistic is $\Lambda = -2(L_{\text{reduced}} - L_{\text{full}})$, where L_{full} and L_{reduced}, respectively, represent the log-likelihood functions under the full model (6) and the reduced model (2) evaluated at the corresponding ML estimates. Closed-form expressions for ML estimates in case of (2) are available in [8, Chapter 1]. Let Λ_{obs} be the observed value of the test statistic.

Oftentimes, when n is large, the null distribution of a likelihood ratio statistic can be approximated by a χ^2-distribution with degrees of freedom equal to the number of free parameters in the full model that are fixed to get the reduced model. However, since in our case, the reduced model (2) can be obtained from full model (6) by setting either $\beta_2 = 0$ or taking limit $\psi \to \infty$, the standard χ^2 approximation does not apply. A similar issue is encountered in segmented linear regression models and some authors, e.g., [13], deal with it by using a χ^2 approximation with 3 degrees of freedom. Asymptotic likelihood ratio tests under certain nonstandard conditions are also discussed by [38], but the condition of interest here that includes the limit of a parameter going to infinity is not covered by that article.

We may follow along the lines of [13] and use a χ^2 approximation with degrees of freedom equal to 2 or 3. Alternatively, we may use bootstrap to approximate the null distribution of Λ and use it to compute the p-value [39, Chapter 4]. The steps in this calculation are as follows:

Step 1: Simulate n independent pairs of observations (Y^*_{i1}, Y^*_{i2}), $i = 1, \ldots, n$ following model (2) with parameters set equal to their ML estimates obtained by fitting (2) to the original data. The starred observations represent a parametric resample of the original data.

Step 2: Fit the full and reduced models to the resample in Step 1 and compute the test statistic Λ.

Step 3: Repeat Steps 1 and 2 a large number of times, say, B, resulting in B values $\Lambda_1^*, \ldots, \Lambda_B^*$ for the test statistic. Take the proportion of these values that are greater than or equal to Λ_{obs} as the approximate p-value for the test.

We may also use model selection criteria such as Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) to compare the two models.

4 Evaluation of similarity and agreement

Under the classical model (1), similarity of two measurement methods is evaluated by examining their biases using intercept β_0 and slope β_1 and their precisions using squared sensitivity ratio $\beta_1^2(\sigma_{e1}^2/\sigma_{e2}^2)$. If $(\beta_0, \beta_1, \sigma_{e1}^2/\sigma_{e2}^2) = (0, 1, 1)$, the methods have the same fixed and proportional biases and precisions, and hence are similar. In this case, the measurement methods have the same marginal distributions. Agreement between the methods is evaluated using measures of agreement such as CCC and TDI [28, 29]. These are defined as follows:

$$\begin{aligned} \text{CCC} &= \frac{2\text{cov}(Y_1, Y_2)}{\{E(Y_1) - E(Y_2)\}^2 + \text{var}(Y_1) + \text{var}(Y_2)}, \\ \text{TDI}(p) &= p\text{th quantile of } |D|, \end{aligned} \tag{8}$$

where p is a large probability specified by the practitioner. Typically, $p \in \{0.85, 0.90, 0.95\}$ is used in application. By definition, $|\text{CCC}| \leq 1$ and $\text{TDI}(p) \geq 0$. Good agreement is implied by a large value for CCC or a small value for TDI. Agreement is perfect in the limiting case when $\text{CCC} = 1$ or $\text{TDI} = 0$. We generally use two-sided confidence intervals for the measures of similarity and one-sided confidence intervals for the measures of agreement.

In case of the segmented model (3), due to the change in the relationship between the methods over the two segments, the evaluation of similarity and agreement must be done separately in each segment using segment-specific versions of the measures. Thus, for similarity evaluation, it follows from (4) that fixed and proportional biases can be compared using β_0 and β_1 in the left segment and $\beta_0 - \beta_2\psi$ and $\beta_1 + \beta_2$ in the right segment. Although the precisions can be compared using squared sensitivity ratio but, under the equal error variance assumption in (3), it equals β_1^2 in the left segment and $(\beta_1 + \beta_2)^2$ in the right segment, whose square-roots are already examined as part of the bias evaluation. Thus, the methods can be considered similar over a segment if the intercept and slope over that segment equal zero and one, respectively.

The segment-specific versions of CCC and TDI are obtained by evaluating (8) under the marginal distribution of (Y_1, Y_2) when b is truncated to be either $b \leq \psi$ (left segment) or $b > \psi$ (right segment). For CCC, this amounts to substituting in (8) the relevant conditional moments from Proposition A.2 in Appendix A. However, such closed-form expressions are not available in case of TDI. For a given p, these are obtained numerically by solving $p = P(|D| \leq q | b \leq \psi)$ and $p = P(|D| \leq q | b > \psi)$ for q where the probabilities are obtained by integrating the relevant marginal density of D from Proposition A.5. We may also compute a single CCC and TDI for the entire measurement range by using the marginal moments of (Y_1, Y_2) given by Proposition A.1 and the marginal density of D given by Proposition A.4. But, unless there is no changepoint in which case the segmented model reduces to the classical model, these overall measures may be misleading.

The various measures needed for evaluation of similarity and agreement are functions of the model parameter vector $\boldsymbol{\theta}$. As in the classical model, they are estimated by replacing $\boldsymbol{\theta}$ in their definitions with its ML estimate $\hat{\boldsymbol{\theta}}$ and their one- and two-sided confidence intervals are computed using the multivariate delta method [37, Chapter 5]. To improve accuracy of confidence intervals for parameters or parameter functions whose range is not the entire real line, the intervals are computed after applying a normalizing transformation and the results are inverted back to the original scale. Specifically, a log transformation is applied to σ_e^2, σ_b^2, and TDI and the Fisher's z-transformation is applied to CCC. Alternatively, the confidence intervals can also be computed using a bootstrap method, e.g., the *normal approximation* bootstrap that uses bias and standard error computed using bootstrap [39, Chapter 5].

5 A simulation study

A simulation study is performed to evaluate performance of point and interval estimators of parameters in the proposed model and the test for changepoint. We are specifically interested in examining the following: (i) biases and mean squared errors (MSEs) for ML estimators; (ii) accuracy of standard large-sample and bootstrap confidence intervals; (iii) accuracy of the test for changepoint where p-value is computed by bootstrap and by approximating the null distribution of the test statistic by a χ^2 distribution with 2 and 3 degrees of freedom; and (iv) the benefits of the proposed method for evaluating similarity and agreement over the naive method that involves fitting the classical model.

We begin with (i) and (ii) for model parameters and measures of similarity and agreement. The model is fit by both ECM algorithm and direct maximization upon using a log transformation for σ_e^2 and σ_b^2 to obtain an unconstrained parameterization. The resulting estimates are denoted by marking them as ECM and DIR, respectively. For the latter, we use `optim` function in `R` with `method` argument of the function set as `BFGS`, which is a quasi-Newton method. We initially consider five settings presented in Table 1 for parameters of the segmented model (6). These are motivated by the point and interval estimates reported in Table 7 for digoxin data. The number of subjects is set to $n \in \{30, 50, 100\}$. The number of bootstrap replications is taken to be $B = 500$. We also choose 0.95 as the nominal confidence level and $p = 0.90$ as the probability for TDI. For each combination of parameter setting and n, the data are simulated from the model (6) and the point and interval estimates are computed as described in Section 3. Then, this process is repeated 500 times and the estimated biases and MSEs of the point estimators and coverage probabilities of the confidence intervals are computed. The results for the three values of n under setting 1a are summarized in Tables 2, 3, and 4. The ratio of MSEs of ML estimates obtained by ECM and direct maximization, with former in the denominator, are also presented in these tables. The results for other parameter settings are omitted as they are qualitatively similar.

From the results regarding point estimates, we conclude that, with a few notable exceptions in case of $n = 30$, both ECM and direct maximization lead to nearly identical MSEs of the estimates. When the exceptions do occur, ECM leads to slightly smaller MSE than direct maximization. Although, in principle, both ECM and direct maximization are expected to provide identical ML estimates, but in practice, direct maximization is more sensitive to starting points than ECM, especially when n is not large, and this explains the difference in the two sets of estimates. Also, as expected, both bias and MSE for estimators of all parameters decrease as n increases.

The coverage probabilities of the standard large-sample confidence intervals are mostly less than the nominal level. Although the situation improves as n increases to 100, these intervals cannot be considered accurate. With a few notable exceptions, the bootstrap intervals are generally more accurate than the standard intervals and may be considered to have acceptable accuracy even with $n = 30$. There is some evidence that in case of $n = 100$ the coverage probabilities for the intervals for agreement measures in the right segment may be higher than the nominal level. Additional simulations in case of $n = 200$ (not presented) show that the coverage probabilities of the standard intervals are quite close to the nominal level. Therefore, on the whole, unless n is 200 or more, bootstrap should be preferred over the standard intervals. We have also explored three other bootstrap methods for constructing confidence intervals, namely, *basic bootstrap*, *studentized bootstrap*, and *percentile bootstrap* [39, Chapter 5]. Among the settings investigated, there is little practical difference in the accuracy of the various bootstrap methods (results omitted).

Now, we consider the issue (iii) by examining how close the estimated type I error probabilities of the changepoint tests are to the nominal level of $\alpha = 0.05$. For this, the data are simulated under the null hypothesis from the classical model (2) with parameter values as in settings 1a through 5a except that the parameters β_2 and ψ are omitted. We refer to these settings as 1b through 5b, respectively. The results presented in Table 5 show that the χ^2_3 approximation is quite conservative in that the corresponding type I error probabilities are much smaller than the nominal level. In contrast, the χ^2_2 approximation appears slightly liberal in that the corresponding type I error probabilities are a bit larger than the nominal level for $n = 30, 50$ but seems quite accurate for $n = 100$. These conclusions hold for both ECM and direction maximization methods. In case of ECM, the bootstrap approximation also works well and it may be considered the best of the three approximations. However, this is not the case for bootstrap when direct maximization is used. On the whole, these results suggest that both χ^2_2 and bootstrap approximations can be used to perform the test of changepoint.

Next, we consider the issue (iv) about benefits of the proposed method over the naive method for evaluating similarity and agreement. For this, we compare biases and MSEs of the various measures estimated using the two methods under the scenario that the true model is the segmented model (6) with parameters given by setting 1a. Ignoring reality, the naive method provides common estimates for both segments, whereas, the proposed method aptly provides separate estimates (using ECM algorithm) for the two segments. Table 6 presents biases and MSEs for the two sets of estimates for $n = 30$ and 100. We see that the proposed estimates are substantially more accurate than the naive estimates as the former have much smaller bias (in absolute value) and MSE than the latter. Furthermore, there is little difference in the bias and MSE of the naive estimates between $n = 30$ and $n = 100$. However, both absolute bias and MSE of the proposed estimates decrease as n increases.

On the whole, the practical implications of the results from the simulation study may be summarized as follows: (a) When the true model is segmented, fitting the classical model leads to estimates with higher bias and MSE than the segmented estimates. Moreover, the bias and MSE of the classical model estimates decrease little as n increases. (b) To fit the segmented model, one may use either direct maximization or the ECM algorithm when $n \geq 50$, otherwise the latter should be preferred. (c) To compute confidence intervals, one may use the standard large-sample approach when $n \geq 200$, otherwise bootstrap should be preferred. (d) To perform the test for changepoint, one may use either the χ_2^2 approximation or bootstrap.

6 Illustration: Analysis of digoxin data

We now return to the digoxin data introduced in Section 1 and analyze them using the proposed methodology. First, we fit the model (6) by ML using both ECM algorithm and direct maximization of the log-likelihood function. Table 7 presents point estimates obtained by ECM, standard errors of the estimates, and 95% bootstrap confidence intervals for model parameters. Estimates produced by direct maximization are nearly identical and hence are omitted. None of the standard errors appears unusually high. We see that the interval $(0.39, 0.57)$ for β_2 does not contain zero, suggesting the need for a changepoint. Next, we test the null hypothesis that the data follow the classical model (2) using the likelihood ratio test. The observed value of the test statistic is 118.12 and the p-value computed using bootstrap with $B = 500$ is practically zero. This confirms the need for the changepoint. Even AIC and BIC prefer the segmented model (6) over the classical model (2) as their respective values for the two models are 215.6 and 329.7 (AIC) and 235.8 and 344.2 (BIC).

The estimated changepoint is $\hat{\psi} = -0.71$. Substituting the unknowns in (4) with their estimates gives the fitted piecewise straight line for $E(Y_2|b)$. The resulting line is $-0.29+0.46b$ in the left segment ($b \leq -0.71$) and $0.05 + 0.94b$ in the right segment ($b > -0.71$). They are superimposed on the scatterplot in Figure 1. They seem to provide a good fit to the underlying trend in the data. For comparison, also superimposed on the plot is the line $0.16 + 0.79b$ obtained by fitting the classical model. It clearly does not fit the data well.

Under the fitted segmented model (6), the bivariate distribution of (Y_1, Y_2) has mean $(-1.32, -0.90)$, variance $(0.27, 0.06)$, and correlation 0.92 in the left segment; and mean $(0.57, 0.59)$, variance $(0.69, 0.61)$, and correlation 0.99 in the right segment. These are obtained by replacing the unknowns in the moments given by Proposition A.2 with their estimates. It follows that the fitted distribution of $D = Y_2 - Y_1$ has mean 0.42 and variance 0.09 in the left segment and 0.01 and 0.02 in the right segment. Thus, assay 2 has higher mean and lower variance than assay 1 in both segments but the difference is much smaller in the right segment than the left segment. The correlation between the assays is also higher in the right segment. These findings are consistent with what we saw in Figure 1.

Next, we consider evaluation of similarity of the assays. Table 8 presents estimates and 95% confidence intervals for the segment-specific similarity measures considered in Section 4. None of the intervals appears unusually wide. In the left segment, the intervals for the intercept β_0 and slope β_1 are $(-0.42, -0.16)$ and $(0.38, 0.55)$, respectively. In the right segment, they are $(0.02, 0.08)$ and $(0.91, 0.97)$ for the intercept $\beta_0 - \beta_2\psi$ and slope $\beta_1 + \beta_2$, respectively. None of the intercept intervals covers zero. Likewise, none of the slope intervals covers one. Thus, because their fixed and proportional biases are not equal, the assays cannot be regarded as similar in either segment. That said, the biases differ considerably in the left segment and only moderately so in the right segment.

Our next task is to evaluate agreement between the assays. Estimates and 95% one-sided confidence bounds for the segment-specific agreement measures considered in Section 4 are also presented in Table 8 on transformed scale. These estimates and bounds are transformed back to the original scale by applying the inverse transformation. In the left segment, the lower bound for CCC is 0.36 and it is 0.98 in the right segment. Further, the upper bounds for TDI(0.90) in the left and right segments are 1.04 and 0.25, respectively. Thus, on the basis of both measures, the assays exhibit much higher agreement in the right segment than in the left segment. This is consistent with what we saw in Figure 1. Focusing on the right segment, we see that the CCC estimate and lower bound are nearly one, indicating potentially excellent agreement between the assays. But this conclusion may be misleading considering that, in these data, $\hat{\sigma}_e^2 = \exp(-4.87) \approx 0.01$ is much smaller than $\hat{\sigma}_b^2 = \exp(0.17) \approx 1.19$. In such a scenario, the CCC estimate tends to be high [40]. A better picture of agreement is given by the TDI upper bound which indicates that 90% of ratios of measurements by the two assays are estimated to fall within $\exp(-0.25) \approx 0.78$ to $\exp(0.25) \approx 1.28$ with 95% confidence. Given how wide this range is around one, the extent of agreement between the assays cannot be considered strong.

Thus, altogether we see that the two digoxin assays exhibit considerably more similarity and agreement at higher analyte levels than at low levels. However, even at high analyte levels, the assays cannot be regarded as similar in the sense of having equal fixed and proportional biases or having well enough agreement for interchangeable use.

There appear to be two outlying observations in the bottom right quadrant of the Bland-Altman plot in Figure 2. To assess their impact, we repeat the analysis by excluding them. The estimated changepoint moves slightly to the left to $\hat{\psi} = -1.13$. Further, the fitted piecewise line for $E(Y_2|b)$ is $-0.55 + 0.35b$ in the left segment ($b \leq -1.13$) and $0.07 + 0.90b$ in the right segment ($b > -1.13$). Moreover, the 95% lower bound for CCC is 0.16 in the left segment and 0.98 in the right segment; and the 95% upper bound for TDI(0.90) in the left and right segments are 1.15 and 0.27, respectively. Thus, upon removal of the outliers, the assays appear slightly less similar and have slightly less agreement than before. This reinforces the earlier conclusion that the assays cannot be regarded as similar or having well enough agreement for interchangeable use.

7 Discussion

This article develops a segmented extension of the classical measurement error model for method comparison data wherein the measurement methods exhibit a piecewise linear relationship. Extensions of existing measures are derived under the model to perform segment-specific evaluation of similarity and agreement. `R` code for implementing the proposed methodology is publicly available at `http://utdallas.edu/~pankaj/`. Although our segmented model assumed equality of error variances, one may easily relax this assumption (see [36, Chapter 3]). While we restrict attention to piecewise linear relationship that is continuous at the changepoint, some extensions of the approach may be of interest. These include allowing for nonlinear relationships, abrupt as well as smooth change in the relationship, and more than one changepoint. Further research is needed to develop these extensions.

Data availability statement: The data used in this paper are from [4] and are publicly available at `http://www.stat.umn.edu/hawkins/`.

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Appendix A. Distribution theory under the segmented model

We now present some distributional results under the segmented model (3) that are of interest in this article. Their proofs are available in [36, Chapter 3]. Let $\phi(x)$ and $\Phi(x)$ respectively denote the probability density function and the cumulative distribution function of a $N(0,1)$ distribution. Next, define the following quantities:

$$
\begin{aligned}
g_1(x,\mu,\sigma) &= \frac{x-\mu}{\sigma},\\
g_2(x,\mu,\sigma) &= \frac{\phi\left(g_1(x,\mu,\sigma)\right)}{1-\Phi\left(g_1(x,\mu,\sigma)\right)},\\
g_3(x,\mu,\sigma) &= \frac{\phi\left(g_1(x,\mu,\sigma)\right)}{\Phi\left(g_1(x,\mu,\sigma)\right)},\\
g_4(\beta,\sigma_1,\sigma_2) &= \left(\frac{1}{\sigma_1^2}+\frac{(\beta_1+\beta)^2}{\sigma_2^2}+\frac{1}{\sigma_b^2}\right)^{-1},\\
g_5(\beta,\sigma_1,\sigma_2) &= \left(\frac{y_1}{\sigma_1^2}+\frac{(y_2-\beta_0+\beta\psi)(\beta_1+\beta)}{\sigma_2^2}+\frac{\mu_b}{\sigma_b^2}\right),\\
g_6(\beta,\sigma_1,\sigma_2) &= g_4(\beta,\sigma_1,\sigma_2)g_5(\beta,\sigma_1,\sigma_2),\\
g_7(\beta,\mu,\sigma^2,\sigma_1,\sigma_2) &= \frac{\sqrt{2\pi\sigma^2}}{\sqrt{\sigma_1^2\sigma_2^2\sigma_b^2}}\phi\left(\frac{y_1}{\sigma_1}\right)\phi\left(\frac{y_2-\beta_0+\beta\psi}{\sigma_{e2}}\right)\phi\left(\frac{\mu_b}{\sigma_b}\right)\exp\left(\frac{\mu^2}{2\sigma^2}\right). \qquad \text{(A.1)}
\end{aligned}
$$

The functions g_4 to g_7 depend on other quantities as well in addition to those explicitly specified as the arguments. However, this dependence is suppressed for notational convenience.

Proposition A.1. *Consider* (Y_1, Y_2) *following the model* (3)*. The mean and variance of* Y_1 *and* Y_2 *and their covariance are as follows:*

(a) $E(Y_1) = \mu_b$ *and* $var(Y_1) = \sigma_b^2 + \sigma_e^2$*,*

(b) $E(Y_2) = \beta_0 + \beta_1\mu_b + \beta_2 m_1$ *and* $var(Y_2) = \beta_1^2\sigma_b^2 + \beta_2^2 m_3 + 2\beta_1\beta_2 m_4 + \sigma_e^2$*,*

(c) $cov(Y_1, Y_2) = \beta_1\sigma_b^2 + \beta_2 m_4$*,*

where

$$
\begin{aligned}
m_1 &= E[(b-\psi)_+] = \{1-\Phi\left(g_1(\psi,\mu_b,\sigma_b)\right)\}(\mu_b-\psi) + \phi\left(g_1(\psi,\mu_b,\sigma_b)\right)\sigma_b,\\
m_2 &= E\left[\{(b-\psi)_+\}^2\right] = \{1-\Phi\left(g_1(\psi,\mu_b,\sigma_b)\right)\}\left\{(\mu_b-\psi)^2+\sigma_b^2\right\}\\
&\qquad + \left(g_1(\psi,\mu_b,\sigma_b)\sigma_b^2 + 2\mu_b\sigma_b - 2\psi\sigma_b\right)\phi\left(g_1(\psi,\mu_b,\sigma_b)\right),\\
m_3 &= var[(b-\psi)_+] = m_2 - m_1^2,\\
m_4 &= cov[b,(b-\psi)_+] = \{1-\Phi\left(g_1(\psi,\mu_b,\sigma_b)\right)\}\sigma_b^2\\
&\qquad + \left\{g_1(\psi,\mu_b,\sigma_b)\sigma_b^2 + \mu_b\sigma_b - \psi\sigma_b\right\}\phi\left(g_1(\psi,\mu_b,\sigma_b)\right). \qquad \text{(A.2)}
\end{aligned}
$$

Proposition A.2. *Consider (Y_1, Y_2) following the model (3). The mean and variance of Y_1 and Y_2 and their covariance when b is truncated to be either $b \le \psi$ or $b > \psi$ are as follows:*

(a) $E(Y_1|b \le \psi) = E(b|b \le \psi)$ *and* $var(Y_1|b \le \psi) = var(b|b \le \psi) + \sigma_e^2$,

(b) $E(Y_2|b \le \psi) = \beta_0 + \beta_1 E(b|b \le \psi)$ *and* $var(Y_2|b \le \psi) = \beta_1^2 var(b|b \le \psi) + \sigma_e^2$,

(c) $cov(Y_1, Y_2|b \le \psi) = \beta_1 var(b|b \le \psi)$,

(d) $E(Y_1|b > \psi) = E(b|b > \psi)$ *and* $var(Y_1|b > \psi) = var(b|b > \psi) + \sigma_e^2$,

(e) $E(Y_2|b > \psi) = (\beta_0 - \beta_2\psi) + (\beta_1 + \beta_2)E(b|b > \psi)$ *and* $var(Y_2|b > \psi) = (\beta_1+\beta_2)^2 var(b|b > \psi) + \sigma_e^2$,

(f) $cov(Y_1, Y_2|b > \psi) = (\beta_1 + \beta_2) var(b|b > \psi)$,

where

$$
\begin{aligned}
E(b|b \le \psi) &= \mu_b - \sigma_b g_3(\psi,\mu_b,\sigma_b),\\
var(b|b \le \psi) &= \sigma_b^2\left\{1 - g_1(\psi,\mu_b,\sigma_b)g_3(\psi,\mu_b,\sigma_b) - g_3^2(\psi,\mu_b,\sigma_b)\right\}.\\
E(b|b > \psi) &= \mu_b + \sigma_b g_2(\psi,\mu_b,\sigma_b),\\
var(b|b > \psi) &= \sigma_b^2\left\{1 + g_1(\psi,\mu_b,\sigma_b)g_2(\psi,\mu_b,\sigma_b) - g_2^2(a_1,\mu_b,\sigma_b)\right\}. \qquad \text{(A.3)}
\end{aligned}
$$

Proposition A.3. *The joint probability density function of* (Y_1, Y_2) *following the model* (3) *is*

$$f(y_1, y_2) = f_1(y_1, y_2) + f_2(y_1, y_2), \tag{A.4}$$

where

$$\begin{aligned} f_1(y_1, y_2) &= \int_{-\infty}^{\psi} f(b, y_1, y_2) db = g_7(0, g_6(0, \sigma_e, \sigma_e), g_4(0, \sigma_e, \sigma_e), \sigma_e, \sigma_e) \\ &\quad \times \Phi\left(g_1(\psi, g_6(0, \sigma_e, \sigma_e), \sqrt{g_4(0, \sigma_e, \sigma_e)})\right) \\ f_2(y_1, y_2) &= \int_{\psi}^{\infty} f(b, y_1, y_2) db = g_7(\beta_2, g_6(\beta_2, \sigma_e, \sigma_e), g_4(\beta_2, \sigma_e, \sigma_e), \sigma_e, \sigma_e) \\ &\quad \times \left[1 - \Phi\left(g_1\left(\psi, g_6(\beta_2, \sigma_e, \sigma_e), \sqrt{g_4(\beta_2, \sigma_e, \sigma_e)}\right)\right)\right]. \end{aligned} \tag{A.5}$$

Proposition A.4. *Consider* (Y_1, Y_2) *following the model* (3)*. The probability density function of* $D = Y_1 - Y_2$ *is*

$$h(d) = h_1(d) + h_2(d), \tag{A.6}$$

where

$$\begin{aligned} h_1(d) &= \int_{-\infty}^{\psi} f(d, b) db = \frac{\sqrt{2\pi c_1}}{\sqrt{\sigma^2 \sigma_b^2}} \phi\left(\frac{d - \beta_0}{\sigma}\right) \phi\left(\frac{\mu_b}{\sigma_b}\right) \exp\left(\frac{c_2^2}{2c_1}\right) \Phi(g_1(\psi, c_2, \sqrt{c_1}), \\ h_2(d) &= \int_{\psi}^{\infty} f(d, b) db = \frac{\sqrt{2\pi c_3}}{\sqrt{\sigma^2 \sigma_b^2}} \phi\left(\frac{d - \beta_0 + \beta_2 \psi}{\sigma}\right) \phi\left(\frac{\mu_b}{\sigma_b}\right) \exp\left(\frac{c_4^2}{2c_3}\right) \\ &\quad \times \left[1 - \Phi(g_1(\psi, c_4, \sqrt{c_3}))\right], \end{aligned} \tag{A.7}$$

and

$$\begin{aligned} \sigma^2 &= 2\sigma_e^2, \\ c_1 &= \left(\frac{(\beta_1 - 1)^2}{\sigma^2} + \frac{1}{\sigma_b^2}\right)^{-1}, \\ c_2 &= \left(\frac{(d - \beta_0)(\beta_1 - 1)}{\sigma^2} + \frac{\mu_b}{\sigma_b^2}\right) c_1 \\ c_3 &= \left(\frac{(\beta_1 + \beta_2 - 1)^2}{\sigma^2} + \frac{1}{\sigma_b^2}\right)^{-1} \\ c_4 &= \left(\frac{(d - \beta_0 + \beta_2 \psi)(\beta_1 + \beta_2 - 1)}{\sigma^2} + \frac{\mu_b}{\sigma_b^2}\right) c_3. \end{aligned} \tag{A.8}$$

Proposition A.5. *Consider* (Y_1, Y_2) *following the model* (3)*. The probability density function of* $D = Y_1 - Y_2$ *when* b *is truncated to be either* $b \le \psi$ *or* $b > \psi$ *are as follows:*

$$h(d|b \le \psi) = \frac{h_1(d)}{\Phi(g_1(\psi, \mu_b, \sigma_b))}, \; h(d|b > \psi) = \frac{h_2(d)}{1 - \Phi(g_1(\psi, \mu_b, \sigma_b))}, \tag{A.9}$$

where $h_1(d)$ *and* $h_2(d)$ *are given by* (A.7) *in Proposition A.4.*

Proposition A.6. *Consider* (Y_1, Y_2) *following the model* (3)*. The first and second moments of* b *and* $(b - \psi)_+$ *conditional on* $(Y_1, Y_2) = (y_1, y_2)$ *are as follows:*

(a) $E[b|y_1, y_2] = (A_1 + A_2)/f(y_1, y_2)$,

(b) $E[b^2|y_1, y_2] = (A_3 + A_4)/f(y_1, y_2)$,

(c) $E\left[(b - \psi)_+|y_1, y_2\right] = (A_2 - \psi f_2(y_1, y_2))/f(y_1, y_2)$,

(d) $E\left[\{(b - \psi)_+\}^2|y_1, y_2\right] = (A_4 - 2\psi A_2 + \psi^2 f_2(y_1, y_2))/f(y_1, y_2)$,

(e) $E\left[b(b - \psi)_+|y_1, y_2\right] = (A_4 - \psi A_2)/f(y_1, y_2)$,

where

$$\begin{aligned}
A_1 &= \int_{-\infty}^{\psi} b f(b, y_1, y_2) db = f_1(y_1, y_2) \Big\{ g_6(0, \sigma_e, \sigma_e) - \sqrt{g_4(0, \sigma_e, \sigma_e)} \\
&\qquad\qquad \times g_3\left(\psi, g_6(0, \sigma_e, \sigma_e), \sqrt{g_4(0, \sigma_e, \sigma_e)}\right) \Big\} \\
A_2 &= \int_{\psi}^{\infty} b f(b, y_1, y_2) db = f_2(y_1, y_2) \Big\{ g_6(\beta_2, \sigma_e, \sigma_e) + \sqrt{g_4(\beta_2, \sigma_e, \sigma_e)} \\
&\qquad\qquad \times g_2\left(\psi, g_6(\beta_2, \sigma_e, \sigma_e), \sqrt{g_4(\beta_2, \sigma_e, \sigma_e)}\right) \Big\} \\
A_3 &= \int_{-\infty}^{\psi} b^2 f(b, y_1, y_2) db = f_1(y_1, y_2) \left\{ g_4(0, \sigma_e, \sigma_e) + g_6^2(0, \sigma_e, \sigma_e) \right. \\
&\quad - g_1(\psi, g_6(0, \sigma_e, \sigma_e), \sqrt{g_4(0, \sigma_e, \sigma_e)}) \\
&\quad \times g_4(0, \sigma_e, \sigma_e) g_3\left(\psi, g_6(0, \sigma_e, \sigma_e), \sqrt{g_4(0, \sigma_e, \sigma_e)}\right) \\
&\quad \left. - 2\sqrt{g_4(0, \sigma_e, \sigma_e)} g_6(0, \sigma_e, \sigma_e) g_3\left(\psi, g_6(0, \sigma_e, \sigma_e), \sqrt{g_4(0, \sigma_e, \sigma_e)}\right) \right\} \\
A_4 &= \int_{\psi}^{\infty} b^2 f(b, y_1, y_2) db = f_2(y_1, y_2) \left\{ g_4(\beta_2, \sigma_e, \sigma_e) + g_6^2(\beta_2, \sigma_e, \sigma_e) \right.
\end{aligned}$$

$$
\begin{aligned}
&+g_1(\psi, g_6(\beta_2, \sigma_e, \sigma_e), \sqrt{g_4(\beta_2, \sigma_e, \sigma_e)}) \\
&\times g_4(\beta_2, \sigma_e, \sigma_e) g_2 \left(\psi, g_6(\beta_2, \sigma_e, \sigma_e), \sqrt{g_4(\beta_2, \sigma_e, \sigma_e)}\right) \\
&+2\sqrt{g_4(\beta_2, \sigma_e, \sigma_e)} g_6(\beta_2, \sigma_e, \sigma_e) g_2 \left(\psi, g_6(\beta_2, \sigma_e, \sigma_e), \sqrt{g_4(\beta_2, \sigma_e, \sigma_e)}\right)\Big\}, \qquad \text{(A.10)}
\end{aligned}
$$

and f_1*,* f_2*, and* f *are given by A.4 and* (A.5) *in Proposition A.3.*

Proposition A.7. *Consider the model* (3)*. The best linear predictor of* b *using* (Y_1, Y_2) *is*

$$
\hat{b} = \mu_b + [\sigma_b^2, \beta_1\sigma_b^2 + \beta_2 m_4] \left(var\left(\left[\begin{smallmatrix} Y_1 \\ Y_2 \end{smallmatrix}\right]\right)\right)^{-1} \left[\begin{smallmatrix} Y_1 - \mu_b \\ Y_2 - E(Y_2) \end{smallmatrix}\right], \qquad \text{(A.11)}
$$

where m_4 *is given by* (A.2) *and the moments involved are given by Proposition A.1.*

Appendix B. ECM algorithm for model fitting

To develop the ECM algorithm, we take b_i in (6) as the *missing data* and (b_i, Y_{i1}, Y_{i2}) as the *complete data* for the ith subject. The logarithm of the joint density $f(b, y_1, y_2|\boldsymbol{\theta})$ can be written as

$$
\begin{aligned}
\log\{f(b, y_1, y_2|\boldsymbol{\theta})\} &= \log f\{(y_1|b, \boldsymbol{\theta})\} + \log\{f(y_2|b, \boldsymbol{\theta})\} + \log\{f(b|\boldsymbol{\theta})\} \\
&= c - \frac{1}{2\sigma_e^2}\left(-2y_1 b + b^2\right) - \frac{1}{2\sigma_e^2}\left\{-2(y_2 - \beta_0)(\beta_1 b + \beta_2 (b-\psi)_+)\right. \\
&\quad \left. + \left(\beta_1^2 b^2 + 2\beta_1\beta_2 b (b-\psi)_+\right) + \beta_2^2 (b-\psi)_+^2\right\} - \frac{1}{2\sigma_b^2}\left(b^2 - 2\mu_b b\right),
\end{aligned} \qquad \text{(B.1)}
$$

where c consists of terms that do not involve b and is given as

$$
c = -\frac{3}{2}\log(2\pi) - \frac{1}{2}\log(\sigma_e^2) - \frac{1}{2}\log(\sigma_e^2) - \frac{1}{2}\log(\sigma_b^2) - \frac{1}{2\sigma_e^2}y_1^2 - \frac{1}{2\sigma_e^2}(y_2 - \beta_0)^2 - \frac{1}{2\sigma_b^2}\mu_b^2. \quad \text{(B.2)}
$$

It follows that the complete data log-likelihood function is

$$
\begin{aligned}
&\sum_{i=1}^{n} \log\{f(b_i, y_{i1}, y_{i2}|\boldsymbol{\theta})\} \\
&= \sum_{i=1}^{n} \left\{c_i - \frac{1}{2\sigma_e^2}\left(-2y_{i1}b_i + b_i^2\right) - \frac{1}{2\sigma_e^2}\left\{-2(y_{i2} - \beta_0)(\beta_1 b_i + \beta_2 (b_i - \psi)_+)\right.\right.
\end{aligned}
$$

$$+\left(\beta_1^2 b_i^2 + 2\beta_1\beta_2 b_i \left(b_i - \psi\right)_+\right) + \beta_2^2 \left(b_i - \psi\right)_+^2\} - \frac{1}{2\sigma_b^2}\left(b_i^2 - 2\mu_b b_i\right)\Bigg\}, \tag{B.3}$$

where c_i is the value of c given by (B.2) evaluated for the ith subject.

In the rth ECM iteration, let $\boldsymbol{\theta}^{(r)}$ be the value of $\boldsymbol{\theta}$ and $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ be the expectation of the complete data log-likelihood (B.3) with respect to the conditional distribution of $b_i|y_{i1}, y_{i2}$ evaluated at $\boldsymbol{\theta}^{(r)}$, i.e., $E\left[\sum_{i=1}^n \log\{f(b_i, y_{i1}, y_{i2}|\boldsymbol{\theta})\}|y_{i1}, y_{i2}, \boldsymbol{\theta}^{(r)}\right]$. Letting $E^{(r)}$ denote the expectation over the conditional distribution of $b_i|y_{i1}, y_{i2}$ evaluated at $\boldsymbol{\theta}^{(r)}$, which can be computed using the expressions given by Proposition A.6 in Appendix A, we can write

$$\begin{aligned}
Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)}) = \sum_{i=1}^n \Bigg\{ & c_i - \frac{1}{2\sigma_e^2}\left(-2y_{i1}E^{(r)}[b_i] + E^{(r)}[b_i^2]\right) - \frac{1}{2\sigma_e^2}\{-2(y_{i2} - \beta_0) \\
& \left(\beta_1 E^{(r)}[b_i] + \beta_2 E^{(r)}\left[(b_i - \psi)_+\right]\right) + \beta_1^2 E^{(r)}[b_i^2] \\
& + 2\beta_1\beta_2 E^{(r)}\left[b_i\left(b_i - \psi\right)_+\right] + \beta_2^2 E^{(r)}\left[(b_i - \psi)_+^2\right]\} \\
& - \frac{1}{2\sigma_b^2}\left(E^{(r)}[b_i^2] - 2\mu_b E^{(r)}[b_i]\right)\Bigg\}.
\end{aligned} \tag{B.4}$$

Next, we find derivative of $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to $\boldsymbol{\theta}$ so that we can perform the CM steps. For this, let $E_{i1}^{(r)}$ and $E_{i2}^{(r)}$ respectively denote the values of $E^{(r)}[b_i]$ and $E^{(r)}[b_i^2]$ and $A_{i1}^{(r)}, \dots, A_{i4}^{(r)}$ respectively denote the values of $A_1, \dots, A_4$ given by (A.10) in Proposition A.6, evaluated at $(\boldsymbol{\theta}, y_1, y_2) = (\boldsymbol{\theta}^{(r)}, y_{i1}, y_{i2})$. Further, let $f^{(r)}(y_{i1}, y_{i2})$ denote the value of $f(y_1, y_2)$ given by (A.4) in Proposition A.3, also evaluated at $(\boldsymbol{\theta}, y_1, y_2) = (\boldsymbol{\theta}^{(r)}, y_{i1}, y_{i2})$. The derivatives of $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to the elements of $\boldsymbol{\theta}$ are as follows:

$$\begin{aligned}
\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \mu_b} &= -\frac{1}{2\sigma_b^2}\sum_{i=1}^n 2\left\{-E_{i1}^{(r)} + \mu_b\right\} \\
\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \beta_0} &= -\frac{1}{2\sigma_e^2}\sum_{i=1}^n 2\left\{\beta_1 E_{i1}^{(r)} + \frac{\beta_2\left(A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2})\right)}{f^{(r)}(y_{i1}, y_{i2})} - (y_{i2} - \beta_0)\right\} \\
\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \beta_1} &= -\frac{1}{2\sigma_e^2}\sum_{i=1}^n 2\left\{-(y_{i2} - \beta_0)E_{i1}^{(r)} + \beta_1 E_{i2}^{(r)} + \frac{\beta_2(A_{i4}^{(r)} - \psi A_{i2}^{(r)})}{f^{(r)}(y_{i1}, y_{i2})}\right\} \\
\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \beta_2} &= -\frac{1}{2\sigma_e^2}\sum_{i=1}^n 2\Bigg\{-\frac{(y_{i2} - \beta_0)\left(A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2})\right) + \beta_1(A_{i4}^{(r)} - \psi A_{i2}^{(r)})}{f^{(r)}(y_{i1}, y_{i2})}
\end{aligned}$$

$$+\frac{\beta_2(A_{i4}^{(r)} - 2\psi A_{i2}^{(r)} + \psi^2 f_2^{(r)}(y_{i1}, y_{i2})}{f^{(r)}(y_{i1}, y_{i2})}\Bigg\}$$

$$\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \sigma_b^2} = -\frac{n}{2\sigma_b^2} + \frac{1}{2\sigma_b^4}\sum_{i=1}^{n}\left\{E_{i2}^{(r)} - 2\mu_b E_{i1}^{(r)} + \mu_b^2\right\}$$

$$\frac{\partial Q(\boldsymbol{b}, \mathbf{Y_1}, \mathbf{Y_2})}{\partial \sigma_e^2} = -\frac{n}{\sigma_e^2} + \frac{1}{2\sigma_e^4}\sum_{i=1}^{n}\Bigg\{-2(Y_{i2} - \beta_0)\left[\beta_1 E_{i1}^{(r)} + \frac{\beta_2(A_{i2}^{(r)} - \psi f_2^{(r)}(Y_{i1}, Y_{i2}))}{f^{(r)}(Y_{i1}, Y_{i2})}\right]$$

$$+\beta_1^2 E_{i2}^{(r)} + \frac{2\beta_1\beta_2(A_{i4}^{(r)} - \psi A_{i2}^{(r)}) + \beta_2^2(A_{i4}^{(r)} - 2\psi A_{i2}^{(r)} + \psi^2 f_2^{(r)}(Y_{i1}, Y_{i2}))}{f^{(r)}(Y_{i1}, Y_{i2})}$$

$$+(Y_{i2} - \beta_0)^2 - 2Y_{i1}E_{i1}^{(r)} + E_{i2}^{(r)} + Y_{i1}^2\Bigg\}$$

$$\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \psi} = -\frac{1}{2\sigma_e^2}\sum_{i=1}^{n} 2\left\{\frac{(y_{i2} - \beta_0)\beta_2 f_2^{(r)}(y_{i1}, y_{i2}) - \beta_1\beta_2 A_{i2}^{(r)} + \beta_2^2(-A_{i2}^{(r)} + \psi f_2^{(r)}(y_{i1}, y_{i2}))}{f^{(r)}(y_{i1}, y_{i2})}\right\} \tag{B.5}$$

By setting each of the derivatives in (B.5) equal to zero and solving for the corresponding parameter, we get:

$$\mu_b = \frac{\sum_{i=1}^{n} E_{i1}^{(r)}}{n}$$

$$\beta_0 = \frac{\sum_{i=1}^{n}\left\{y_{i2} - \beta_1 E_{i1}^{(r)} - \frac{\beta_2\left(A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2})\right)}{f^{(r)}(y_{i1}, y_{i2})}\right\}}{n}$$

$$\beta_1 = \frac{\sum_{i=1}^{n}\left\{(y_{i2} - \beta_0)E_{i1}^{(r)} - \frac{\beta_2\left(A_{i4}^{(r)} - \psi A_{i2}^{(r)}\right)}{f^{(r)}(y_{i1}, y_{i2})}\right\}}{\sum_{i=1}^{n} E_{i2}^{(r)}}$$

$$\beta_2 = \frac{\sum_{i=1}^{n}\frac{\left\{(y_{i2} - \beta_0)\left(A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2})\right) - \beta_1\left(A_{i4}^{(r)} - \psi A_{i2}^{(r)}\right)\right\}}{f^{(r)}(y_{i1}, y_{i2})}}{\sum_{i=1}^{n}\frac{A_{i4}^{(r)} - 2\psi A_{i2}^{(r)} + \psi^2 f_2^{(r)}(y_{i1}, y_{i2})}{f^{(r)}(y_{i1}, y_{i2})}}$$

$$\sigma_b^2 = \frac{\sum_{i=1}^{n}\left\{E_{i2}^{(r)} - 2\mu_b E_{i1}^{(r)} + \mu_b^2\right\}}{n}$$

$$\sigma_e^2 = \frac{1}{2n}\sum_{i=1}^{n}\Bigg\{y_{i1}^2 + (y_{i2} - \beta_0)^2 - 2y_{i1}E_{i1}^{(r)} + E_{i2}^{(r)} - 2(y_{i2} - \beta_0)\Bigg[\beta_1 E_{i1}^{(r)}$$

$$+\frac{\beta_2(A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2}))}{f^{(r)}(y_{i1}, y_{i2})}\Bigg] + \beta_1^2 E_{i2}^{(r)}$$

$$+\frac{2\beta_1\beta_2(A_{i4}^{(r)} - \psi A_{i2}^{(r)}) + \beta_2^2(A_{i4}^{(r)} - 2\psi A_{i2}^{(r)} + \psi^2 f_2^{(r)}(y_{i1}, y_{i2}))}{f^{(r)}(y_{i1}, y_{i2})}\Bigg\}$$

$$\psi = \frac{\sum_{i=1}^{n} \left\{ \frac{(\beta_1+\beta_2)A_{i2}^{(r)} - (y_{i2}-\beta_0) f_2^{(r)}(y_{i1}, y_{i2})}{f^{(r)}(y_{i1}, y_{i2})} \right\}}{\beta_2 \sum_{i=1}^{n} \frac{f_2^{(r)}(y_{i1}, y_{i2})}{f^{(r)}(y_{i1}, y_{i2}))}}. \tag{B.6}$$

Taken together, the E and CM steps in the rth iteration of our ECM algorithm are as follows:

E-step: Compute $A_{i1}^{(r)}, \ldots, A_{i4}^{(r)}$ and hence the conditional expectations in $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$.

CM-step 1: Update μ_b by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to μ_b while holding all other parameters at their current values. This yields $\mu_b^{(r+1)}$ as the value of μ_b given in (B.6).

CM-step 2: Update β_0 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to β_0 while holding μ_b at the updated value and all other parameters at their current values. This yields $\beta_0^{(r+1)}$ as the value of β_0 given in (B.6).

CM-step 3: Update β_1 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to β_1 while holding μ_b and β_0 at their updated values and all other parameters at their current values. This yields $\beta_1^{(r+1)}$ as the value of β_1 given in (B.6).

CM-step 4: Update β_2 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to β_2 while holding μ_b, β_0, and β_1 at their updated values and all other parameters at their current values. This yields $\beta_2^{(r+1)}$ as the value of β_2 given in (B.6).

CM-step 5: Update σ_b^2 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to σ_b^2 while holding μ_b, β_0, β_1, and β_2 at their updated values and all other parameters at their current values. This yields $\sigma_b^{2,(r+1)}$ as the value of σ_b^2 given in (B.6).

CM-step 6: Update σ_e^2 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to σ_e^2 while holding μ_b, β_0, β_1, β_2, and σ_b^2 at their updated values and all other parameters at their current values. This yields $\sigma_e^{2,(r+1)}$ as the value of σ_e^2 given in (B.6).

CM-step 7: Update ψ by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to ψ while holding all other parameters at their updated values. This yields $\psi^{(r+1)}$ as the value of ψ given in (B.6).

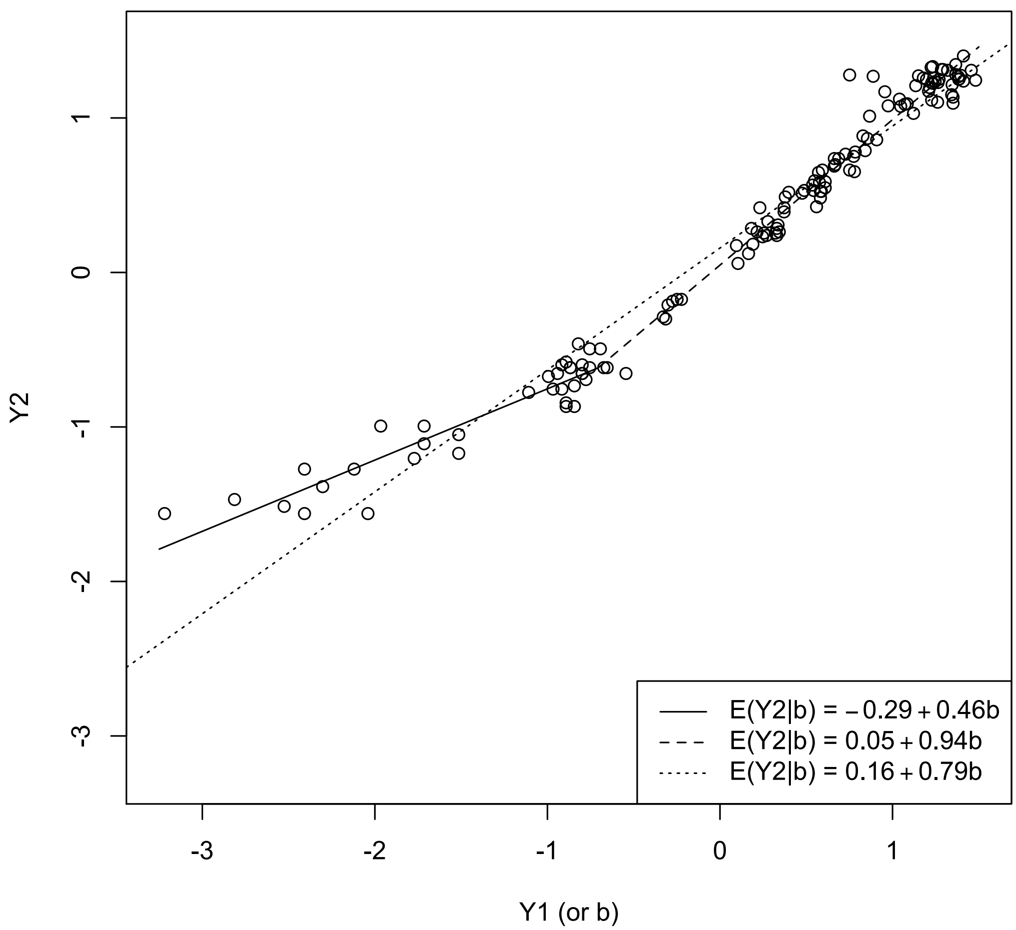

Figure 1: Scatterplot for log-scale digoxin data superimposed with the estimated straight line for $E(Y_2|b)$ under the classical model (dotted line) given by (2) and the piecewise straight line (solid and dashed lines) under the segmented model given by (6).

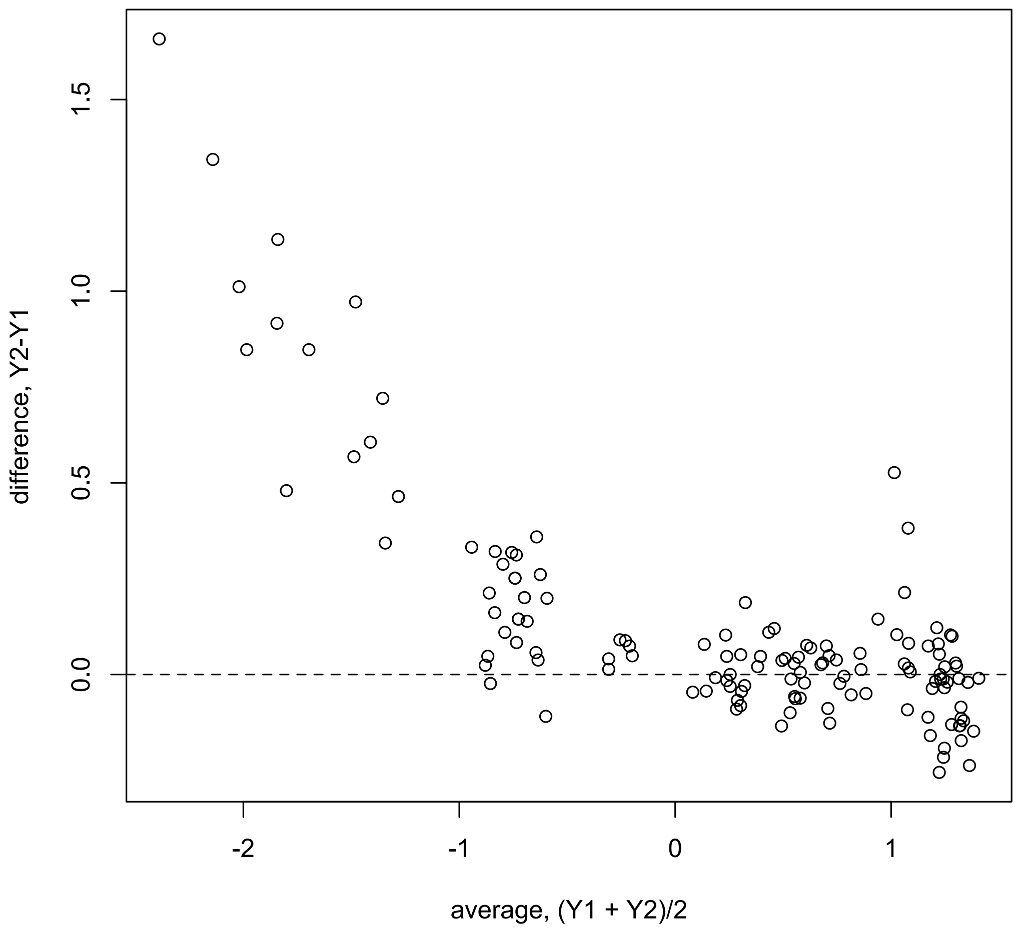

Figure 2: Bland-Altman plot for log-scale digoxin data superimposed with a horizontal line at zero.

Table 1: Parameter settings for simulation study.

Setting	$(\mu_b, \beta_0, \beta_1, \beta_2, \log(\sigma_e^2), \log(\sigma_b^2), \psi)$
1a	$(0.180, -0.292, 0.461, 0.480, -4.871, 0.172, -0.707)$
2a	$(-0.005, -0.387, 0.406, 0.417, -4.871, 0.172, -0.707)$
3a	$(0.365, -0.197, 0.516, 0.543, -4.871, 0.172, -0.707)$
4a	$(0.180, -0.292, 0.461, 0.480, -5.110, -0.069, -0.707)$
5a	$(0.180, -0.292, 0.461, 0.480, -4.632, 0.413, -0.707)$

Table 2: Bias, MSE, and ratio of MSEs of estimates obtained by ECM and direct maximization (DIR) and coverage probabilities for 95% standard and bootstrap confidence intervals in case of $n = 30$.

	Bias		MSE		MSE	Coverage Probability			
						Standard		Bootstrap	
Parameter	ECM	DIR	ECM	DIR	Ratio	ECM	DIR	ECM	DIR
μ_b	-0.002	-0.002	0.037	0.037	1.000	0.930	0.930	0.908	0.908
β_0	-0.060	-0.065	0.047	0.054	0.872	0.866	0.862	0.928	0.928
β_1	-0.044	-0.049	0.026	0.031	0.835	0.886	0.884	0.938	0.956
β_2	0.050	0.055	0.026	0.032	0.826	0.892	0.890	0.938	0.954
$\log(\sigma_e^2)$	-0.154	-0.154	0.089	0.089	0.999	0.922	0.922	0.950	0.952
$\log(\sigma_b^2)$	-0.118	-0.118	0.076	0.076	1.000	0.924	0.924	0.938	0.938
ψ	-0.001	-0.001	0.049	0.048	1.018	0.832	0.834	0.872	0.890
$\beta - \beta_2\psi$	-0.004	-0.004	0.001	0.001	1.017	0.894	0.898	0.908	0.910
$\beta_1 + \beta_2$	0.005	0.005	0.001	0.001	1.023	0.916	0.922	0.940	0.944
z(CCC) (L)†	-0.034	-0.037	0.054	0.058	0.939	0.918	0.918	0.952	0.964
z(CCC) (R)†	-0.013	-0.013	0.027	0.027	0.993	0.966	0.966	0.980	0.980
log(TDI) (L)†	-0.030	-0.026	0.048	0.050	0.949	0.928	0.924	0.950	0.966
log(TDI) (R)†	-0.033	-0.034	0.021	0.021	1.003	0.912	0.910	0.952	0.952

† L and R respectively denote left and right segments.

Table 3: Bias, MSE, and ratio of MSEs of estimates obtained by ECM and direct maximization (DIR) and coverage probabilities for 95% standard and bootstrap confidence intervals in case of $n = 50$.

	Bias		MSE		MSE	Coverage Probability			
						Standard		Bootstrap	
Parameter	ECM	DIR	ECM	DIR	Ratio	ECM	DIR	ECM	DIR
μ_b	0.008	0.008	0.024	0.024	1.000	0.934	0.934	0.914	0.914
β_0	-0.036	-0.035	0.022	0.023	0.936	0.896	0.890	0.940	0.940
β_1	-0.024	-0.023	0.012	0.013	0.928	0.916	0.908	0.952	0.956
β_2	0.025	0.024	0.012	0.013	0.930	0.926	0.920	0.964	0.960
$\log(\sigma_e^2)$	-0.066	-0.066	0.040	0.040	1.001	0.952	0.952	0.964	0.964
$\log(\sigma_b^2)$	-0.084	-0.084	0.045	0.045	1.000	0.922	0.922	0.930	0.930
ψ	-0.012	-0.009	0.027	0.028	0.965	0.858	0.850	0.906	0.910
$\beta - \beta_2\psi$	-0.002	-0.003	0.001	0.001	0.997	0.934	0.934	0.930	0.932
$\beta_1 + \beta_2$	0.002	0.002	0.001	0.001	0.997	0.944	0.944	0.968	0.962
z(CCC) (L)†	-0.022	-0.019	0.027	0.029	0.940	0.944	0.942	0.970	0.972
z(CCC) (R)†	-0.023	-0.023	0.015	0.015	0.995	0.978	0.978	0.982	0.982
log(TDI) (L)†	-0.030	-0.033	0.029	0.030	0.951	0.908	0.904	0.952	0.956
log(TDI) (R)†	-0.007	-0.008	0.009	0.009	0.998	0.960	0.960	0.978	0.978

† L and R respectively denote left and right segments.

Table 4: Bias, MSE, and ratio of MSEs of estimates obtained by ECM and direct maximization (DIR) and coverage probabilities for 95% standard and bootstrap confidence intervals in case of $n = 100$.

	Bias		MSE		MSE	Coverage Probability			
						Standard		Bootstrap	
Parameter	ECM	DIR	ECM	DIR	Ratio	ECM	DIR	ECM	DIR
μ_b	-0.004	-0.004	0.012	0.012	1.000	0.936	0.936	0.938	0.938
β_0	-0.008	-0.008	0.008	0.009	0.981	0.912	0.910	0.952	0.952
β_1	-0.005	-0.005	0.004	0.004	0.980	0.904	0.902	0.952	0.952
β_2	0.006	0.007	0.004	0.004	0.982	0.926	0.926	0.958	0.956
$\log(\sigma_e^2)$	0.011	0.011	0.017	0.017	1.000	0.972	0.972	0.956	0.956
$\log(\sigma_b^2)$	-0.069	-0.069	0.025	0.025	1.000	0.926	0.926	0.946	0.946
ψ	0.004	0.004	0.013	0.013	0.991	0.910	0.908	0.938	0.940
$\beta - \beta_2\psi$	-0.001	-0.001	0.000	0.000	0.999	0.942	0.940	0.962	0.960
$\beta_1 + \beta_2$	0.001	0.001	0.000	0.000	1.000	0.942	0.940	0.954	0.954
z(CCC) (L)†	-0.009	-0.009	0.012	0.012	0.985	0.962	0.962	0.970	0.970
z(CCC) (R)†	-0.040	-0.040	0.009	0.009	1.000	0.992	0.992	0.986	0.986
log(TDI) (L)†	-0.029	-0.028	0.015	0.015	0.995	0.912	0.908	0.946	0.948
log(TDI) (R)†	0.012	0.012	0.006	0.006	0.999	0.970	0.970	0.980	0.980

† L and R respectively denote left and right segments.

Table 5: Estimated type I error probabilities for the test of changepoint for when the null distribution of the likelihood ratio test statistic is approximated by χ^2 distributions with 2 and 3 degrees of freedom and bootstrap.

		ECM			DIR		
Setting	n	χ^2_2	χ^2_3	Bootstrap	χ^2_2	χ^2_3	Bootstrap
1b	30	0.066	0.024	0.052	0.064	0.024	0.052
	50	0.068	0.028	0.056	0.054	0.018	0.060
	100	0.044	0.026	0.044	0.036	0.014	0.042
2b	30	0.074	0.038	0.056	0.060	0.026	0.054
	50	0.076	0.036	0.064	0.048	0.018	0.052
	100	0.046	0.012	0.034	0.016	0.008	0.020
3b	30	0.064	0.032	0.054	0.048	0.022	0.060
	50	0.040	0.024	0.036	0.028	0.012	0.050
	100	0.048	0.018	0.050	0.020	0.012	0.054
4b	30	0.052	0.026	0.050	0.044	0.028	0.044
	50	0.044	0.024	0.044	0.030	0.018	0.036
	100	0.054	0.026	0.058	0.040	0.018	0.056
5b	30	0.052	0.024	0.046	0.040	0.022	0.046
	50	0.052	0.020	0.050	0.050	0.028	0.068
	100	0.040	0.022	0.036	0.024	0.008	0.030

Table 6: Estimates of bias and MSE for measures of similarity and agreement when the classical model is naively fit while the true model is segmented with parameters given by setting 1a.

		$n = 30$				$n = 100$			
		Naive		Proposed		Naive		Proposed	
Measure	True	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
Left Segment									
Intercept	−0.292	0.413	0.172	−0.058	0.049	0.415	0.173	−0.015	0.006
Slope	0.461	0.389	0.153	−0.043	0.028	0.387	0.150	−0.009	0.003
z(CCC)	0.517	1.544	2.429	−0.035	0.049	1.520	2.325	−0.011	0.009
log(TDI)	−0.181	−0.706	0.562	0.008	0.057	−0.667	0.464	−0.001	0.011
Right Segment									
Intercept	0.047	0.074	0.007	−0.003	0.001	0.076	0.006	−0.001	0.000
Slope	0.941	−0.091	0.010	0.002	0.001	−0.093	0.009	0.000	0.000
z(CCC)	2.487	−0.427	0.228	0.010	0.032	−0.451	0.218	0.000	0.008
log(TDI)	−1.514	0.627	0.458	−0.033	0.022	0.666	0.463	−0.010	0.006

Table 7: ML estimates, their standard errors (SE), and 95% confidence intervals (CI) for parameters of the segmented model (6) for digoxin data.

Parameter	Estimate	SE	95% CI
μ_b	0.18	0.09	$(0.00, 0.36)$
β_0	-0.29	0.05	$(-0.42, -0.16)$
β_1	0.46	0.03	$(0.38, 0.55)$
β_2	0.48	0.03	$(0.39, 0.57)$
$\log(\sigma_e^2)$	-4.87	0.12	$(-5.07, -4.59)$
$\log(\sigma_b^2)$	0.17	0.12	$(-0.05, 0.44)$
ψ	-0.71	0.13	$(-0.90, -0.52)$

Table 8: Summary of estimates for segment-specific measures of similarity and agreement. Two-sided confidence intervals are presented for similarity measures and one-sided confidence intervals are presented for agreement measures. The intercept and slope respectively refer to β_0 and β_1 in the left segment and $\beta_0 - \beta_2\psi$ and $\beta_1 + \beta_2$ in the right segment.

	Left Segment			Right Segment		
Measure	Estimate	SE	95% CI	Estimate	SE	95% CI
Intercept	-0.29	0.05	$(-0.42, -0.16)$	0.05	0.02	$(0.02, 0.08)$
Slope	0.46	0.03	$(0.38, 0.55)$	0.94	0.03	$(0.91, 0.97)$
z(CCC)	0.52	0.08	$(0.37, \infty)$	2.49	0.09	$(2.37, \infty)$
$\log\{\text{TDI}(0.90)\}$	-0.18	0.09	$(-\infty, 0.04)$	-1.51	0.09	$(-\infty, -1.40)$

Supplementary Materials for "A Segmented Measurement Error Model for Modeling and Analysis of Method Comparison Data" by Lak N. K. Rankothgedara and Pankaj K. Choudhary

S1 Distribution theory under the segmented model

We now present some distributional results under the segmented model (3) that are of interest in this article. Their proofs are available elsewhere.[1, Chapter 3] Let $\phi(x)$ and $\Phi(x)$ respectively denote the probability density function and the cumulative distribution function of a $N(0,1)$ distribution. Next, define the following quantities:

$$
\begin{aligned}
g_1(x,\mu,\sigma) &= \frac{x-\mu}{\sigma}, \\
g_2(x,\mu,\sigma) &= \frac{\phi\left(g_1(x,\mu,\sigma)\right)}{1-\Phi\left(g_1(x,\mu,\sigma)\right)}, \\
g_3(x,\mu,\sigma) &= \frac{\phi\left(g_1(x,\mu,\sigma)\right)}{\Phi\left(g_1(x,\mu,\sigma)\right)}, \\
g_4(\beta,\sigma_1,\sigma_2) &= \left(\frac{1}{\sigma_1^2}+\frac{(\beta_1+\beta)^2}{\sigma_2^2}+\frac{1}{\sigma_b^2}\right)^{-1}, \\
g_5(\beta,\sigma_1,\sigma_2) &= \left(\frac{y_1}{\sigma_1^2}+\frac{(y_2-\beta_0+\beta\psi)(\beta_1+\beta)}{\sigma_2^2}+\frac{\mu_b}{\sigma_b^2}\right), \\
g_6(\beta,\sigma_1,\sigma_2) &= g_4(\beta,\sigma_1,\sigma_2)g_5(\beta,\sigma_1,\sigma_2), \\
g_7(\beta,\mu,\sigma^2,\sigma_1,\sigma_2) &= \frac{\sqrt{2\pi\sigma^2}}{\sqrt{\sigma_1^2\sigma_2^2\sigma_b^2}}\phi\left(\frac{y_1}{\sigma_1}\right)\phi\left(\frac{y_2-\beta_0+\beta\psi}{\sigma_{e2}}\right)\phi\left(\frac{\mu_b}{\sigma_b}\right)\exp\left(\frac{\mu^2}{2\sigma^2}\right).
\end{aligned}
\tag{S1}
$$

The functions g_4 to g_7 depend on other quantities as well in addition to those explicitly specified as the arguments. However, this dependence is suppressed for notational convenience.

Proposition S1. *Consider (Y_1, Y_2) following the model (3). The mean and variance of Y_1 and Y_2 and their covariance are as follows:*

(a) $E(Y_1) = \mu_b$ *and* $var(Y_1) = \sigma_b^2 + \sigma_e^2$,

(b) $E(Y_2) = \beta_0 + \beta_1\mu_b + \beta_2 m_1$ and $var(Y_2) = \beta_1^2\sigma_b^2 + \beta_2^2 m_3 + 2\beta_1\beta_2 m_4 + \sigma_e^2$,

(c) $cov(Y_1, Y_2) = \beta_1\sigma_b^2 + \beta_2 m_4$,

where

$$\begin{aligned}
m_1 &= E[(b-\psi)_+] = \{1 - \Phi(g_1(\psi, \mu_b, \sigma_b))\}(\mu_b - \psi) + \phi(g_1(\psi, \mu_b, \sigma_b))\sigma_b, \\
m_2 &= E\left[\{(b-\psi)_+\}^2\right] = \{1 - \Phi(g_1(\psi, \mu_b, \sigma_b))\}\left\{(\mu_b - \psi)^2 + \sigma_b^2\right\} \\
&\qquad + \left(g_1(\psi, \mu_b, \sigma_b)\sigma_b^2 + 2\mu_b\sigma_b - 2\psi\sigma_b\right)\phi(g_1(\psi, \mu_b, \sigma_b)), \\
m_3 &= var[(b-\psi)_+] = m_2 - m_1^2, \\
m_4 &= cov[b, (b-\psi)_+] = \{1 - \Phi(g_1(\psi, \mu_b, \sigma_b))\}\sigma_b^2 \\
&\qquad + \left\{g_1(\psi, \mu_b, \sigma_b)\sigma_b^2 + \mu_b\sigma_b - \psi\sigma_b\right\}\phi(g_1(\psi, \mu_b, \sigma_b)). \qquad \text{(S2)}
\end{aligned}$$

Proposition S2. *Consider (Y_1, Y_2) following the model (3). The mean and variance of Y_1 and Y_2 and their covariance when b is truncated to be either $b \le \psi$ or $b > \psi$ are as follows:*

(a) $E(Y_1|b \le \psi) = E(b|b \le \psi)$ and $var(Y_1|b \le \psi) = var(b|b \le \psi) + \sigma_e^2$,

(b) $E(Y_2|b \le \psi) = \beta_0 + \beta_1 E(b|b \le \psi)$ and $var(Y_2|b \le \psi) = \beta_1^2 var(b|b \le \psi) + \sigma_e^2$,

(c) $cov(Y_1, Y_2|b \le \psi) = \beta_1 var(b|b \le \psi)$,

(d) $E(Y_1|b > \psi) = E(b|b > \psi)$ and $var(Y_1|b > \psi) = var(b|b > \psi) + \sigma_e^2$,

(e) $E(Y_2|b > \psi) = (\beta_0 - \beta_2\psi) + (\beta_1 + \beta_2)E(b|b > \psi)$ and $var(Y_2|b > \psi) = (\beta_1 + \beta_2)^2 var(b|b > \psi) + \sigma_e^2$,

(f) $cov(Y_1, Y_2|b > \psi) = (\beta_1 + \beta_2) var(b|b > \psi)$,

where

$$\begin{aligned}
E(b|b \le \psi) &= \mu_b - \sigma_b g_3(\psi, \mu_b, \sigma_b), \\
var(b|b \le \psi) &= \sigma_b^2\left\{1 - g_1(\psi, \mu_b, \sigma_b)g_3(\psi, \mu_b, \sigma_b) - g_3^2(\psi, \mu_b, \sigma_b)\right\}.
\end{aligned}$$

$$E(b|b>\psi) = \mu_b + \sigma_b g_2(\psi, \mu_b, \sigma_b),$$

$$var(b|b>\psi) = \sigma_b^2 \left\{1 + g_1(\psi, \mu_b, \sigma_b) g_2(\psi, \mu_b, \sigma_b) - g_2^2(a_1, \mu_b, \sigma_b)\right\}. \tag{S3}$$

Proposition S3. *The joint probability density function of* (Y_1, Y_2) *following the model* (3) *is*

$$f(y_1, y_2) = f_1(y_1, y_2) + f_2(y_1, y_2), \tag{S4}$$

where

$$\begin{aligned} f_1(y_1, y_2) &= \int_{-\infty}^{\psi} f(b, y_1, y_2) db = g_7(0, g_6(0, \sigma_e, \sigma_e), g_4(0, \sigma_e, \sigma_e), \sigma_e, \sigma_e) \\ &\quad \times \Phi\left(g_1(\psi, g_6(0, \sigma_e, \sigma_e), \sqrt{g_4(0, \sigma_e, \sigma_e)})\right) \\ f_2(y_1, y_2) &= \int_{\psi}^{\infty} f(b, y_1, y_2) db = g_7(\beta_2, g_6(\beta_2, \sigma_e, \sigma_e), g_4(\beta_2, \sigma_e, \sigma_e), \sigma_e, \sigma_e) \\ &\quad \times \left[1 - \Phi\left(g_1\left(\psi, g_6(\beta_2, \sigma_e, \sigma_e), \sqrt{g_4(\beta_2, \sigma_e, \sigma_e)}\right)\right)\right]. \end{aligned} \tag{S5}$$

Proposition S4. *Consider* (Y_1, Y_2) *following the model* (3)*. The probability density function of* $D = Y_2 - Y_1$ *is*

$$h(d) = h_1(d) + h_2(d), \tag{S6}$$

where

$$\begin{aligned} h_1(d) &= \int_{-\infty}^{\psi} f(d, b) db = \frac{\sqrt{2\pi c_1}}{\sqrt{\sigma^2 \sigma_b^2}} \phi\left(\frac{d - \beta_0}{\sigma}\right) \phi\left(\frac{\mu_b}{\sigma_b}\right) \exp\left(\frac{c_2^2}{2c_1}\right) \Phi(g_1(\psi, c_2, \sqrt{c_1}), \\ h_2(d) &= \int_{\psi}^{\infty} f(d, b) db = \frac{\sqrt{2\pi c_3}}{\sqrt{\sigma^2 \sigma_b^2}} \phi\left(\frac{d - \beta_0 + \beta_2 \psi}{\sigma}\right) \phi\left(\frac{\mu_b}{\sigma_b}\right) \exp\left(\frac{c_4^2}{2c_3}\right) \\ &\quad \times \left[1 - \Phi(g_1(\psi, c_4, \sqrt{c_3}))\right], \end{aligned} \tag{S7}$$

and

$$\begin{aligned} \sigma^2 &= 2\sigma_e^2, \\ c_1 &= \left(\frac{(\beta_1 - 1)^2}{\sigma^2} + \frac{1}{\sigma_b^2}\right)^{-1}, \\ c_2 &= \left(\frac{(d - \beta_0)(\beta_1 - 1)}{\sigma^2} + \frac{\mu_b}{\sigma_b^2}\right) c_1 \end{aligned}$$

$$
\begin{aligned}
c_3 &= \left(\frac{(\beta_1+\beta_2-1)^2}{\sigma^2} + \frac{1}{\sigma_b^2} \right)^{-1} \\
c_4 &= \left(\frac{(d-\beta_0+\beta_2\psi)(\beta_1+\beta_2-1)}{\sigma^2} + \frac{\mu_b}{\sigma_b^2} \right) c_3.
\end{aligned} \tag{S8}
$$

Proposition S5. *Consider (Y_1, Y_2) following the model (3). The probability density function of $D = Y_2 - Y_1$ when b is truncated to be either $b \le \psi$ or $b > \psi$ are as follows:*

$$
h(d|b \le \psi) = \frac{h_1(d)}{\Phi(g_1(\psi, \mu_b, \sigma_b))}, \;\; h(d|b > \psi) = \frac{h_2(d)}{1-\Phi(g_1(\psi, \mu_b, \sigma_b))}, \tag{S9}
$$

where $h_1(d)$ and $h_2(d)$ are given by (S7) *in Proposition S4.*

Proposition S6. *Consider (Y_1, Y_2) following the model (3). The first and second moments of b and $(b-\psi)_+$ conditional on $(Y_1, Y_2) = (y_1, y_2)$ are as follows:*

(a) $E[b|y_1, y_2] = (A_1 + A_2)/f(y_1, y_2)$,

(b) $E[b^2|y_1, y_2] = (A_3 + A_4)/f(y_1, y_2)$,

(c) $E\left[(b-\psi)_+|y_1, y_2\right] = (A_2 - \psi f_2(y_1, y_2))/f(y_1, y_2)$,

(d) $E\left[\{(b-\psi)_+\}^2|y_1, y_2\right] = (A_4 - 2\psi A_2 + \psi^2 f_2(y_1, y_2))/f(y_1, y_2)$,

(e) $E\left[b(b-\psi)_+|y_1, y_2\right] = (A_4 - \psi A_2)/f(y_1, y_2)$,

where

$$
\begin{aligned}
A_1 &= \int_{-\infty}^{\psi} b f(b, y_1, y_2) db = f_1(y_1, y_2) \Big\{ g_6(0, \sigma_e, \sigma_e) - \sqrt{g_4(0, \sigma_e, \sigma_e)} \\
&\qquad \times g_3\left(\psi, g_6(0, \sigma_e, \sigma_e), \sqrt{g_4(0, \sigma_e, \sigma_e)}\right) \Big\} \\
A_2 &= \int_{\psi}^{\infty} b f(b, y_1, y_2) db = f_2(y_1, y_2) \Big\{ g_6(\beta_2, \sigma_e, \sigma_e) + \sqrt{g_4(\beta_2, \sigma_e, \sigma_e)} \\
&\qquad \times g_2\left(\psi, g_6(\beta_2, \sigma_e, \sigma_e), \sqrt{g_4(\beta_2, \sigma_e, \sigma_e)}\right) \Big\} \\
A_3 &= \int_{-\infty}^{\psi} b^2 f(b, y_1, y_2) db = f_1(y_1, y_2) \left\{ g_4(0, \sigma_e, \sigma_e) + g_6^2(0, \sigma_e, \sigma_e) \right. \\
&\qquad - g_1(\psi, g_6(0, \sigma_e, \sigma_e), \sqrt{g_4(0, \sigma_e, \sigma_e)})
\end{aligned}
$$

$$\times g_4(0,\sigma_e,\sigma_e)g_3\left(\psi, g_6(0,\sigma_e,\sigma_e), \sqrt{g_4(0,\sigma_e,\sigma_e)}\right)$$
$$-2\sqrt{g_4(0,\sigma_e,\sigma_e)}g_6(0,\sigma_e,\sigma_e)g_3\left(\psi, g_6(0,\sigma_e,\sigma_e), \sqrt{g_4(0,\sigma_e,\sigma_e)}\right)\Big\}$$

$$A_4 = \int_\psi^\infty b^2 f(b,y_1,y_2)db = f_2(y_1,y_2)\left\{g_4(\beta_2,\sigma_e,\sigma_e) + g_6^2(\beta_2,\sigma_e,\sigma_e)\right.$$
$$+g_1(\psi, g_6(\beta_2,\sigma_e,\sigma_e), \sqrt{g_4(\beta_2,\sigma_e,\sigma_e)})$$
$$\times g_4(\beta_2,\sigma_e,\sigma_e)g_2\left(\psi, g_6(\beta_2,\sigma_e,\sigma_e), \sqrt{g_4(\beta_2,\sigma_e,\sigma_e)}\right)$$
$$\left.+2\sqrt{g_4(\beta_2,\sigma_e,\sigma_e)}g_6(\beta_2,\sigma_e,\sigma_e)g_2\left(\psi, g_6(\beta_2,\sigma_e,\sigma_e), \sqrt{g_4(\beta_2,\sigma_e,\sigma_e)}\right)\right\}, \quad \text{(S10)}$$

and f_1, f_2, and f are given by S4 and (S5) *in Proposition S3.*

Proposition S7. *Consider the model* (3)*. The best linear predictor of b using (Y_1, Y_2) is*

$$\hat{b} = \mu_b + [\sigma_b^2, \beta_1\sigma_b^2 + \beta_2 m_4]\left(var\left(\left[\begin{smallmatrix} Y_1 \\ Y_2 \end{smallmatrix}\right]\right)\right)^{-1}\left[\begin{smallmatrix} Y_1-\mu_b \\ Y_2-E(Y_2) \end{smallmatrix}\right], \quad \text{(S11)}$$

where m_4 is given by (S2) *and the moments involved are given by Proposition S1.*

This result can be used to get the fitted values under the model.

S2 ECM algorithm for model fitting

To develop the ECM algorithm, we take b_i in (6) as the *missing data* and (b_i, Y_{i1}, Y_{i2}) as the *complete data* for the ith subject. The logarithm of the joint density $f(b, y_1, y_2|\boldsymbol{\theta})$ can be written as

$$\begin{aligned}\log\{f(b,y_1,y_2|\boldsymbol{\theta})\} &= \log f\{(y_1|b,\boldsymbol{\theta})\} + \log\{f(y_2|b,\boldsymbol{\theta})\} + \log\{f(b|\boldsymbol{\theta})\} \\ &= c - \frac{1}{2\sigma_e^2}\left(-2y_1 b + b^2\right) - \frac{1}{2\sigma_e^2}\left\{-2(y_2-\beta_0)(\beta_1 b + \beta_2(b-\psi)_+)\right. \\ &\quad \left. + \left(\beta_1^2 b^2 + 2\beta_1\beta_2 b(b-\psi)_+\right) + \beta_2^2(b-\psi)_+^2\right\} - \frac{1}{2\sigma_b^2}\left(b^2 - 2\mu_b b\right),\end{aligned} \quad \text{(S12)}$$

where c consists of terms that do not involve b and is given as

$$c = -\frac{3}{2}\log(2\pi) - \frac{1}{2}\log(\sigma_e^2) - \frac{1}{2}\log(\sigma_e^2) - \frac{1}{2}\log(\sigma_b^2) - \frac{1}{2\sigma_e^2}y_1^2 - \frac{1}{2\sigma_e^2}(y_2-\beta_0)^2 - \frac{1}{2\sigma_b^2}\mu_b^2. \quad \text{(S13)}$$

It follows that the complete data log-likelihood function is

$$\sum_{i=1}^{n} \log\{f(b_i, y_{i1}, y_{i2}|\boldsymbol{\theta})\}$$
$$= \sum_{i=1}^{n} \left\{ c_i - \frac{1}{2\sigma_e^2}\left(-2y_{i1}b_i + b_i^2\right) - \frac{1}{2\sigma_e^2}\left\{-2(y_{i2}-\beta_0)(\beta_1 b_i + \beta_2 (b_i - \psi)_+)\right.\right.$$
$$\left.\left. + \left(\beta_1^2 b_i^2 + 2\beta_1\beta_2 b_i (b_i-\psi)_+\right) + \beta_2^2 (b_i - \psi)_+^2\right\} - \frac{1}{2\sigma_b^2}\left(b_i^2 - 2\mu_b b_i\right)\right\}, \qquad \text{(S14)}$$

where c_i is the value of c given by (S13) evaluated for the ith subject.

In the rth ECM iteration, let $\boldsymbol{\theta}^{(r)}$ be the value of $\boldsymbol{\theta}$ and $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ be the expectation of the complete data log-likelihood (S14) with respect to the conditional distribution of $b_i|y_{i1}, y_{i2}$ evaluated at $\boldsymbol{\theta}^{(r)}$, i.e., $E\left[\sum_{i=1}^{n} \log\{f(b_i, y_{i1}, y_{i2}|\boldsymbol{\theta})\}|y_{i1}, y_{i2}, \boldsymbol{\theta}^{(r)}\right]$. Letting $E^{(r)}$ denote the expectation over the conditional distribution of $b_i|y_{i1}, y_{i2}$ evaluated at $\boldsymbol{\theta}^{(r)}$, which can be computed using the expressions given by Proposition S6 in Section S1, we can write

$$Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)}) = \sum_{i=1}^{n} \left\{ c_i - \frac{1}{2\sigma_e^2}\left(-2y_{i1}E^{(r)}[b_i] + E^{(r)}[b_i^2]\right) - \frac{1}{2\sigma_e^2}\left\{-2(y_{i2}-\beta_0)\right.\right.$$
$$\left(\beta_1 E^{(r)}[b_i] + \beta_2 E^{(r)}\left[(b_i-\psi)_+\right]\right) + \beta_1^2 E^{(r)}[b_i^2]$$
$$\left. +2\beta_1\beta_2 E^{(r)}\left[b_i (b_i - \psi)_+\right] + \beta_2^2 E^{(r)}\left[(b_i-\psi)_+^2\right]\right\}$$
$$\left. -\frac{1}{2\sigma_b^2}\left(E^{(r)}[b_i^2] - 2\mu_b E^{(r)}[b_i]\right)\right\}. \qquad \text{(S15)}$$

Next, we find derivative of $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to $\boldsymbol{\theta}$ so that we can perform the CM steps. For this, let $E_{i1}^{(r)}$ and $E_{i2}^{(r)}$ respectively denote the values of $E^{(r)}[b_i]$ and $E^{(r)}[b_i^2]$ and $A_{i1}^{(r)}, \ldots, A_{i4}^{(r)}$ respectively denote the values of $A_1, \ldots, A_4$ given by (S10) in Proposition S6, evaluated at $(\boldsymbol{\theta}, y_1, y_2) = (\boldsymbol{\theta}^{(r)}, y_{i1}, y_{i2})$. Further, let $f^{(r)}(y_{i1}, y_{i2})$ denote the value of $f(y_1, y_2)$ given by (S4) in Proposition S3, also evaluated at $(\boldsymbol{\theta}, y_1, y_2) = (\boldsymbol{\theta}^{(r)}, y_{i1}, y_{i2})$. The derivatives of $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to the elements of $\boldsymbol{\theta}$ are as follows:

$$\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \mu_b} = -\frac{1}{2\sigma_b^2}\sum_{i=1}^{n} 2\left\{-E_{i1}^{(r)} + \mu_b\right\}$$

$$\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \beta_0} = -\frac{1}{2\sigma_e^2}\sum_{i=1}^{n} 2\left\{\beta_1 E_{i1}^{(r)} + \frac{\beta_2\left(A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2})\right)}{f^{(r)}(y_{i1}, y_{i2})} - (y_{i2} - \beta_0)\right\}$$

$$\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \beta_1} = -\frac{1}{2\sigma_e^2}\sum_{i=1}^{n} 2\left\{-(y_{i2} - \beta_0)E_{i1}^{(r)} + \beta_1 E_{i2}^{(r)} + \frac{\beta_2(A_{i4}^{(r)} - \psi A_{i2}^{(r)})}{f^{(r)}(y_{i1}, y_{i2})}\right\}$$

$$\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \beta_2} = -\frac{1}{2\sigma_e^2}\sum_{i=1}^{n} 2\left\{-\frac{(y_{i2} - \beta_0)\left(A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2})\right) + \beta_1(A_{i4}^{(r)} - \psi A_{i2}^{(r)})}{f^{(r)}(y_{i1}, y_{i2})}\right.$$
$$\left. + \frac{\beta_2(A_{i4}^{(r)} - 2\psi A_{i2}^{(r)} + \psi^2 f_2^{(r)}(y_{i1}, y_{i2})}{f^{(r)}(y_{i1}, y_{i2})}\right\}$$

$$\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \sigma_b^2} = -\frac{n}{2\sigma_b^2} + \frac{1}{2\sigma_b^4}\sum_{i=1}^{n}\left\{E_{i2}^{(r)} - 2\mu_b E_{i1}^{(r)} + \mu_b^2\right\}$$

$$\frac{\partial Q(\boldsymbol{b}, \mathbf{Y_1}, \mathbf{Y_2})}{\partial \sigma_e^2} = -\frac{n}{\sigma_e^2} + \frac{1}{2\sigma_e^4}\sum_{i=1}^{n}\left\{-2(Y_{i2} - \beta_0)\left[\beta_1 E_{i1}^{(r)} + \frac{\beta_2(A_{i2}^{(r)} - \psi f_2^{(r)}(Y_{i1}, Y_{i2}))}{f^{(r)}(Y_{i1}, Y_{i2})}\right]\right.$$
$$+\beta_1^2 E_{i2}^{(r)} + \frac{2\beta_1\beta_2(A_{i4}^{(r)} - \psi A_{i2}^{(r)}) + \beta_2^2(A_{i4}^{(r)} - 2\psi A_{i2}^{(r)} + \psi^2 f_2^{(r)}(Y_{i1}, Y_{i2}))}{f^{(r)}(Y_{i1}, Y_{i2})}$$
$$\left. +(Y_{i2} - \beta_0)^2 - 2Y_{i1}E_{i1}^{(r)} + E_{i2}^{(r)} + Y_{i1}^2\right\}$$

$$\frac{\partial Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})}{\partial \psi} = -\frac{1}{2\sigma_e^2}\sum_{i=1}^{n} 2\left\{\frac{(y_{i2} - \beta_0)\beta_2 f_2^{(r)}(y_{i1}, y_{i2}) - \beta_1\beta_2 A_{i2}^{(r)} + \beta_2^2(-A_{i2}^{(r)} + \psi f_2^{(r)}(y_{i1}, y_{i2}))}{f^{(r)}(y_{i1}, y_{i2})}\right\} \tag{S16}$$

By setting each of the derivatives in (S16) equal to zero and solving for the corresponding parameter, we get:

$$\mu_b = \frac{\sum_{i=1}^{n} E_{i1}^{(r)}}{n}$$

$$\beta_0 = \frac{\sum_{i=1}^{n}\left\{y_{i2} - \beta_1 E_{i1}^{(r)} - \frac{\beta_2\left(A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2})\right)}{f^{(r)}(y_{i1}, y_{i2})}\right\}}{n}$$

$$\beta_1 = \frac{\sum_{i=1}^{n}\left\{(y_{i2} - \beta_0)E_{i1}^{(r)} - \frac{\beta_2\left(A_{i4}^{(r)} - \psi A_{i2}^{(r)}\right)}{f^{(r)}(y_{i1}, y_{i2})}\right\}}{\sum_{i=1}^{n} E_{i2}^{(r)}}$$

$$\beta_2 = \frac{\sum_{i=1}^{n} \frac{\left\{(y_{i2} - \beta_0)\left(A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2})\right) - \beta_1\left(A_{i4}^{(r)} - \psi A_{i2}^{(r)}\right)\right\}}{f^{(r)}(y_{i1}, y_{i2})}}{\sum_{i=1}^{n} \frac{A_{i4}^{(r)} - 2\psi A_{i2}^{(r)} + \psi^2 f_2^{(r)}(y_{i1}, y_{i2})}{f^{(r)}(y_{i1}, y_{i2})}}$$

$$
\begin{aligned}
\sigma_b^2 &= \frac{\sum_{i=1}^n \left\{ E_{i2}^{(r)} - 2\mu_b E_{i1}^{(r)} + \mu_b^2 \right\}}{n} \\
\sigma_e^2 &= \frac{1}{2n} \sum_{i=1}^n \Bigg\{ y_{i1}^2 + (y_{i2} - \beta_0)^2 - 2y_{i1} E_{i1}^{(r)} + E_{i2}^{(r)} - 2(y_{i2} - \beta_0) \Bigg[\beta_1 E_{i1}^{(r)} \\
&\quad + \frac{\beta_2 (A_{i2}^{(r)} - \psi f_2^{(r)}(y_{i1}, y_{i2}))}{f^{(r)}(y_{i1}, y_{i2})} \Bigg] + \beta_1^2 E_{i2}^{(r)} \\
&\quad + \frac{2\beta_1 \beta_2 (A_{i4}^{(r)} - \psi A_{i2}^{(r)}) + \beta_2^2 (A_{i4}^{(r)} - 2\psi A_{i2}^{(r)} + \psi^2 f_2^{(r)}(y_{i1}, y_{i2}))}{f^{(r)}(y_{i1}, y_{i2})} \Bigg\} \\
\psi &= \frac{\sum_{i=1}^n \left\{ \frac{(\beta_1 + \beta_2) A_{i2}^{(r)} - (y_{i2} - \beta_0) f_2^{(r)}(y_{i1}, y_{i2})}{f^{(r)}(y_{i1}, y_{i2})} \right\}}{\beta_2 \sum_{i=1}^n \frac{f_2^{(r)}(y_{i1}, y_{i2})}{f^{(r)}(y_{i1}, y_{i2}))}}.
\end{aligned}
\tag{S17}
$$

Taken together, the E and CM steps in the rth iteration of our ECM algorithm are as follows:

E-step: Compute $A_{i1}^{(r)}, \ldots, A_{i4}^{(r)}$ and hence the conditional expectations in $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$.

CM-step 1: Update μ_b by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to μ_b while holding all other parameters at their current values. This yields $\mu_b^{(r+1)}$ as the value of μ_b given in (S17).

CM-step 2: Update β_0 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to β_0 while holding μ_b at the updated value and all other parameters at their current values. This yields $\beta_0^{(r+1)}$ as the value of β_0 given in (S17).

CM-step 3: Update β_1 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to β_1 while holding μ_b and β_0 at their updated values and all other parameters at their current values. This yields $\beta_1^{(r+1)}$ as the value of β_1 given in (S17).

CM-step 4: Update β_2 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to β_2 while holding μ_b, β_0, and β_1 at their updated values and all other parameters at their current values. This yields $\beta_2^{(r+1)}$ as the value of β_2 given in (S17).

CM-step 5: Update σ_b^2 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to σ_b^2 while holding μ_b, β_0, β_1, and β_2 at their updated values and all other parameters at their current values. This yields $\sigma_b^{2,(r+1)}$ as the value of σ_b^2 given in (S17).

CM-step 6: Update σ_e^2 by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to σ_e^2 while holding μ_b, β_0, β_1, β_2, and σ_b^2 at their updated values and all other parameters at their current values. This yields $\sigma_e^{2,(r+1)}$ as the value of σ_e^2 given in (S17).

CM-step 7: Update ψ by maximizing $Q(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)})$ with respect to ψ while holding all other parameters at their updated values. This yields $\psi^{(r+1)}$ as the value of ψ given in (S17).

The algorithm begins with a starting point and the above steps are iterated until convergence. As is true with any EM-type algorithm, one needs to try a number of starting points to have some assurance that the algorithm converges to a global maxima $\hat{\boldsymbol{\theta}}$.

S3 Impact of Model Violations

To assess the impact of equal error variance assumption in (6), we conduct a simulation study as in Section 5 by simulating data under setting 5a but with the change that $\sigma_{e2}^2 = 2\sigma_{e1}^2$ and $\sigma_{e2}^2 = 4\sigma_{e1}^2$ (instead of $\sigma_{e1}^2 = \sigma_{e2}^2 = \sigma_e^2$). The results for the model parameters are presented in Table S4 in the next section. The common variance σ_e^2 is omitted from the table as it does not have a counterpart under the true model.

To assess the impact of non-normality of b in (6), we again simulate data using setting 5a but with two types of deviations from normality. In one, b follows a t_ν distribution with center μ_b and scale σ_b with degrees of freedom $\nu = 3$ and 5. In the other, b follows a contaminated normal distribution, specifically a 90:10 mixture of two normals where the first component follows $N(\mu_b, \sigma_b^2)$ and the second component follows $N(\mu_{b1}, \sigma_{b1}^2)$ with $(\mu_{b1}, \sigma_{b1}) = (4\mu_b, \sigma_b)$ and $(\mu_b, 4\sigma_b)$. The results for the model parameters are presented in Tables S5 and S6 in the next section. The parameter σ_b^2 is omitted from the tables as its interpretation under the true model is not the same as in the assumed model.

S4 Figures and Tables

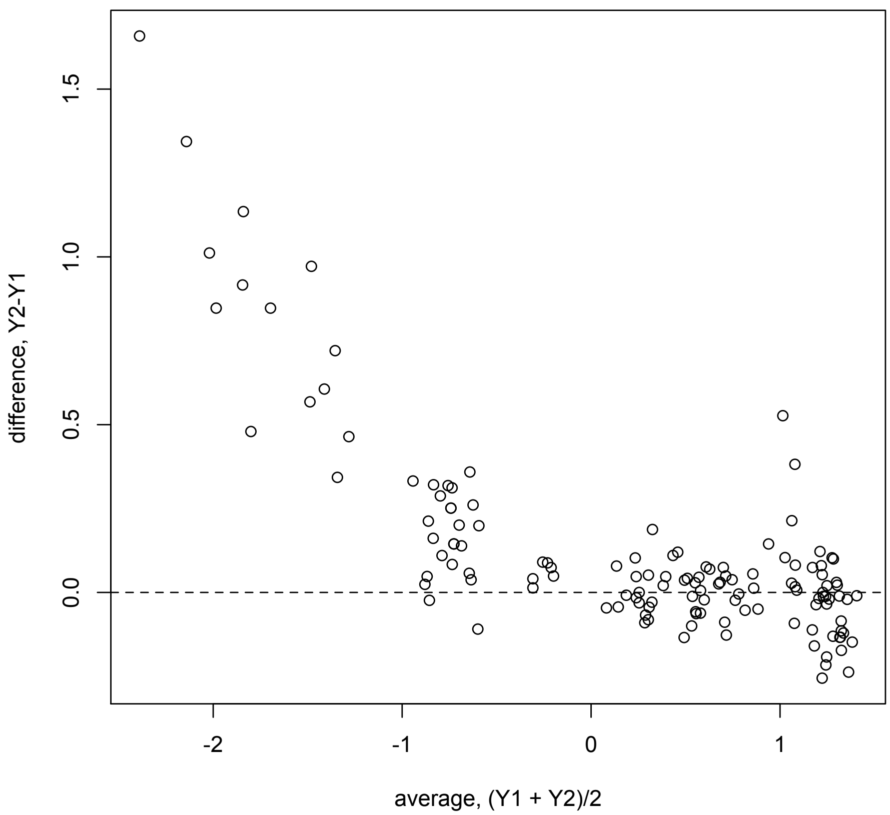

Figure S1: Bland-Altman plot for log-scale digoxin data superimposed with a horizontal line at zero.

Table S1: Bias, MSE, and ratio of MSEs of estimates obtained by ECM and direct maximization (DIR) and coverage probabilities for 95% standard and bootstrap confidence intervals in case of setting 1a with $n = 50$.

	Bias		MSE		MSE	Coverage Probability			
						Standard		Bootstrap	
Parameter†	ECM	DIR	ECM	DIR	Ratio	ECM	DIR	ECM	DIR
μ_b	0.008	0.008	0.024	0.024	1.000	0.934	0.934	0.914	0.914
β_0	-0.036	-0.035	0.022	0.023	0.936	0.896	0.890	0.940	0.940
β_1	-0.024	-0.023	0.012	0.013	0.928	0.916	0.908	0.952	0.956
β_2	0.025	0.024	0.012	0.013	0.930	0.926	0.920	0.964	0.960
$\log(\sigma_e^2)$	-0.066	-0.066	0.040	0.040	1.001	0.952	0.952	0.964	0.964
$\log(\sigma_b^2)$	-0.084	-0.084	0.045	0.045	1.000	0.922	0.922	0.930	0.930
ψ	-0.012	-0.009	0.027	0.028	0.965	0.858	0.850	0.906	0.910
$\beta - \beta_2\psi$	-0.002	-0.003	0.001	0.001	0.997	0.934	0.934	0.930	0.932
$\beta_1 + \beta_2$	0.002	0.002	0.001	0.001	0.997	0.944	0.944	0.968	0.962
z(CCC) (L)	-0.022	-0.019	0.027	0.029	0.940	0.944	0.942	0.970	0.972
z(CCC) (R)	-0.023	-0.023	0.015	0.015	0.995	0.978	0.978	0.982	0.982
log(TDI) (L)	-0.030	-0.033	0.029	0.030	0.951	0.908	0.904	0.952	0.956
log(TDI) (R)	-0.007	-0.008	0.009	0.009	0.998	0.960	0.960	0.978	0.978

† L and R respectively denote left and right segments.

Table S2: Bias, MSE, and ratio of MSEs of estimates obtained by ECM and direct maximization (DIR) and coverage probabilities for 95% standard and bootstrap confidence intervals in case of setting 1a with $n = 100$.

	Bias		MSE		MSE	Coverage Probability			
						Standard		Bootstrap	
Parameter †	ECM	DIR	ECM	DIR	Ratio	ECM	DIR	ECM	DIR
μ_b	-0.004	-0.004	0.012	0.012	1.000	0.936	0.936	0.938	0.938
β_0	-0.008	-0.008	0.008	0.009	0.981	0.912	0.910	0.952	0.952
β_1	-0.005	-0.005	0.004	0.004	0.980	0.904	0.902	0.952	0.952
β_2	0.006	0.007	0.004	0.004	0.982	0.926	0.926	0.958	0.956
$\log(\sigma_e^2)$	0.011	0.011	0.017	0.017	1.000	0.972	0.972	0.956	0.956
$\log(\sigma_b^2)$	-0.069	-0.069	0.025	0.025	1.000	0.926	0.926	0.946	0.946
ψ	0.004	0.004	0.013	0.013	0.991	0.910	0.908	0.938	0.940
$\beta - \beta_2\psi$	-0.001	-0.001	0.000	0.000	0.999	0.942	0.940	0.962	0.960
$\beta_1 + \beta_2$	0.001	0.001	0.000	0.000	1.000	0.942	0.940	0.954	0.954
z(CCC) (L)	-0.009	-0.009	0.012	0.012	0.985	0.962	0.962	0.970	0.970
z(CCC) (R)	-0.040	-0.040	0.009	0.009	1.000	0.992	0.992	0.986	0.986
log(TDI) (L)	-0.029	-0.028	0.015	0.015	0.995	0.912	0.908	0.946	0.948
log(TDI) (R)	0.012	0.012	0.006	0.006	0.999	0.970	0.970	0.980	0.980

† L and R respectively denote left and right segments.

Table S3: Estimates of bias and MSE for measures of similarity and agreement when the classical model is naively fit while the true model is segmented with parameters given by setting 1a.

		$n = 30$				$n = 100$			
		Naive		Proposed		Naive		Proposed	
Measure	True	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
Left Segment									
Intercept	−0.292	0.413	0.172	−0.058	0.049	0.415	0.173	−0.015	0.006
Slope	0.461	0.389	0.153	−0.043	0.028	0.387	0.150	−0.009	0.003
z(CCC)	0.517	1.544	2.429	−0.035	0.049	1.520	2.325	−0.011	0.009
log(TDI)	−0.181	−0.706	0.562	0.008	0.057	−0.667	0.464	−0.001	0.011
Right Segment									
Intercept	0.047	0.074	0.007	−0.003	0.001	0.076	0.006	−0.001	0.000
Slope	0.941	−0.091	0.010	0.002	0.001	−0.093	0.009	0.000	0.000
z(CCC)	2.487	−0.427	0.228	0.010	0.032	−0.451	0.218	0.000	0.008
log(TDI)	−1.514	0.627	0.458	−0.033	0.022	0.666	0.463	−0.010	0.006

Table S4: Bias and MSE of estimates obtained by ECM and coverage probability (CP) of 95% bootstrap confidence intervals in case of $n = 50$ under setting 5a with equal and unequal error variances.

	$\sigma_{e2}^2 = \sigma_{e1}^2$			$\sigma_{e2}^2 = 2\sigma_{e1}^2$			$\sigma_{e2}^2 = 4\sigma_{e1}^2$		
Parameter	Bias	MSE	CP	Bias	MSE	CP	Bias	MSE	CP
μ_b	−0.007	0.032	0.934	−0.007	0.029	0.942	0.016	0.030	0.948
β_0	−0.016	0.015	0.960	−0.023	0.030	0.926	−0.112	0.133	0.918
β_1	−0.008	0.006	0.964	−0.010	0.012	0.944	−0.052	0.043	0.920
β_2	0.009	0.006	0.968	0.016	0.012	0.956	0.064	0.041	0.932
$\log(\sigma_b^2)$	−0.083	0.051	0.940	−0.055	0.046	0.948	−0.042	0.039	0.964
ψ	−0.001	0.032	0.930	0.016	0.058	0.886	−0.031	0.121	0.866

Table S5: Bias and MSE of estimates obtained by ECM and coverage probability (CP) of 95% bootstrap confidence intervals in case of $n = 50$ under setting 5a with normal and t distributions for b.

	normal			t_3			t_5		
Parameter	Bias	MSE	CP	Bias	MSE	CP	Bias	MSE	CP
μ_b	−0.007	0.032	0.934	0.052	0.078	0.932	0.008	0.039	0.936
β_0	−0.016	0.015	0.960	−0.010	0.010	0.952	−0.009	0.011	0.952
β_1	−0.008	0.006	0.964	−0.006	0.003	0.962	−0.004	0.004	0.968
β_2	0.009	0.006	0.968	0.008	0.004	0.958	0.007	0.004	0.972
$\log(\sigma_e^2)$	−0.067	0.041	0.960	−0.034	0.047	0.936	−0.029	0.040	0.954
ψ	−0.001	0.032	0.930	0.002	0.023	0.950	0.006	0.032	0.918

Table S6: Bias and MSE of estimates obtained by ECM and coverage probability (CP) of 95% bootstrap confidence intervals in case of $n = 50$ under setting 5a with normal and contaminated normal distributions for b. The latter has two settings, $(\mu_{b1}, \sigma_{b1}) = (4\mu_b, \sigma_b)$ and $(\mu_b, 4\sigma_b)$.

	normal			$(\mu_{b1}, \sigma_{b1}) = (4\mu_b, \sigma_b)$			$(\mu_{b1}, \sigma_{b1}) = (\mu_b, 4\sigma_b)$		
Parameter	Bias	MSE	CP	Bias	MSE	CP	Bias	MSE	CP
μ_b	−0.007	0.032	0.934	−0.005	0.029	0.942	0.028	0.053	0.956
β_0	−0.016	0.015	0.960	−0.026	0.021	0.940	0.003	0.010	0.948
β_1	−0.008	0.006	0.964	−0.016	0.009	0.960	0.002	0.004	0.954
β_2	0.009	0.006	0.968	0.018	0.009	0.974	−0.001	0.004	0.962
$\log(\sigma_e^2)$	−0.067	0.041	0.960	−0.063	0.041	0.970	−0.050	0.047	0.934
ψ	−0.001	0.032	0.930	0.003	0.037	0.924	0.018	0.024	0.950

References

1. Rankothgedara LNK. *Contributions to Modeling and Analysis of Method Comparison Data*. PhD Dissertation, University of Texas at Dallas; 2018.