Identification of probiotic responders in cross-over trials using the Bayesian statistical model considering lags of effect period

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Abstract

Recent advances in microbiome research have led to the further development of microbial interventions, such as probiotics and prebiotics, which are potential treatments for constipation. However, the effects of probiotics vary from person to person; therefore, the effectiveness of probiotics needs to be verified for each individual. Individuals showing significant effects of the target probiotic is called responders. A statistical model for the evaluation of responders was proposed in a previous study. However, the previous model does not consider the lag in the effect of the probiotic. It is expected that there are lags between the period of time when probiotics are administered and when they are effective. In this study, we propose a Bayesian statistical model to estimate the probability that a subject is a responder, by considering the lag of the effect period. In synthetic dataset experiments, the proposed model was found to outperform the base model, which did not factor in the lag. Further, we found that the proposed model could distinguish responders showing large uncertainty in terms of the lag of the effect period against the intake period.

1 Introduction

Recent advances in microbiome research have resulted in the rapid development of microbial interventions, such as probiotics and prebiotics, which are potential treatments for constipation [1]. Probiotics are defined as living microbes that have a beneficial effect on the host when ingested in sufficient quantities and are reported to improve defecation frequencies and treat constipation [1, 2]. The effects of probiotics vary from person to person [3]. Individuals exhibiting significant effects of probiotics, are called “responders” [4]: each responder exhibits a significant effect of a different probiotic. That is, the different responders respond to different probiotics, and the individual differences make it difficult to evaluate the effects of probiotics. Therefore, experimental designs used for probiotic research should take into account the individual differences between subjects.

One type of a sophisticated experimental design is a cross-over trial, in which each subject takes both the target probiotic and placebo. Specifically, a cross-over trial comprises the following steps: (1) Each individual is first administered a capsule containing the target probiotic or placebo for several days. (2) After a washout period, which lasts several weeks and is set to remove the effects of the former capsule, each individual is administered the other capsule (containing either probiotic or placebo) for a specific period of time. Cross-over trials are widely applied in various fields of research, including research related to probiotics [5], prebiotics [6], neurorehabilitation [7], and spinal manipulation [8]. The main advantage of cross-over trials is that they enable the evaluation of individual differences, which are determined by attributes such as gender, genetics, and habits. Accordingly, datasets obtained from a cross-over trial demand a reasonable analysis method that considers individual differences.

An approach to estimate individual differences have been already conducted in a previous study. Nakamura \textit{et al.} evaluated improvements in defecation frequencies using a Weibull regression model [9]. They revealed individual differences in the improvement of defecation frequency by grouping subjects into three groups: strong responders, weak responders, and non-responders. However, their model used an unreasonable assumption that the effects of the target probiotics start on the day when the probiotic is administered to the subject. A previous study suggested that orally ingested material should be excreted for one or more days [10]. In addition, it has been estimated that it can take more than ten hours for microbes to increase dramatically [11], which has been reported for fecal samples that were ingested [12]. Therefore, we believe that does not consider...
the lag between the intake time and the effect time can lead to a misidentification of responders, especially in short-term intervention experiments.

In this study, we propose a Bayesian statistical model for estimating the efficacy of a target probiotic in improving defecation frequency, by considering the lag between the intake and effect time (Fig. 1). The model considered individual differences in a cross-over trial dataset. The proposed model is based on the segmented linear regression model, which represents each periodic term using linear regression, and has discrete parameters of lag days. The proposed model evaluates the cumulative sum of the number of times a subject defecated. An individual can be evaluated based on the posterior probability that the individual is a responder to probiotics. With the proposed model, we estimated if each subject is a responder using synthetic datasets and the real dataset used in the previous study [9]. We compared the results of the proposed model with those of a base model that did not consider the lag period. Our analysis showed that taking into consideration the effect time lag was useful in the synthetic dataset experiments. Real data experiments show that the proposed model estimated the posterior distribution considering the effect lag and led to different conclusions from the base model. We found that the proposed model could eliminate uncertain responders (responders whose response to a probiotic is uncertain) according to the lag in the effect period against the intake period.

![Figure 1: Schematic illustration of the effect lag in cross-over trials. The time when an effect of the probiotic is observed is delayed compared to the time when the probiotic is ingested. The subject is first administered the placebo capsule and then the target probiotic capsule.](image)

## 2 Materials and methods

### 2.1 Overview

Here, we provide an overview of the proposed model. The proposed model requires a dataset of the cumulative sum of the number of defecation events, collected from a cross-over trial. Figure 1 shows the schematic illustration of the respective cross-over trial, whose dataset was used in this study. The terms of the trial are divided into several periodic terms with respect to capsule intake/effect, and are denoted as “segments.” Here, \( S = 5 \) is used in this figure and in the dataset used in this study, where \( S \) is the number of segments. The proposed model is a Bayesian statistical model based on segmented linear models for the cumulative sum of defecation events. The proposed model can take the lag of the effect time \((\text{cf. Section 1})\) into account using the number of lag days as discrete parameters.

### 2.2 Generative process

Here, we describe the generative process of the proposed model. The proposed model demands the cumulative sum of the defecation frequency \( y_i (i = 1 \ldots N) \), where \( N \) is the number of days in the entire trial term. This model is for one subject. Let \( \alpha \in \mathbb{R}, \eta \in \mathbb{R}, \) and \( \bar{\eta} \in \mathbb{R} \) be the logarithmic defecation frequency during normal periods, the effect of target probiotics, and the effect of capsules, respectively. Here, the effect of the capsule indicates the effects of ingesting the capsule itself, regardless of its content. That is, the effect of the capsule is observed in both the target probiotic and placebo periods. The prior distributions of \( \alpha, \eta, \) and \( \bar{\eta} \) are as follows.

\[
\alpha \sim \text{WIP}, \\
\eta \sim \text{WIP}, \\
\bar{\eta} \sim \text{WIP},
\]
where WIP denotes the weakly informative prior distribution. We use Cauchy(0, 10) as the weakly informative prior in this study, where Cauchy(\(x_0, \gamma\)) denotes the Cauchy distribution with the location parameter \(x_0\) and scale parameter \(\gamma\). Let \(\mu\) and \(\nu\) be the lag of effect start and end, respectively. \(\mu\) and \(\nu\) are shared by the effect of capsules and probiotics. Specifically, the effects of the capsules and probiotics emerged \(\mu\) days after the subject ingested the capsule and expired \(\nu\) days after the subject stopped taking the capsule. Here, we assume that \(\mu\) and \(\nu\) are up to several days long using the following prior distributions:

\[
\begin{align*}
\mu &\sim \text{DiscreteUniform}(0, \mu_{\text{max}}), \\
\nu &\sim \text{DiscreteUniform}(0, \nu_{\text{max}}),
\end{align*}
\]

where \(\text{DiscreteUniform}(a, b)\) denotes the discrete uniform distribution with minimum value \(a\) and maximum value \(b\), and \(\mu_{\text{max}}\) and \(\nu_{\text{max}}\) are the maximum values of \(\mu\) and \(\nu\), respectively. We used \(\mu_{\text{max}} = \nu_{\text{max}} = 5\) in this paper. We modified the segment in which the subject ingested the capsule using \(\mu\) and \(\nu\) as follows:

\[
\begin{align*}
d_1' &= d_1 + \mu, \\
d_2' &= d_2 + \nu, \\
d_3' &= d_3 + \mu, \\
d_4' &= d_4 + \nu,
\end{align*}
\]

where \(d_1, d_2, d_3,\) and \(d_4\) represent the start day index of the first capsule, the end day index of the first capsule, the start day index of the second capsule, and the end day index of the second capsule, respectively; and \(d_1', d_2', d_3',\) and \(d_4'\) indicate the effect start day index of the first capsule, the effect end day index of the first capsule, the effect start day index of the second capsule, and the effect end day index of the second capsule, respectively. Let \(O, P,\) and \(T\) be the sets of the day indices in the normal, placebo, and target probiotic periods, respectively. \(O, P,\) and \(T\) are given by

\[
\begin{align*}
O &= \{i \mid 1 \leq i < d_1' \lor d_2' \leq i < d_3' \lor d_4' \leq i \}, \\
P &= \begin{cases} 
\{i \mid d_1' \leq i < d_2' \} & C = 0, \\
\{i \mid d_3' \leq i < d_4' \} & C = 1,
\end{cases} \\
T &= \begin{cases} 
\{i \mid d_3' \leq i < d_4' \} & C = 0, \\
\{i \mid d_1' \leq i < d_2' \} & C = 1,
\end{cases}
\]

where \(C\) is an indicator of the cross-over type, which shows the order of the capsules of the target probiotic and placebo. The subject was first administered placebos and then the target probiotic when \(C = 0\), and the subject was first administered the target probiotic and then the placebo when \(C = 1\). Let \(\beta_i\) be the rate of increase in the cumulative sum of the defecation frequency on the \(i\)-th day. \(\beta_i\) depends on the period in which the \(i\)-th day lies, as given below:

\[
\beta_i = \begin{cases} 
\exp(\alpha) & i \in O, \\
\exp(\alpha + \bar{\eta}) & i \in P, \\
\exp(\alpha + \bar{\eta} + \bar{\eta}) & i \in T.
\end{cases}
\]

The intercept of the \(i\)-th segment \(\gamma_i\) is defined as

\[
\gamma_i = \begin{cases} 
0 & i \in G_1, \\
y_{d_{t-1}} - \beta_i (d_{t-1} - 1) & i \in G_t \land t > 1,
\end{cases}
\]

where \(G_t\) is the set of the day indices in the \(t\)-th segment. Here, \(\gamma_i\) is calculated such that the regression line passes through the observation point \((d_{t-1} - 1, y_{d_{t-1}})\). This calculation enables the precise evaluation of the increase in the cumulative sum of the defecation frequencies in each segment. \(\gamma_1\) in the first segment is equal to zero, because the cumulative sum of defecation frequencies is 0 before the first day. The distribution of the \(i\)-th day cumulative sum of defecation frequencies \(y_i\) is as follows:

\[
y_i \sim \text{Normal}(\beta_i i + \gamma_i, \sigma^2)
\]

where \(\sigma^2 \sim \text{WIP}_{>\varepsilon}\).

Here, \(\text{WIP}_{>\varepsilon}\) denotes the truncated weakly informative prior distribution, whose domain of definition is \(x > \varepsilon\) with a random variable \(x\). We used 0.1 as \(\varepsilon\).
2.3 Parameter estimation

We estimated the posterior distribution of the parameters of the proposed model using the No-U-Turn-Sampler (NUTS) [13], which is a Markov chain Monte Carlo (MCMC) method. Because NUTS can sample only continuous parameters, we estimate the following posterior distribution marginalized with respect to $\mu$ and $\nu$:

$$
\sum_{\mu} \sum_{\nu} p(\alpha, \eta, \bar{\eta}, \mu, \nu, \sigma^2|y_{1:N}, d_{1:4}),
$$

where $\cdot_{1:N}$ denotes the set $\{i\}_{i=1}^N$. We implemented a parameter estimation algorithm using PyStan (https://github.com/stan-dev/pystan). We used five chains of MCMC and then sampled parameters 1000 times randomly for each chain and discarded the first half of the samples as burn-in samples, which were supposed to depend on the initial sample. We used 15 as the maximum of the tree depth in the NUTS algorithm (called the “max_treedepth” option in the PyStan library). The other hyperparameters were set by default.

2.4 Evaluation by scoring improvement of defecation frequency

We defined the following defecation frequency improvement (DFI) score $\text{DFI}(\mu, \nu)$:

$$
\text{DFI}(\mu, \nu) \equiv \ln \left( \frac{\sum_{i \in T} x_i}{\sum_{i \in P} x_i} \right)
$$

where $x_i$ is the defecation frequency of the $i$-th day, and $T$ and $P$ are computed by Eq. (1) and Eq. (2), respectively, for for the score parameters $\mu$ and $\nu$. The DFI score indicates the log-ratio of the defecation frequency in the target probiotic period to that in the placebo period.

2.5 Synthetic data experiment

We generated synthetic datasets and estimated the parameters using these datasets to evaluate the performance of the proposed model. We generated $\alpha$, $\eta$, $\bar{\eta}$, $\mu$, and $\nu$ by using the following distribution:

$$
\begin{align*}
\alpha & \sim \text{Normal}(0, 0.1), \\
\eta & \sim \text{Normal}(0, 0.2), \\
\bar{\eta} & \sim \text{Normal}(0, 0.2), \\
\mu & \sim \text{DiscreteUniform}(0, 5), \\
\nu & \sim \text{DiscreteUniform}(0, 5).
\end{align*}
$$

After computing $\beta_i$ using $\alpha$, $\eta$, $\bar{\eta}$, $\mu$, and $\nu$, The number of days between the $l$-th and $l+1$-th defecation events for subject $v_l \in \mathbb{R}$ was obtained as follows:

$$
v_l \sim \text{Gamma}\left(\frac{1}{\sigma^{(v)}}, \frac{\sigma^{(v)}}{\beta_i}, \frac{\sigma^{(v)^2}}{\beta_i}\right),
$$

where Gamma$(a, b)$ denotes the gamma distribution with the shape parameter $a$ and scale parameter $b$ and $\sigma^{(v)^2}$ is the variance of the interval. The mean and variance of this gamma distribution were $1/\beta_i$ and $\sigma^{(v)^2}$, respectively. We generated $v_l$ until $\sum v_l$ exceeded the number of days in each segment and obtained $y_l$ by transforming the defecation intervals. We randomly generated datasets 1000 times and estimated the posterior distributions of the parameters once on each dataset. We used $(d_1, d_2, d_3, d_4) = (29, 43, 71, 85), (51, 76, 126, 151), (101, 151, 251, 301), N = 85, 151, 301, \sigma^{(v)^2} = 0.001, 0.01, 0.1$, and $C = 0$ in one half of the subjects and $C = 1$ in the other half of the subjects for each dataset.

2.6 Real data experiment

We used a real dataset from a previous study [9]. Twenty subjects received $\textit{Bifidobacterium longum}$ capsules in the experiment. Eleven subjects were first administered placebo capsules ($C = 0$) and the remaining subjects were first administered the target probiotic capsules ($C = 1$). $(d_1, d_2, d_3, d_4) = (29, 43, 71, 85)$ was used in this dataset.

2.7 Bayesian beta regression of responder probability on the microbial relative abundances

We conducted regression analysis using the beta regression model [14]. Let $r_i$ be the response probability of the $i$-th subject. The Bayesian beta regression model represents $r_i$ using the standardized relative abundances of the bacteria in the $i$-th subject.
shortly before the start of capsule administration, which is denoted by \( m_i \). \( m_i \) is the \( D \)-dimensional vector and \( D \) is the number of the different bacteria. The generative process is as follows:

\[
\begin{align*}
\phi & \sim \text{WIP}_{>0}, \\
\lambda & \sim \text{WIP}_{>0}, \\
b_j & \sim \text{Normal}(0, \lambda), \\
\theta_i & = \text{logit}^{-1}\left( b_i^T m_i \right), \\
r_i & \sim \text{Beta}(\theta_i \phi, (1 - \theta_i) \phi),
\end{align*}
\]

where \( \phi \) is the precision parameter obtained by reparameterizing the parameters of the beta distribution. \( \lambda \) is the regularization parameter. \( b = (b_1, \ldots, b_D)^T \) is the regression parameter vector; \( \text{logit}^{-1}(\cdot) \) is the inverse-logit function; and \( \text{Beta}(a, b) \) denotes the beta distribution with the shape parameters \( a \) and \( b \). Because the domain of definition of the beta distribution does not include zero or one, we added \( 10^{-5}/-10^{-5} \) to \( r_i \) when \( r_i \) is zero or one. The same method as in Section 2.3 was used for the parameter estimation.

### 2.8 Microbiome data

The 16S rRNA sequence data were obtained from the DDBJ DRA(DRA006874). QIIME2 (version 2019.10) was used for the 16S rRNA gene analysis [15]. In the analytical pipeline, sequence data were processed using the DADA2 pipeline for quality filtering and denoising (options: \(-p\text{-trunc-len-f} 150 -p\text{-trunc-len-r} 190 -p\text{-max-ee-f} 3.0 -p\text{-max-ee-r} 3.0\) [16]. The filtered output sequences were assigned to taxa by using the "qiime feature-classifier classify-sklearn" command with the default parameters. Silva SSU Ref Nr 99 (version 132) was used as the reference database for taxonomy assignment [17]. We used only those taxa that had non-zero abundance in at least 15 subjects for the regression analysis.

### 3 Results

#### 3.1 Performance evaluation with synthetic datasets

We evaluated the performance of the proposed model under various conditions using synthetic datasets (cf. Section 2.5). To verify the accuracy of \( \eta \), we compared the estimated and true values (Supplementary Figure S1). In the case of \( \sigma_{(v)}^2 \leq 0.01 \), the proposed model could accurately estimate \( \eta \). \( \sigma_{(v)}^2 \leq 0.01 \), that is, the standard deviation \( \sigma_{(v)} \leq 0.1 \) means that defecation events with the one-sigma error are within ±2.4 hours (cf. Section 2.5).

We also verified the accuracy of the estimation of \( \mu \) and \( \nu \). Figure 2 shows the sum of the probabilities for each true \( \mu \) and \( \nu \) to evaluate the uncertainty of the estimation. The diagonal elements in Fig. 2def, which shows the results of \( \nu \), are high in the experiments of \( \sigma_{(v)}^2 \leq 0.01 \). However, as can be observed in Fig. 2abc, which shows the results for \( \mu \), the proposed model tends to overestimate the \( \mu \) value.

To evaluate the performance improvement by considering the lag, we identified responders based on the posterior distributions. Here, we defined responders as the subjects with \( \eta > 0 \). Figure 3 shows the AUC-ROC curve of the proposed model and the base model. We use the proposed model with \( \mu_{\text{max}} = \nu_{\text{max}} = 0 \) (cf. Section 2.2), which does not consider the lag of the effect period, as the base model. The proposed model outperformed the base model, and the effectiveness of considering the lag of the effect period is demonstrated in the case where a lag exists. Figure 3 also shows the performance for each threshold of the posterior probability of \( \eta > 0 \). In the case of \( \sigma_{(v)}^2 \leq 0.01 \), identification with a threshold of 0.95 showed a low false positive rate.

#### 3.2 Responder evaluation using a real dataset

We conducted an experiment using a real dataset (cf. Section 2.6). To evaluate the effect of the target probiotic on each subject, we visualized the estimated posterior distribution of \( \eta \) (Fig. 4). Subjects MO04, MO05, MO10, and MO16 exhibited high values of \( \eta \), whereas subjects MO06 and MO18 exhibited low values of \( \eta \). The 95% Bayesian credible intervals of subjects MO02, MO04, MO05, MO06, MO08, MO10, MO12, MO13, MO16, MO18, and MO23 do not include zero. The posterior distributions of \( \mu \) and \( \nu \) are shown in Supplementary Figure S2. We can see that the estimated values of \( \mu \) and \( \nu \) vary from person to person.

We also examined the estimated probability that each subject was a responder (Fig. 5). We counted the number of samples that satisfied \( \eta > 0 \) and computed the ratio of the count to the number of all samples as the posterior probability. The probabilities of subjects MO02, MO04, MO05, MO08, MO09, MO10, and MO16 exceed 0.95. In a previous study, subjects MO04, MO05, and MO10 were also reported to be responders, whereas subject MO16 was reported to be a non-responder [9]. Supplementary Figure S3 shows the posterior distributions of \( \eta \) estimated by the base model, which did not consider the lag \( (\mu_{\text{max}} = \nu_{\text{max}} = 0) \). The Bayesian credible interval of subject MO16 also did not include zero, but the median was estimated
While the DFI scores for the proposed and the base models. The median values of the base model were larger than those of the proposed model, and their
values to be lower than that of the proposed model. The results for subjects MO22 and MO24 show large differences between the
estimated by the proposed model for each synthetic dataset, where the number of observation points is the same as that of the real dataset. The x- and y-axes indicate the true µ, ν and estimated µ, ν values, respectively. Each column represents the sum of the probabilities of each estimate for the subject whose true value is that in the column. a, b, and c indicate the µ results when σ(ν)² = 0.1, σ(ν)² = 0.01, and σ(ν)² = 0.001, respectively. d, e, and f indicate the ν results when σ(ν)² = 0.1, σ(ν)² = 0.01, and σ(ν)² = 0.001, respectively.

Figure 3: The AUC-ROC curve for identifying responders based on the estimated posterior distributions of η in the synthetic datasets of N = 85 and (d1, d2, d3, d4) = (29, 43, 71, 85) using the proposed model (µmax = νmax = 5) and the base model (µmax = νmax = 0). The x- and y-axes indicate the false positive and true positive rates, respectively. The blue and orange dashed lines indicate the results for µmax = νmax = 5 and µmax = νmax = 0, respectively. The red circle, blue triangle, and green square indicate the performance of responder identification with the threshold of the probability of η > 0 0.5, 0.7, and 0.95, respectively, when µmax = νmax = 5.

To verify the consistency between the posterior distributions and the used dataset, we evaluated the improvement in the defecation frequency using scoring (cf. Section 2.4). Figure 6 shows the DFI score of subjects where µ = 0 . . . 5 and ν = 0 . . . 5.

Figure 2: The heat map of the true µ, ν and µ, ν estimated by the proposed model for each synthetic dataset, where the number of observation points is the same as that of the real dataset. The x- and y-axes indicate the true µ, ν and estimated µ, ν values, respectively. Each column represents the sum of the probabilities of each estimate for the subject whose true value is that in the column. a, b, and c indicate the µ results when σ(ν)² = 0.1, σ(ν)² = 0.01, and σ(ν)² = 0.001, respectively. d, e, and f indicate the ν results when σ(ν)² = 0.1, σ(ν)² = 0.01, and σ(ν)² = 0.001, respectively.

to be lower than that of the proposed model. The results for subjects MO22 and MO24 show large differences between the proposed and the base models. The median values of the base model were larger than those of the proposed model, and their identification of responders based on 95% Bayesian credible intervals led to different conclusions (Fig. 5 and Supplementary Figure S4).
frequency if a lag of the effect period existed, and the proposed model reflected the specifications of subject MO24. We also examined the fit of the predictive distribution to the data set (Fig. 7). We observed that the use of the cumulative sum enabled the consideration of the uncertainty caused by uneven defecation frequencies. For example, the defecation frequencies of MO04 and MO12 were comparable, but the uncertainty was estimated to be larger for MO04 because of the uneven defecation frequencies.

To investigate the relationship between the response to probiotics and gut microbiota, we performed Bayesian beta regression of the responder probability on the microbial abundance features before the target probiotic periods. Figure 8 shows the posterior distribution of the regression parameters. As in the previous study, the negative effect of *Agathobacter* was estimated. The 95% Bayesian credible intervals for all regression parameters included zero.

4 Discussion

In this study, we proposed a model for estimating the improvement in defecation frequencies using cross-over trial datasets, and considering the lag of the effect period. Using synthetic datasets, we verified that the proposed model could identify responders better than the base model. In the real dataset experiments, we identified seven responders based on the probability of $\eta > 0$. The base model, which assumed that the lag of the effect period did not exist, identified subjects MO22 and MO24 as responders, in addition to the responders identified by the proposed model. Subjects MO22 and MO24 did not have high DFI scores when $\mu \neq 0$ and $\nu \neq 0$ (Fig. 6). The proposed model reflected these observations. The proposed model was suggested to eliminate uncertain responders in terms of the lag of the effect period against the intake period. In the regression analysis of the responder probabilities on the microbial relative abundances before target probiotic intake, we found that *Agathobacter* had a negative effect. These results are consistent with those of the previous study. However, we could not conclude any microbial effects based on the 95% Bayesian credible intervals.
Figure 6: DFI scores (cf. Section 2.4) of all subjects. The title of each panel indicates the subject and the result of the responder identification by the proposed and base models. The left and right circles indicate the proposed and base model cf. responder identification by the proposed and base models. The filled circle indicates that the subject is identified as a responder, and the open circle indicates that the subject is not. The $x$- and $y$-axes indicate $\nu$ and $\mu$ of the score parameters, respectively. Each value indicates the score. A darker color indicates a higher score.

We used the same lag of the start/end day for the placebo and target probiotic periods. However, these two types of lags may differ because of their sources. That is, while the lag in the target probiotic period is likely to be caused by physical factors (digestion and changes in physical conditions), the lag in the placebo period is likely to be caused by cognitive factors [18]. Therefore, introducing different lag parameters for the placebo and target probiotic periods may enable a better estimation. However, these parameters can render the estimation computationally expensive.

We used uniform distributions with fixed hyperparameters as prior distributions of $\mu$ and $\nu$. There are several options for the prior distribution. Setting prior distributions based on the literature enables a more accurate estimation of parameters. In addition, the covariance between $\mu$ and $\nu$ can reflect the consistency of the score parameters, respectively. Each value indicates the score.

$\mu$ and $\nu$ play key roles in the proposed model. In the synthetic data experiments (Section 3.1), the estimation performance of $\mu$ and $\nu$ was not very accurate. However, the proposed model is effective for estimating responders, as seen in the synthetic data experiments (Fig. 3). This is because considering all cases of $(\mu, \nu)$ contributes to the detection of responders when there is lag in the effect period. However, $\mu$ and $\nu$ are not always useful for all datasets. $\mu$ and $\nu$ are not necessary for the long-term datasets because the number of lag days is small relative to the number of days in the trial. Indeed, the difference between the base model and the proposed model is smaller for synthetic long-term datasets containing observations made under similar conditions (Supplementary Figure S5 and Supplementary Figure S6). Nevertheless, lag consideration is still important because, in most cases, the experiments will be conducted in a short period of time due to cost considerations.

There is a limitation to determining responders based only on defecation frequencies, which is suggested to be unreliable by the U.S. Department of Health and Human Services Food and Drug Administration [19]. According to them, the identification of responders needs to be evaluated based not only on the defecation frequency but also on abdominal pain intensity. That is, deterministic estimation of responders may lead to wrong conclusions. We believe that the responder estimation based on the posterior distribution of $\eta$ conducted in this study enables us to consider the uncertainty of the estimation and contribute to solving this problem.
Figure 7: Data used and predictive distributions. The x- and y-axes indicate the day and cumulative sum of the defecation frequencies, respectively. The blue line and the blue area indicate real data and the 2.5% and 97.5% percentiles of predictive distributions, respectively. The red and black areas indicate the intake periods of the target probiotic and placebo, respectively.

Figure 8: Posterior distributions of the coefficients of Bayesian beta regression. The x- and y-axes indicate bacteria and regression coefficients, respectively. The bar shows the median of the posterior distribution. The error bars represent the 2.5% and 97.5% percentiles.

Author contributions

Shion Hosoda: Conceptualization, Methodology, Software, Investigation, Validation, Visualization, Writing-Original Draft. Yuichiro Nishimoto: Software, Investigation, Writing - Review & Draft. Yohsuke Yamauchi: Software, Investigation, Writing - Review & Draft. Takuji Yamada: Investigation, Writing - Review & Draft. Michiaki Hamada: Investigation,
Supervision, Writing - Review & Draft.

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Data availability

Stan and Python source codes are available at https://github.com/shion-h/LagBasedResponderIdentifier.

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Supplementary data

Supplementary data, including Figures S1, S2, S3, S4, and S5, are available.

Declarations

The randomized controlled trial whose dataset was used in this study was conducted with the approval of the clinical trial ethics review committee of Chiyoda Paramedical Care Clinic.

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