[1]

A Bayesian Hierarchical Modeling Approach Can Improve Measurement Accuracy of Microcystin Concentrations

Sabrina Jaffe,[*,†] Duane Gossiaux,[‡] Reagan M. Errera,[‡] Emanuela Gionfriddo,[¶,§] and Song S. Qian[†]

[2]

†*Department of Environmental Sciences, The University of Toledo, Toledo, OH*

‡*Great Lakes Environmental Research Laboratory, National Oceanic and Atmospheric Administration, Ann Arbor, MI*

¶*Department of Chemistry, The University of Toledo, Toledo, Ohio 43606*

§*Current address: Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York 14260-3000*

E-mail: sabrina.jaffe@rockets.utoledo.edu

Abstract

The Bayesian hierarchical model (BHM) is a framework that improves parameter estimation by leveraging information from different sources. In an environmental monitoring program, we often measure important chemical concentrations using calibration-based methods, which require fitting a calibration curve repeatedly each time with a small number of standard solutions of known concentrations (hence often associated with large estimation uncertainty in the measured concentrations). BHM is a perfect method for reducing calibration curve uncertainty, thereby enhancing the accuracy and stability of the resulting concentration measurements. We demonstrate the effectiveness of a BHM approach by estimating microcystin concentrations from the Lake Erie HABs monitoring program operated by the Great Lakes Environmental Research Laboratory of the National Oceanic and Atmospheric Administration. We introduced a sequential updating approach to implement the BHM approach so that the BHM model can be fit and updated one test at a time. Through comparing the estimated concentrations of quality control samples to their known value, we show that the BHM method yields the best accuracy compared to the currently used methods. Due to the sequential updating approach, the BHM approach can be readily incorporated into a lab without requiring additional changes.

Synopsis: The calibration-based methods commonly used for measuring chemical concentrations is highly uncertain. This study introduces an alternative statistical approach that improves the accuracy and consistency of the resulting concentrations.

Keywords: Bayesian statistics, calibration, hierarchical modeling, missing data problem, shrinkage estimator

Introduction

Cyanobacterial toxins threaten water quality worldwide[1,2]. Major toxins of concern include microcystins (MC), which are a class of cyclic heptapeptides representing over 240 identified compounds[3–5] with varying toxicities. Toxic blooms of Microcystis spp., the major freshwater cyanobacteria producer of microcystins, occur annually within the western basin of Lake Erie[6] impacting both human and ecosystem health. The cyanobacteria harmful algal bloom (HAB) is extensively monitored to provide stakeholders (water managers, public, etc.) with data regarding bloom toxin concentrations, assisting their decision-making for public safety. Accurately measuring MC concentrations is not only of public safety concern, but also a social and economic concern. For instance, in 2014, high concentrations of MC in the western basin caused a "do not drink " water advisory in Toledo, Ohio, that lasted 3 days and left 500,000 residents without potable water.

The most common method for measuring MC concentrations is the Enzyme-Linked Immunosorbent Assay (ELISA), which is a calibration-based method shown to be highly variable[7]. Calibration curves are regression models fit with instrument measured absorbances of standard solutions as the response and their corresponding known analyte concentrations as the predictor. The absorbances of samples with unknown concentrations are measured, and the analyte concentrations are calculated using the inverse function of the calibration curve. However, the calibration curve approach used to estimate MC concentrations has a high level of uncertainty because of the small sample size used to establish the calibration curve which results in highly variable estimated concentrations, which can be problematic when the estimated concentrations are used to make decisions that impact management and public safety[7,8]. The small sample size used for fitting the calibration curve is likely due to the limited space on the ELISA plates used for processing samples. One way to improve the ELISA methods is to increase the

number of standard samples used to develop the calibration curve. However, dedicating more space to standard samples may not be practical or cost effective for labs. Therefore, a statistical approach that can improve estimation accuracy and be implemented without needing to change lab procedures is preferred.

An alternative to the currently used calibration curve regression method is to estimate concentrations using a Bayesian hierarchical model (BHM)[7,8]. The BHM is a flexible framework that can be used to leverage relevant information from similar sources to improve parameter estimation[9]. In the case of ELISA tests, information can be leveraged from within individual tests and across different tests to improve the overall estimation accuracy of MC concentrations. Within a single ELISA test, multiple water samples are estimated at the same time. According to Stein's paradox, when estimating three or more concentrations together, it is always better to shrink the estimates toward the overall average of the estimates[10,11]. The BHM approach can be implemented to achieve estimation accuracy improvement predicted by Stein's paradox[12]. Across multiple tests, there is information available on the calibration curve parameters. The BHM is a modeling structure that can share information across all tests to develop prior distributions for the calibration curve estimated based on multiple curves. This would reduce the estimation uncertainty for individual MC estimates by shrinking curves toward the "average" curve. The BHM approach is mathematically predicted to improve the estimation accuracy of the individual samples within each test compared to the currently used two-step process of (1) fitting the calibration curve and (2) estimating unknown concentrations using the inverse function of the fitted regression model.

Although BHM has been shown to be effective in improving estimation accuracy[8], data from multiple tests are needed when sharing information across tests. Therefore, running a BHM model can be impractical because it requires the availability of data from multiple tests. Even for labs with such data already available, using BHM for

each additional test requires combining the most recent data with data from previous tests. As the number of tests increases, not only is the process of combining data cumbersome, but also the computational burden will inevitably become increasingly intolerable. To avoid these problems and to prevent changes to current lab procedures, we propose a sequential updating algorithm to easily implement the BHM approach to new and established labs. The algorithm is based on the idea that the posterior distribution from previous tests can serve as the priors for future tests[13]. The subsequent (updated) posterior distribution can then be used as priors for the next test which allows for new tests to be analyzed one at a time.

To assess the practical feasibility of the BHM approach, we applied it to data from a long-term water quality monitoring program conducted by the Great Lakes Environmental Research Laboratory (GLERL) of the National Oceanography and Atmospheric Administration (NOAA). This program has been regularly monitoring MC concentrations in the western basin of Lake Erie since 2012. Through our study, we illustrate how the BHM approach can be effectively implemented in real-world laboratory settings and how it significantly improves estimation accuracy when estimating unknown concentrations.

Methods

Microcystin Data and ELISA Protocol

NOAA GLERL established eight monitoring sites in 2012 that are sampled weekly during the HAB season for a variety of water quality parameters, including microcystin concentrations[6]. MC concentrations are analyzed using an ELISA kit (Abraxis) and data are distributed to stakeholders within 48-hours of collection. We obtained 214 sets of ELISA test results from NOAA-GLERL, encompassing data processed between 2012 and 2021. Each test includes six standard solutions with

known MC concentrations ranging from 0 to 5.00 μg/L and a quality control sample with an MC concentration of 0.75 μg/L. Throughout the 214 tests, the instrumental responses exhibited considerable variation (Figure 1).

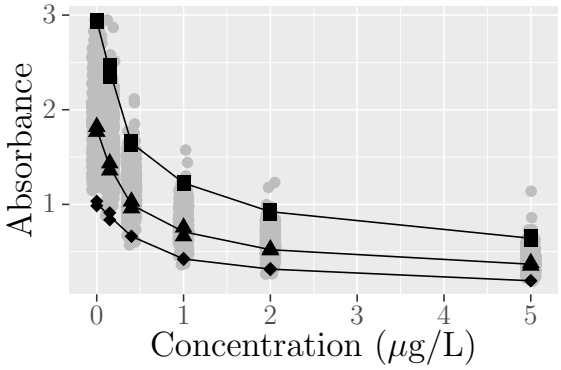

Figure 1: Raw ELISA testing data from GLERL Western Lake Erie Harmful Algal Bloom Monitoring Program. The grey, solid circles are the measured standard solution data points from the 214 tests. The black shapes are the results from three tests with the highest (squares) lowest (diamonds) and median response value (triangles) at the 0 concentration point.

Up to 40 water samples with unknown MC concentrations could be tested with each test kit, and all samples were tested with a replicate. Before fitting the calibration curve and estimating unknown MC concentrations, the measured instrumental responses from each pair of replicates were averaged. The instrumental responses were fit as a linear function of log MC concentrations for tests conducted until 18 July 2016 (tests 1-83) except for the test from 31 August 2015 which was fit with a nonlinear function. The calibration curve followed the form:

$$\log(y) = \beta_0 + \beta_1 \log(x) + \varepsilon \tag{1}$$

where y represents the instrumental response, x is the known MC concentration, and ε is the residual assumed to follow a normal distribution $N(0, \sigma^2)$. The measured response values for standard solutions (each with two replicates) were averaged and divided by the average of the 0-concentration standard solution (relative absorbance).

Due to the log transformation of x, the calibration coefficients (β_0 and β_1) are estimated based on the five non-zero standard solutions (relative absorbances), resulting in a regression model fit with five data points. Consequently, the residual variance σ^2 was estimated with degrees of freedom of 3. Starting from 25 July 2016 and the test conducted on 31 August 2015 (tests 84-214), the calibration curve was described by a nonlinear regression model in the form of the four-parameter logistic function:

$$y = \theta_4 + \frac{\theta_1 - \theta_4}{1 + \left(\frac{x}{\theta_3}\right)^{\theta_2}} + \varepsilon. \tag{2}$$

This model involves four unknown parameters, and the residual variance estimation has a degree of freedom of 1. In both the linear and nonlinear calibration models, the degrees of freedom are below 4, making it difficult to perform a reliable statistical assessment of predictive uncertainty for the fitted regression models because the sampling distribution of σ^2 is an inverse-Chi-square distribution and its variance does not exist when its degrees of freedom is less than 4. Alternatively, a Bayesian approach could help avoid the problems with the inverse-function method. However, priors are needed for the parameters when using a Bayesian approach[14]. BHM is a form of empirical Bayes which derives priors using data from, in this case, the ELISA tests.

Bayesian Hierarchical Model as an Alternative Approach

The MC ELISA dataset is well suited for implementing a BHM approach because each test estimates multiple MC concentrations that can be leveraged to improve concentration estimation and there are multiple ELISA tests that can be leveraged to improve the estimation of calibration curve coefficients. Therefore, we proposed a BHM with two levels of information sharing.

Within an ELISA test, there are multiple MC concentrations to be estimated simultaneously. Stein's paradox suggests that the best estimator for each concentration is determined by shrinking all concentrations toward the overall average concentration of a test. This is because we know that each concentration is either over or underestimated, but we have no gauge for whether the estimate is over or underestimated if we only estimate one concentration. However, when multiple samples are estimated simultaneously, the overall average serves as a reference, hence, shrinking individual estimates can improve overall estimation accuracy. Accordingly, we can implement a hierarchical structure within each ELISA test to improve the estimates for individual concentration. The shrinkage effect is achieved in the BHM through a common prior for all unknown concentrations:

$$\log(x_0^j) \sim N\left(\mu_{x_0}, \sigma_{x_0}^2\right) \tag{3}$$

Where $\log(x_0)$ is the log transformed concentration and $N\left(\mu_{x_0}, \sigma_{x_0}^2\right)$ is the normal prior distribution, with overall mean μ_{x_0} and between sample variance $\sigma_{x_0}^2$. Both parameters are estimated from data along with the unknown concentrations. We used weakly informative priors for μ_{x_0} and $\sigma_{x_0}^2$ for fitting the hierarchical model.

Likewise, because we have multiple different ELISA tests that each fit their own calibration curve, we can also leverage calibration curve information across different tests to further improve estimation accuracy. By imposing a common prior on calibration curve coefficients across multiple tests, the BHM induces the shrinkage effect on calibration curves:

$$\theta_k \sim N(\mu_\theta, \sigma_\theta^2). \tag{4}$$

Where θ_k is model coefficients and $N(\mu_\theta, \sigma_\theta^2)$ is the normal prior distribution with μ_θ as the mean for coefficients over multiple tests and σ_θ^2 being the among test

variance. Again, we used weakly informative priors for μ_θ and σ_θ^2. We started the BHM modeling process by pooling data from the first nine tests to obtain posterior distributions of μ_θ and σ_θ^2. These posteriors are used as the priors for the subsequent sequential updating process.

Sequential Updating

Because the hyperparameters of μ_θ and σ_θ^2 of equation (4) are also interpreted as the overall mean coefficient of multiple curves and the among curve variance, Efron[13] suggested that the BHM approach is ideal for reducing the estimation uncertainty in an individual test. In other words, we can use posterior distributions of μ_θ and σ_θ^2 from the initial nine tests as the prior for the next test (4), instead of non- or weakly-informative priors[13]. With Markov chain Monte Carlo (MCMC) as the computational method, posterior random samples of μ_θ and σ_θ^2 are obtained from their joint distribution. Qian and Reckhow[15] recommended that information represented by these random samples be summarized to quantify the conjugate prior of a normal distribution with unknown mean and variance:

$$\begin{aligned} \mu_\theta \mid \sigma_\theta &\sim N(\mu_0, \sigma_\theta/\lambda) \\ \sigma_\theta &\sim IG(\alpha, \beta) \end{aligned} .$$

This distribution can then be used as the prior distribution for the next calibration curve coefficient. Consequently, we can fit the next calibration curve using the Bayesian method with informative priors for model coefficients derived from the posterior from the previous BHM model, thereby avoiding fitting the BHM combining data from all tests. Because we used MCMC method, the posterior distribution of μ_θ and σ_θ^2 are represented by random samples and we can derive the four distribution parameters (μ_θ, λ, α, β) using the method of moments. That is, given random samples of μ_θ and σ_θ^2, we calculate their sample means and variances, and equate

them to the theoretical mean and variance formulae of the two parameters. The joint prior distribution for the hyper-parameters is specified by four hyper-parameters: μ_θ, λ, α, and β . Assuming the joint posterior distribution of μ_θ and σ_θ^2 can be represented by a N-IG distribution, the posterior parameters can be summarized using the method of moments:

$$\begin{aligned} E(\theta) &= \mu, & Var(\theta) &= \tfrac{\beta_\theta}{(\alpha_\theta - 1)\lambda_\theta} \\ E(\sigma_\theta^2) &= \tfrac{\beta_\theta}{\alpha_\theta - 1}, & Var(\sigma_\theta^2) &= \tfrac{\beta_\theta^2}{(\alpha_\theta - 1)^2(\alpha_\theta - 2)} \end{aligned}$$

Solving for the unknown parameters:

$$\begin{aligned} \mu_\theta^0 &= E(\theta), & \lambda_\theta &= E(\sigma_\theta^2)/Var(\theta) \\ \alpha_\theta &= 2 + E^2(\sigma_\theta^2)/Var(\sigma_\theta^2), & \beta_\theta &= E(\sigma_\theta^2)(\alpha_\theta - 1) \end{aligned}$$

These parameters are then used as prior parameters for analyzing data from the next test and their updated posterior distribution can be used to derive the prior for the next iteration. After a number of rounds of updating, the posterior parameters should converge and the subsequent updatings are essentially fitting a Bayesian linear/nonlinear regression model. Given that most labs conducting ELISA tests have data from previous tests, implementing the sequential updating process is feasible.

Model Evaluation

To determine the effectiveness of the BHM approach, we used six different modeling methods for model evaluation:

1. Standard Inverse-Function Estimator (IFE5): Following the protocol of the Abaxis ELISA test kits, we fitted calibration curves using the five observations from the standard solutions. Then, the unknown concentrations are estimated using the inverse function of the fitted regression model:

$$\log(x) = \log(\theta_3) - \frac{\log\left(\frac{\theta_1 - y}{y - \theta_4}\right)}{\theta_2} \tag{5}$$

2. Inverse-Function Estimator with All 12 Standard Sample Observations (IFE12): The same inverse-function method as IFE5, but instead the calibration curve was fit using the two replicates for all six standards, resulting in 12 data points for the model.

3. Bayesian Estimator (Bayes): This method combines the fitting and estimating processes, without leveraging information within and across tests. We used a non-informative prior for all concentration values (no hierarchical structure).

4. BHM with Information Shared Within Each Test (BHM1): Information from all unknown calibration samples within a test is shared to improve estimation accuracy. Across-test information is not shared.

5. BHM with Information Shared Across Each Test (BHM2): Information of calibration curve coefficients across all tests is shared to reduce estimation uncertainty. Within-test information is not shared and sequential updating was implemented to analyze one test at a time.

6. BHM with Information Shared Within and Across All Tests (BHM3). Information from unknown calibration samples and calibration curve coefficients are shared. Sequential updating was implemented to analyze one test at a time.

For all six models, we employed the nonlinear calibration curve (equation (2)) for all 214 tests to estimate MC concentrations. We compared the results of IFE5 and IFE12 to assess the impact of sample size on calibration results. The outcome of IFE12 is then contrasted with the four Bayesian methods (Bayes, BHM1, BHM2, and BHM3), which also used the two replicates for all six standard samples (12 data points total) and instrumental responses from water samples with unknown MC

concentrations to fit the standard curve and estimate the unknown MC concentrations. For BHM2 and BHM3, we implemented a sequential updating algorithm, where tests 1 - 9 were used to establish the initial priors. The algorithm allows us to evaluate tests 10-214 one at a time. Model fitting and estimation was completed using Stan[16] through R[17,18].

We used posterior simulation for IFE5 and IFE12 to estimate their estimation uncertainty (as illustrated in Chapter 9 of Qian[19]). Within each Abraxis kit, a control sample with a known MC concentration of 0.75 μg/L was provided. To assess estimation accuracy, we compared the posterior distribution of the estimated control sample MC concentration (represented by 5,000 random samples from Monte Carlo simulations) with the known value. To quantify the estimation uncertainty for each test, we define the accuracy as the absolute values of the differences between the 5,000 random samples and known value of 0.75 μg/L of the control sample. The median of these absolute differences represents the deviance of the estimated values from the true value, where a smaller deviance represents better accuracy.

Results and Discussion

As expected, increasing the sample size for fitting the calibration curve from 5 (degrees of freedom or df = 1) to 12 (df = 8) significantly improved the estimation accuracy (Figure 2). This reduction is evidenced by the accuracy of 0.261 and 0.134 for IFE5 and IFE12, respectively. The accuracy is in comparison to the known concentration of 0.75 μg/L. When employing the Bayesian estimator (Bayes), the accuracy is 0.127 μg/L (Figure 2). This value is smaller than that of the inverse function estimator (IFE12), a result of using the weakly informative prior on all unknown concentrations, which prevented extreme values of the estimated concentrations. As such, we expect that the Bayes estimator will consistently

outperform the inverse-function estimator. By implementing the BHM approach to utilize relevant information, accuracy was further improved (Figure 2). Leveraging multiple water samples within a test only (BHM1) resulted in an accuracy of 0.114 μg/L, while leveraging multiple calibration curves to improve estimation accuracy of calibration curve coefficients only (BHM2) resulted in an accuracy of 0.121. Leveraging both within and across tests (BHM3) resulted in an accuracy of 0.109, which is similar to BHM1. The similarity between the accuracy of BHM3 and BHM1 is likely due to the high across-test variance (Figure 1), therefore, the across-test overall mean is downweighed, and the results are dominated by the within-test level[9].

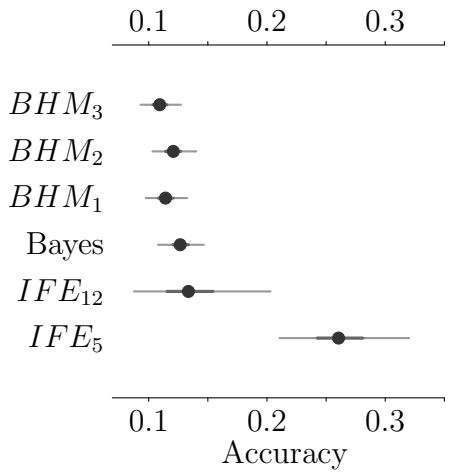

Figure 2: Estimation accuracy of the quality control sample from the six methods (listed on the vertical axis) are compared. The accuracy is the absolute value of the difference between the estimated and the true concentration value (0.75 μg/L), labeled on the horizontal axis. The solid circles are the medians, the black (thick) lines are the 50% credible intervals, and the gray (thin) lines are the 95% credible intervals.

Given the importance of effectively monitoring HABs, our study demonstrates that the estimation accuracy of MC concentrations can be greatly improved by implementing a BHM approach. The four Bayesian estimators produced accuracy distributions with comparable and low variances, indicating improved consistency. In contrast, the two inverse estimators have much larger variances (Figure 2). We note

that the spread of IFE5 accuracy is considerably underestimated due to a large number of posterior simulations of the IFE5 model resulting in non-real estimates. Likewise, the accuracy of IFE12 is also underestimated to a lesser extent. In short, Bayesian estimators demonstrate smaller accuracy and greater consistency compared to the inverse-function estimators, with the within-test (BHM1) and two-level BHM (BHM3) having the largest improvement. Because calibration-based methods are commonly used in analytical chemistry[20], this approach can be used for a wide range of calibration-based problems[8].

The sequential updating algorithm is necessary for implementing the BHM approach in a typical lab setting. Without sequential updating, new tests need to be analyzed with previous data which can be computationally burdensome as the number of tests increases. With sequential updating, the algorithm stores the prior information accumulated from the previous tests which allows for new tests to be analyzed one at a time. As tests are constantly improving, information from older tests can be irrelevant. Accordingly, we can modify the sequential updating process to allow systematic discounting of information from older tests by inflating the variance (σ_θ^2, equation (4)) from the previous iteration, similar to the discount factor used in Bayesian time series analysis[21]. For example, Qian and Reckhow[15] suggested that "we can set the sum of prior parameters α_θ and β_θ to be similar to the data sample size if we want to give the prior information a weight similar to that given to the data." Both the BHM and sequential updating algorithm can be easily automated through the development of a computer application. An application would allow users to use these methods without needing the statistical or coding knowledge to run the analyses in its current form, thus allowing these methods to be easily integrated into the current lab setting.

Acknowledgments

Qian and Jaffe's work is partially supported by a grant from Ohio Sea Grant (2020-2023), Qian and Gionfriddo were partially supported by the University of Toledo Interdisciplinary grant (2020-2021).

Declarations

- Authors declare no conflict of interest/competing interests
- Authors' contributions:
  - SJ – Conceptualization, study design, data analysis, drafting/editing manuscript
  - SSQ – Conceptualization, study and data analysis design, drafting the manuscript, securing funding
  - EG – Study design, data curation, securing funding, reviewing/editing manuscript/supporting materials
  - DG – Data curation, reviewing manuscript
  - RME – reviewing/editing manuscript, data curation

Data Availability

Data and R code are available at `GitHub.com/songsqian/Calibration`

References

(1) Huisman, J.; Codd, G. A.; Paerl, H. W.; Ibelings, B. W.; Verspagen, J. M.; Visser, P. M. Cyanobacterial blooms. *Nature Reviews Microbiology* **2018**, *16*, 471–483.

(2) Chorus, I.; Welker, M. Toxic Cyanobacteria in Water–a Guide to Their Public Health Consequences, Monitoring and Man-agement: the totally revised second edition is now available. **2021**,

(3) Svirčev, Z.; Drobac, D.; Tokodi, N.; Mijović, B.; Codd, G. A.; Meriluoto, J. Toxicology of microcystins with reference to cases of human intoxications and epidemiological investigations of exposures to cyanobacteria and cyanotoxins. *Archives of toxicology* **2017**, *91*, 621–650.

(4) Babica, P.; Bláha, L.; Maršálek, B. Exploring the natural role of microcystins—A review of effects on photoautotrophic organisms 1. *Journal of Phycology* **2006**, *42*, 9–20.

(5) Gan, N.; Xiao, Y.; Zhu, L.; Wu, Z.; Liu, J.; Hu, C.; Song, L. The role of microcystins in maintaining colonies of bloom-forming Microcystis spp. *Environmental Microbiology* **2012**, *14*, 730–742.

(6) Boegehold, A. G.; Burtner, A. M.; Camilleri, A. C.; Carter, G.; DenUyl, P.; Fanslow, D.; Fyffe Semenyuk, D.; Godwin, C. M.; Gossiaux, D.; Johengen, T. H. Routine monitoring of western Lake Erie to track water quality changes associated with cyanobacterial harmful algal blooms. *Earth System Science Data Discussions* **2023**, *2023*, 1–39.

(7) Qian, S.; Chaffin, J.; DuFour, M.; Sherman, J.; Golnick, P.; Collier, C.; Nummer, S.; Margida, M. Quantifying and reducing uncertainty in estimated

microcystin concentrations from the ELISA method. *Environmental Science and Technology* **2015**, *49*, 14221–14229.

(8) Qian, S.; Jaffe, S.; Gionfriddo, E.; Wang, H.; Richardson, C.; Godage‡, N. Rethinking Calibration as A Statistical Estimation Problem to Improve Measurement Accuracy. *Analytic Chemistry* **2024**, *In review*, available at `github.com\songsqian\calibration`.

(9) Gelman, A.; Carlin, J.; Stern, H.; Dunson, D. B.; Vehtari, A.; Rubin, D. *Bayesian Data Analysis*, 3rd ed.; CRC Press: Boca Raton, Florida, 2014.

(10) Stein, C. Inadmissibility of the usual estimator for the mean of a multivariate normal distribution. Proceedings of the Third Berkeley Symposium on Mathematical Statistics and Probability. Berkeley, California, 1956; pp 197–206.

(11) Efron, B. Biased versus unbiased estimation. *Advances in Mathematics* **1975**, *16*, 259–277.

(12) Gelman, A.; Chew, G. L.; Shnaidman, M. Bayesian analysis of serial dilution assays. *Biometrics* **2004**, *60*, 407–417.

(13) Efron, B. Empirical Bayes methods for combining likelihoods. *Journal of the American Statistical Association* **1996**, *91*, 538–550.

(14) Box, G.; Tiao, G. *Bayesian Inference in Statistical Analysis*; Addison-Wesley: Reading, MA, 1973.

(15) Qian, S.; Reckhow, K. H. Combining model results and monitoring data for water quality assessment. *Environmental Science and Technology* **2007**, *41*, 5008–5013.

(16) Stan Development Team Stan Modeling Language User's Guide and Reference Manual, Version 2.30. 2022.

(17) R Core Team R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing: Vienna, Austria, 2022.

(18) Stan Development Team RStan: the R interface to Stan, Version 2.21.5. 2022; `http://mc-stan.org/rstan.html`.

(19) Qian, S. S. *Environmental and ecological statistics with R*; Chapman and Hall/CRC, 2016.

(20) Miller, J.; Miller, J. *Statistics and Chemometrics for Analytical Chemistry*, 6th ed.; Pearson/Prentice Hall: Essex, UK, 2010.

(21) West, M.; Harrison, J. *Bayesian Forecasting and Dynamic Models*, 2nd ed.; Springer, 1997.