Comparison of hierarchical EMAX and NDLM models in dose-response for early phase clinical trials

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Abstract

Phase II clinical trials are primarily aimed to find the optimal dose and investigate the relation between dose and efficacy relative to standard of care (control). Therefore, before moving forward to phase III confirmatory trial, the most effective dose is needed to be identified. The primary endpoint of phase II trial is typically a binary endpoint of success or failure. The EMAX model, ubiquitous in pharmacology research, was fit for many compounds and described the data well, except for a single compound, which had nonmonotone dose–response (Thomas et al., 2014). To mitigate the risk of nonmonotone dose response one of the alternative options is Bayesian hierarchical EMAX model (Gajewski et al., 2019). The hierarchical EMAX is a Proteus dose-response model, it adapts to its environment. When dose-response is monotonic it enjoys efficiency of EMAX. When dose-response is non-monotonic the additional random effect hyperprior makes the hierarchical EMAX model more adjustable and flexible. However, the normal dynamic linear model (NDLM) is a useful model to explore dose-response relation in that the efficacy at the current dose depends on the efficacy of the previous dose(s). Previous research has compared the EMAX to the hierarchical EMAX (Gajewski et al., 2019) and the EMAX to the NDLM (Liu et al., 2017), however, the hierarchical EMAX has not been directly compared to the NDLM. The focus of this paper is to compare these models and discuss the relative merit for each of their uses for an ongoing early phase dose selection study.

Keywords: Dosing design; Bayesian models; hierarchical EMAX; logistic; NDLM
1. Introduction

The primary objective of phase II design is to explore the dose-response curve and find out the most effective dose for the subsequent phase III confirmative trial. The optimal dose, the dose level with the greatest probability of improvement in the rate of good outcome compared with the standard care is also determined. To identify the best dose, several statistical models have been proposed. Specifically, we are going to compare three statistical models using an illustrative example, the HOBIT trial (Gajewski et al., 2019). Then, simulation is used to investigate operating characteristics of different designs of the HOBIT trial with the goal to select the treatment arm which is most likely to perform better than the control arm.

The EMAX model, ubiquitous in pharmacology research, was fit for many compounds and described the data well, except for a single compound, which had nonmonotone dose–response (Thomas et al., 2014). The EMAX model is a nonlinear model frequently used in pharmacodynamic (Basu et al., 2016). To mitigate the risk of nonmonotone dose response one of the alternative options is Bayesian hierarchical EMAX model (Gajewski et al 2019). The additional random effect hyperprior makes the hierarchical EMAX model more adjustable and flexible. The hierarchical EMAX is a Proteus dose-response model, it adapts to its environment. When dose-response is monotonic it enjoys efficiency of EMAX. When dose-response is non-monotonic it enjoys flexibility. However, the normal dynamic linear model (NDLM) is a useful model to explore dose-response relation in that the efficacy at the current dose depends on the efficacy of the previous dose(s). Previous research has compared the EMAX to the hierarchical EMAX (Gajewski et al., 2019) and the EMAX to the NDLM (Liu et al., 2019), however, the hierarchical EMAX has not been compared to the NDLM. It was found that under monotonicity the EMAX is better than hierarchical EMAX and NDLM; but under nonmonotonicity hierarchical
and NDLM are better than EMAX. Specifically, the hierarchical EMAX enjoys a compromise and shared benefits of EMAX and independent models and is preferred under assumed monotonicity but a risk of nonmonotonicity. It is an excellent prespecified model for phase II designs. The focus of this paper is to compare these two class of models and discuss the relative merit for each of their use for an early phase dose selection study.

To be specific, the hierarchical EMAX model (Gajewski et al. 2019), simple NDLM, and 2\textsuperscript{nd} order NDLM order are explored and compared. NDLM was originated in time series modeling and it is a method for model smoothing using the information borrowed from neighboring doses (Liu et al., 2017). It combines variability from two sources, observational and system (Grieve et al., 2005). Furthermore, both 1\textsuperscript{st} order and 2\textsuperscript{nd} order NDLM are to be applied so that it can be seen which NDLM does better for selecting the most effective drug.

2. Method

2.1 Motivating Trial

The motivating study is the Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial. This is a phase II Bayesian clinical trial for selecting the best dose of hyperbaric oxygen treatment, which produces the greatest improvement in the rate of good neurological outcome versus standard of care for subjects with severe traumatic brain injury (TBI). A second goal of this phase II trial is to determine whether there is any hyperbaric treatment that has at least a 50% probability of demonstrating improvement in the rate of good neurological outcome versus a standard treatment in a subsequent phase III confirmatory trial, assuming 500 in the control and 500 in the arm treated with the selected optimal dose regimen of hyperbaric oxygen (Gajewski et al., 2019). The allocation of this phase II trial has a fixed allocation of 20% subjects to control and equal allocation of the 80% to the seven active arms. The total sample size is 200 subjects.
2.2 Dose

Two factors of treatment are considered in the design of dose. To be specific, 4 levels of atmospheric pressure, 1.0, 1.5, 2.0, and 2.5 ATA were used. Another factor is whether NBH is added or not. The dose was defined as a singular monotonic dose as a function of the total oxygen toxicity acquired during treatment. Table 1 summarizes the eight treatment arms involved in the trial. Dose strength as defined in Table 1 is the daily oxygen toxicity units per 100 (OTU/100) (Gajewski et al., 2019). Table 1 below displays the conditions for each active treatment arm and dose strength.

| Dose index | Arm Name                                      | OTUs $\nu_d * 100$ | Dose strength $\nu_d$ |
|------------|-----------------------------------------------|---------------------|-----------------------|
| $d=1$      | Control (1.0 ATA)                             | N/A*                | N/A*                  |
| $d=2$      | 1.5 ATA                                       | 260                 | $\nu_2=2.60$          |
| $d=3$      | 2 ATA                                         | 417                 | $\nu_3=4.17$          |
| $d=4$      | NBH (100% FiO2 at 1.0 ATA)                    | 540                 | $\nu_4=5.40$          |
| $d=5$      | 2.5 ATA                                       | 592                 | $\nu_5=5.92$          |
| $d=6$      | 1.5 ATA+NBH                                   | 620                 | $\nu_6=6.20$          |
| $d=7$      | 2 ATA+NBH                                     | 776                 | $\nu_7=7.76$          |
| $d=8$      | 2.5 ATA+NBH                                   | 952                 | $\nu_8=9.52$          |

Table 1. Conditions for each active treatment arm and dose strength. The control arm is modeled separately since standard of care dose not have a known OTU.

2.3 Models

This section introduces the three models considered: hierarchical EMAX model, simple NDLM, and 2nd order NDLM. For the Bayesian hierarchical EMAX model, a drift parameter is to be used to allow for more adjustment depending on the data. Furthermore, both 1st order and 2nd order NDLM are to be applied so that it can be seen which NDLM does better for selecting the most effective drug.

The probability an individual subject has a favorable outcome, $P_d$, is modeled for each dose, where dose is indexed $d \in \{1, \ldots, 8\}$. We use $\nu_d \in \{N/A, 2.6, 4.17, 5.4, 5.92, 6.2, 7.76, 9.52\}$ as the effective dose strength. The probability of a favorable outcome across doses is modeled with
three different dose-response models. Assume all the subjects randomized to dose index $d$ have a summed binomial outcome $Y_d$:

$$Y_d \sim \text{Binomial}(n_d, P_d).$$

The log-odds of the probability of favorable outcomes, $\theta_d = \log\left(\frac{P_d}{1-P_d}\right)$, are modeled. In addition, for all models the single control arm (indexed $d=1$) is modeled separately from the active doses and has a prior distribution of $\theta_1 \sim N(-.41, .75^2)$. This vague prior on the $P_1$ scale has a median of 0.40 and 95% equal-tailed interval of .09-.83 (Gajewski et al., 2019).

### 2.3.1 Hierarchical EMAX model

The hierarchical EMAX model is the following

$$\theta_d = \phi_1 + \frac{\phi_2 v_d}{v_d + \phi_3} + \psi_d, \quad d \in \{2, \ldots, 8\}.$$ 

The hierarchical EMAX has EMAX parameters $\phi_1$, $\phi_2$, and $\phi_3$, as well as hierarchical parameters $\psi_2, \psi_3, \ldots, \psi_8$, and $\phi_4^2$:

- $\phi_1$ is a constant offset, and the logistic response when the effective dose strength is 0. The prior distribution is $\phi_1 \sim N(-0.41, 1^2)$.

- $\phi_2$ is a scalar coefficient of the fraction of the response due to the effective dose strength. It is the theoretical maximum effect above the constant offset that can be achieved. The prior distribution is $\phi_2 \sim N(0,5^2)$.

- $\phi_3$ is a positive scalar representing the effective dose strength that achieves 50% of the theoretical maximal effect. The prior distribution is $\phi_3 \sim N^+(3,10^2)$. The notation $N^+$ represents a positively truncated normal distribution.
• $\psi_d$ is the off-curve effect that allows for a more flexible model (e.g. nonmonotone) and is modeled hierarchically $\psi_d \sim N(0, \phi_d^2)$, $d \in \{2,\ldots,8\}$. The variance parameter is modeled $\phi_d^2 \sim \text{Inverse-Gamma}(0.1,0.001)$ and its specification is critical.

The off-curve effect parameters are constrained such that $\sum \psi_d = 0$. The advantage of adding the random effect modeling is that when the EMAX provides a good fit to the data the random effect parameters, $\psi_d$, are shrunk toward 0, on the other hand, when there are significant deviations from the EMAX model, the hyperparameter $\phi_d^2$ will be larger and therefore is less shrinkage towards the EMAX model, allowing the individual dose effects to create a custom fit (Gajewski et al., 2019).

### 2.3.2 Simple NDLM

It is a first order simple dynamic linear model since the current state depends on the previous one, except for the first active dose ($d=2$):

$$\theta_2 \sim N(-.41,.75^2).$$

Then after that ($d>2$):

$$\theta_d \sim N(\theta_{d-1}, \tau_{d-1}^2),$$

where $\theta_{d-1}$ represents the previous mean and $\tau_{d-1}^2$ represents the variance from the previous stage, specifically:

$$\tau_d^2 = \tau^2 (v_{d+1} - v_d),$$

and

$$\tau^2 \sim IG(\tau_n^2, \frac{\tau_u^2 \tau_n^2}{2}).$$

$\tau_u$ is the prior central value and $\tau_n$ is the hierarchical prior weight. We let the prior central value to be $\tau_u = 0.2$ and prior weight to be $\tau_n = 0.1$.

### 2.3.3 Second order NDLM
The next model to be considered is the second order (2\textsuperscript{nd}) NDLM. It is second order because the current state depends on previous two states. To be specific, the parameter $\zeta_d$ depends on the previous two stages, where involves $\theta_{d-1}, \theta_{d-2}$ and the dose strengths $v_{d-1}$ and $v_{d-2}$, therefore the current value is more correlated with the each other. The control is modeled separately as before and then the first active dose ($d=2$):

$$\theta_2 \sim N(-.41, .75^2).$$

Then after that ($d>2$):

$$\theta_d = \frac{\theta_{d-2} - \theta_{d-1}}{v_{d-2} - v_{d-1}} + \zeta_d (v_d - v_{d-1}) + \theta_{d-1},$$

where

$$\zeta_d \sim N(0, \tau^2_2),$$

and

$$\tau^2_2 \sim IG(\tau_n^2, \frac{\tau^2 u}{2}).$$

Where $\tau_u = .1$ is the prior central is value, and $\tau_n = .2$ is the hierarchical prior weight.

2.4 Bayesian quantities of interest

We are interested in three Bayesian quantities, specifically, they are: the probability that each active dose is the maximal effective dose; the probability that each active dose performs better than the standard treatment (control group) and the predictive probability a dose would do better in a phase III trial compared to the standard treatment. These Bayesian quantities are used to draw conclusion.

2.4.1. Posterior distribution of treatment difference

This is the probability that the dose is superior to control, $Pr(P_d - P_I > 0)$ is calculated for each active dose using OpenBUGS (Appendix). The estimate of this quantity is the proportion of MCMC samples in which $P_d > P_I$.

2.4.2. Maximum effective dose
This is the dose with the greatest probability of a better outcome. The posterior probability of each dose is the maximum effective dose \( \Pr(D_{\text{Max}}) \) is calculated as the frequency of the MCMC samples in which each dose is the maximum.

### 2.4.3 Posterior predictive probability of future trial success

A future phase III trial is a fixed design with 500 subjects in control and one active dose. For each dose, the predictive probability of success in future trial is found by \( \Pr(\text{Phase III success}; n=500, \alpha=0.025, \sigma=0) \). For each dose it is calculated by averaging power function over the posterior distribution for each dose. Therefore, the treatment effect and uncertainty is formally incorporated (Gajewski et al., 2019).

### 2.4.4 Final evaluation criteria

At the final analysis, the trial is considered successful if all of the following criteria are satisfied:

\[
\Pr(P_d > P_I) > \beta \quad \text{for } d = \text{greatest } \Pr(D_{\text{Max}}), \text{and}
\]

\[
\Pr(\text{Phase III Success}; n = 500, \alpha = 0.025, \delta = 0) > 0.5 \quad \text{for } d = \text{greatest } \Pr(D_{\text{Max}}).
\]

Type I error rate changes depending on the choice of model for fixed \( \beta \) for the final analysis. In order to make sure that all models have the same type I error rate, which is set to be 10%, \( \beta \) will vary by the choice of model used. To provide 10% type I error rates across models, \( \beta \) is set to 0.922, 0.903, 0.938 for hierarchical EMAX, simple NDLM, 2\textsuperscript{nd} order NDLM respectively.

### 3. Result

#### 3.1 Illustrative example

In this section, three models are used for the purpose of comparison, they are hierarchical EMAX model, simple NDLM, and second order NDLM. An illustrative example, Hyperbaric Oxygen Brain Injury Treatment trial, is used as motivation. It is a phase II clinical trial. The goal
is to find out the optimal dose, which is defined as the dose regime with the greatest probability of improvement in the rate of good neurological outcome versus the standard care for patients with severe traumatic brain injury. The second goal is to find out the hyperbaric oxygen regime with at least 50% probability to demonstrate improvement in rate of good neurological outcome versus the control in the upcoming phase III confirmatory clinical trial given that 500 in the control and 500 in the selected optimal treatment arm (Gajewski et al., 2019).

The primary outcome is a sliding dichotomized severity adjusted GOS-E at 6 months (26 weeks). The trial will explore seven different active treatment arms for relative efficacy in comparison of the control arm. Subjects may be randomized to hyperbaric oxygen at one of four possible atmospheric pressures (1.0, 1.5, 2.0 and 2.5 atmospheres absolute (ATA)) with or without additional 100% normobaric oxygen (NBH). Further, there is a control group plus seven novel therapies each expressed by their respective dose of oxygen toxicity units (OTU) (Gajewski et al., 2019).

Three simulated datasets (scenarios) are used to compare the effect of each model. Namely, large monotone effect, NBH only effect, and over dose effect. For the large monotone effect, a monotonic increasing with the dose strength is assumed. For NBH effect, higher response rate takes place only in the treatment arms with additional 100% hyperbaric oxygen. Then for overdose effect, toxicity prevails in the treatments with higher oxygen unit which result in large numbers of poor responses in the dose with higher strength. Therefore, the plot is upside down curve with a bump in the middle.

The following plots illustrate the distribution of the three datasets, as it is shown below, the green line represents NBH effect, the normobaric oxygen only takes place in arms 4, 6, 7, and 8 because additional 100% normobaric oxygen is added. And the red line represents overdose effect.
effect. The green line is an upside-down “U” shaped curve since drug toxicity prevails with the increasing dose. Figure 1 is the graphical representation of the three scenarios for exploration of posterior distribution for assumed response. Table 2 is the summary of example simulated observed response under large monotone, NBH only, and overdose effects.

Figure 1: Illustrative data for exploration of posterior distribution for assumed response

| Dose Strength | d=1 | d=2 | d=3 | d=4 | d=5 | d=6 | d=7 | d=8 |
|---------------|-----|-----|-----|-----|-----|-----|-----|-----|
| n             | 39  | 23  | 23  | 23  | 23  | 23  | 23  | 23  |
| Large Monotone |     |     |     |     |     |     |     |     |
| Response      | y   | 16  | 8   | 10  | 11  | 12  | 14  | 16  | 18  |
| % Response    | 100*y/n | 41.0% | 34.8% | 43.5% | 47.8% | 52.2% | 60.9% | 69.6% | 78.3% |
| NBH Only      |     |     |     |     |     |     |     |     |
| Response      | y   | 16  | 8   | 8   | 18  | 8   | 18  | 18  | 18  |
| % Response    | 100*y/n | 41.0% | 34.8% | 34.8% | 78.3% | 34.8% | 78.3% | 78.3% | 78.3% |
| Over-Dose     |     |     |     |     |     |     |     |     |
| Response      | y   | 16  | 8   | 10  | 12  | 18  | 12  | 4   | 2   |
| % Response    | 100*y/n | 41.0% | 34.8% | 43.5% | 52.2% | 78.3% | 52.2% | 17.4% | 8.7% |

Table 2: Illustrative data for exploration of posterior distribution for assumed response

3.1.1 Large monotone effect
The section compares the results obtained using all three models and gives graphical representation of how they perform. As it is shown in Figure 2, the simple NDLM has a wider credible interval than the hierarchical EMAX model and 2\textsuperscript{nd} order NDLM. The monotonic increasing trend of response and the observed response rates are covered by all models. All the models indicate that \( d = \text{greatest} \) \( \Pr(D_{\text{max}}) = 8 \), which has an effective dose strength 9.52. And at this dose all the models have Bayesian quantities that lead to trial success since all \( \Pr(P_d > P_l) > 0.922, 0.903, 0.938 \) for hierarchical EMAX mode, simple NDLM, 2\textsuperscript{nd} order respectively. And they all have the future trial success probability greater than 0.5 for \( d = 8 \). Therefore, to sum up, hierarchical EMAX model, 2\textsuperscript{nd} order models have better precision. Figure 2 depicts the result for model fitting in large monotone effect and 95\% confidence interval. Table 3 is the summary of Bayesian quantities for model fitting in large monotone effect.

**Figure 2.** Results for fitting models in the large monotone effect example. The black squares in the first three frames represent the observed rate and the shaded regions are the 2.5\% percentile and 97.5\% percentile from models, which is the 95\% confidence interval for \( P_d \) for all three models. The last frame shows the 50\% percentile point estimate and 2.5\% percentile and 97.5\% percentile for \( \psi_d \) in the hierarchical EMAX model.
Table 3. Bayesian quantity results from fitting the large monotonic effect example

| Large monotonic effect | d=1  | d=2  | d=3  | d=4  | d=5  | d=6  | d=7  | d=8  |
|------------------------|------|------|------|------|------|------|------|------|
|                         | Control | 2.60 | 4.17 | 5.40 | 5.92 | 6.20 | 7.76 | 9.52 |
| pMAX                   | Hierarchical | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.08 | 0.90 |
|                        | simple NDLM | 0.00 | 0.00 | 0.00 | 0.00 | 0.02 | 0.13 | 0.24 | 0.61 |
|                        | 2nd order NDLM | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.03 | 0.97 |
| Pr(Pd>Pl)              | Hierarchical | 0.00 | 0.37 | 0.63 | 0.75 | 0.84 | 0.95 | 0.99 | 1.00 |
|                        | simple NDLM | 0.00 | 0.59 | 0.68 | 0.78 | 0.90 | 0.99 | 0.00 | 1.00 |
|                        | 2nd order NDLM | 0.00 | 0.80 | 0.88 | 0.96 | 0.98 | 0.99 | 1.00 | 1.00 |
| Pr(phaseIII success)   | Hierarchical | 0.03 | 0.21 | 0.44 | 0.56 | 0.69 | 0.86 | 0.96 | 0.99 |
|                        | simple NDLM | 0.02 | 0.33 | 0.43 | 0.54 | 0.72 | 0.98 | 0.97 | 0.98 |
|                        | 2nd order NDLM | 0.03 | 0.49 | 0.70 | 0.93 | 0.99 | 0.93 | 0.99 | 1.00 |

3.1.2 NBH only effect

This section is to compare the results obtained from hierarchical EMAX mode, simple NDLM, and second order NDLM under NBH condition. Figure 3 illustrates the median and 95%
credible interval with observed response rate for four models. In this scenario, the hierarchical EMAX model and simple NDLM cover all the points estimates but they have wider credible intervals compared to 2nd order NDLM. However, 2nd order NDLM does not represent non-linear effect. To be specific, 2nd order NDLM underestimates treatment 4 and 6 since the observed response rates are above the 95% credible interval. And it overestimates treatment 3 and 5 in that the credible intervals are well above the observed response rate. By contrast, hierarchical EMAX model and simple NDLM do well in that they both cover observed response rate though they have wider credible intervals compared to 2nd order NDLM. The reason is that the adding off-curve effect is larger than zero at each four NBH doses, which is as displayed by the plot. Figure 3 displays the results for model fitting in NBH only effect, the squares represent the observed rate. And Table 4 displays the results of Bayesian quantities of model fitting in the NBH only effect.

**Figure 3.** Results for fitting models in the **NBH only effect** example. The black squares in the first three frames represent the observed rate and the shaded regions are the 2.5% percentile and 97.5% percentile from models, which is the 95% confidence interval for \( P_d \) for all three models. The last frame shows the 50% percentile point estimate and 2.5% percentile and 97.5% percentile for \( \psi_d \) in the hierarchical EMAX model.
3.1.3 Overdose effect

Figure 4 displays the 95% credible intervals and median with the observed response rate for the overdose example. Both hierarchical EMAX model and simple NDLM cover the entire observed rate. On the contrary, 2nd order NDLM fails to respond to the nonlinear effect in the
middle in that it underestimate effect of treatment 5. The reason why hierarchical EMAX well represent the nonlinear response is that the off-curve random term bumps up at the maximum effective dose strength at $d=5$ with $v_d=5.92$, but the 2nd order NDLM covered the observed response rate at $d=5$.

**Figure 4.** Results for fitting models in the **overdose effect** example. The black squares in the first three frames represent the observed rate and the shaded regions are the 2.5% percentile and 97.5% percentile from models, which is the 95% confidence interval for $P_d$ for all three models. The last frame shows the 50% percentile point estimate and 2.5% percentile and 97.5% percentile for $\psi_d$ in the hierarchical EMAX model.

| Large monotonic effect | $d=1$ | $d=2$ | $d=3$ | $d=4$ | $d=5$ | $d=6$ | $d=7$ | $d=8$ |
|------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| pMAX                   | Hierarchical | 0.00 | 0.00 | 0.01 | 0.03 | 0.92 | 0.04 | 0.00 | 0.00 |
|                       | simple NDLM   | 0.00 | 0.00 | 0.01 | 0.04 | 0.95 | 0.01 | 0.00 | 0.00 |
|                       | 2nd order NDLM | 0.00 | 0.03 | 0.11 | 0.33 | 0.46 | 0.07 | 0.00 | 0.00 |
| Pr(Pd>Pl)              | Hierarchical | 0.00 | 0.32 | 0.56 | 0.79 | 1.00 | 0.78 | 0.03 | 0.00 |
|                       | simple NDLM   | 0.00 | 0.41 | 0.62 | 0.86 | 1.00 | 0.64 | 0.03 | 0.00 |
Table 5. Bayesian quantity results from fitting the overdose effect example.

3.2 Simulation study

This purpose of this section is to use simulations to obtain operating characteristics of trial designs, such as the probability of selecting a right arm (an arm that is correctly better than control) and the probability of selecting the best arm. To be specific, Fixed and Adaptive Clinical Trial Simulator 6.2 (FACTS) (Berry Consultants, Austin, TX) is used to study the characteristics of the three models (Hierarchical EMAX, simple NDLM, and second order NDLM). The shaded region in Table 6 represents the treatment arms expected to perform better than the control, as well as the absolute best in bold.

| Effect         | $d=1$ Control | $d=2$ | $d=3$ | $d=4$ | $d=5$ | $d=6$ | $d=7$ | $d=8$ |
|---------------|--------------|-------|-------|-------|-------|-------|-------|-------|
| Large         | 0.40         | 0.59  | 0.60  | 0.61  | 0.62  | 0.63  | 0.64  | 0.65  |
| NBH           | 0.40         | 0.40  | 0.40  | 0.70  | 0.40  | 0.70  | 0.70  | 0.70  |
| Over Dose     | 0.40         | 0.40  | 0.50  | 0.55  | 0.70  | 0.40  | 0.35  | 0.30  |

Table 6. The arms expected to perform better than the control, represented by the shaded region. The best arm(s) is on bold.

3.2 Probability of selecting the right arm

The probability of selecting the right arms is the probability of selecting the treatment arms which are expected to perform better than the control group. Specifically, for large monotone effect, all the 7 treatment arms are expected to have a higher response rate than that of control, therefore the probability of selecting the right groups is the probability that all 7 treatment arms are chosen. For NBH effect, since 100% additional normbaric oxygen is added to group 4, 6, 7 and 8 treatment, then theses arms are expected to have a higher response rate. Then for overdose effect, toxicity is
taken into consideration, drug toxicity prevails with the increasing dose. Therefore arm 3, 4, 5 are expected to have a better performance.

Figure 5 shows the results of $\text{Pr}(D_{\text{Max}})$ selection among all the models, for large monotone effect. They all select 7 treatment arms to be the arms that expected to do better than the control, most of the time with hierarchical EMAX and 2\textsuperscript{nd} order NDLM doing better than simple NDLM.

**Figure 5.** Large monotone effect.

| Hierarchical EMAX | Simple NDLM | Second order NDLM |
|-------------------|-------------|-------------------|
| ![Hierarchical EMAX Graph](image1) | ![Simple NDLM Graph](image2) | ![Second order NDLM Graph](image3) |
For NBH only effects, the probability for each model of selecting the right arms are roughly the same, all of them have leans towards treatment 7.

**Figure 6.** NBH only effect.

Hierarchical EMAX

Simple NDLM

Second order NDLM

However, there is a noticeable divergence when it comes to over dose effect (Figure 7). Obviously, hierarchical EMAX model and simple NDLM have probabilities much greater than those of 2nd order NDLM. And the 2nd order NDLM has the probability of choosing the incorrect arms much greater than those of hierarchical EMAX model and simple NDLM. This is in fact consistent with the result obtained previously, which indicates that 2nd order NDLM does not well
represent the nonlinear effect. Figure 7 shows the deviation between hierarchical EMAX model and NDLM in that hierarchical model well responds to the nonlinear effect, but 2nd order NDLM fails to respond to the nonlinear pattern.

**Figure 7.** Overdose effect.

**Hierarchical EMAX**

**Simple NDLM**

**Second order NDLM**

Table 7 below displays the probability of selecting the right arms for each model. Specifically, for large monotone effect, we expect all the treatment arms perform better than the control dose, therefore, the probability of selecting the right arms is the probability that any of the
treatment arms are chosen. The hierarchical EMAX model has the highest probability compared to the other three. Especially for 2\textsuperscript{nd} order NDLM, their probability of detecting the right arms is 0.877, which is much lower than that of hierarchical EMAX model. For NBH only effect, we assume that four treatment arms, 4\textsuperscript{th}, 6\textsuperscript{th}, 7\textsuperscript{th} and 8\textsuperscript{th}, to be chosen since the additional 100\% oxygen is added to these arms. Therefore, the probability of choosing the right arms is the probability that all the four arms are selected. Based on the result, it seems that all the four models did approximately equally well in that all the models have a probability well above 90\% and they slightly differ. However, the results diverge when it comes to overdose effect: as it is shown in table 5, we can see that the probability of selecting the right arms of hierarchical EMAX model is 0.504, which is the highest among all the models. For simple and 2\textsuperscript{nd} order NDLM, we expect treatment arms 5\textsuperscript{th}, 6\textsuperscript{th} and 7\textsuperscript{th} to be selected since they are assumed to have a higher probability compared to the control. This result is in fact consistent with the fact that nonlinear response is not well represented by either 2\textsuperscript{nd} model NDLM.

| Effect   | Hier. EMAX P(correct) | P(incorrect) | Simple NDLM P(correct) | P(incorrect) | 2\textsuperscript{nd} order NDLM P(correct) | P(incorrect) |
|----------|------------------------|--------------|------------------------|--------------|---------------------------------------------|--------------|
| Large    | 0.946                  | 0.000        | 0.946                  | 0.000        | 0.878                                       | 0.000        |
| NBH      | 0.949                  | 0.001        | 0.961                  | 0.001        | 0.941                                       | 0.000        |
| overdose | 0.477                  | 0.067        | 0.442                  | 0.062        | 0.296                                       | 0.105        |

\textbf{Table 7.} The probability for selecting the right effective dose (n_{\text{max}}=200). All designs are calibrated to have a Type I error rate of 10\%.

\textbf{4.2 The probability for selecting the maximum effective dose}

This section is devoted to comparing the probability of selecting the maximum effective dose. Based on the result of P(Dmax) obtained from section 2, the most effective arm for large effect is \(d=8\) with dose strength of 9.52; For NBH only effect, since 100\% additional normabrics oxygen is added to 4\textsuperscript{th}, 6\textsuperscript{th}, 7\textsuperscript{th}, and 8\textsuperscript{th} arms, therefore they are the most effective arms; then for
over dose effect, the best arm is 5th group since toxicity prevails with higher dose strengths, it is why there is a large number of poor responses at higher dose strength. According to the result displayed in Table 8, we can see that the hierarchical EMAX model works the best among those four models since it has the greatest probabilities of detecting the best arm for each scenario compared to the rest. Consistently with the conclusion previously obtained, since the 2nd order NDLM did not well represent the nonlinear effect, the probabilities of selecting the best arm is much lower compared to hierarchical EMAX model and simple NDLM. This can be seen especially when it comes to over dose effect: the probability of selecting the maximum effective dose for legacy 2nd order NDLM is 0.150, it is much lower than that of hierarchical EMAX model, which is 0.391.

| Effect       | Hier. EMAX | Simple NDLM | 2nd order NDLM |
|--------------|------------|-------------|----------------|
|              | P(correct) | P(incorrect) | P(correct)     | P(incorrect)  |
| Large        | 0.734      | 0.212       | 0.674          | 0.272         | 0.697 | 0.181 |
| NBH          | 0.949      | 0.001       | 0.961          | 0.001         | 0.941 | 0.000 |
| overdose     | 0.401      | 0.143       | 0.232          | 0.272         | 0.100 | 0.289 |

Table 8. The probability for selecting the maximum effective dose\(n_{\text{max}}=200\). All designs are calibrated to have a Type I error rate of 10%.

4.2 Ideal design percentage comparing models and literature

Presented is the ideal design percentage (Viele et al., 2019), the ratio of the difference in the expected and the minimum true rate and the difference in the maximum true rate and minimum true rate, assuming that when a treatment is not successful the control arm is used in practice. The possibility of non-monotone pattern produces a combination of the effects Large, NBH Only, and Over Dose. Let \(\pi\) be the probability of a non-monotone pattern (this probability is split between the two non-monotone patterns NBH Only and Over Dose), ideal design percentage (ID), for each model is calculated as a function of the probability of the effects, therefore this operating characteristic becomes \((1 - \pi)ID_{\text{Large}} + (\pi/2)ID_{\text{NBH}} + (\pi/2)ID_{\text{Over Dose}}\). The ID was
calculated for all of the models in this paper as well as for EMAX and independent models (Gajewski et al., 2019. As in the previous work, no model is best across all possibilities of non-monotone patterns however hierarchical EMAX and NDLM models work very well across a broad range, with hierarchical EMAX having an edge over NDLM.

**Figure 8.** Comparison of models in this paper (hierarchical EMAX and the NDLMs) to models in the literature (independent and EMAX).

![Graph showing comparison of models](image)

5. **Discussion**

It has been found out that both Bayesian hierarchical EMAX model and simple NDLM work well when the response curve is non-linear. And they work equally well in terms of the probability of selecting the right dose. However, second order NDLM failed to react to the nonlinear spikes. Therefore, when the response it assumed to be nonlinear, the higher order NDLM may not be a good option. On the other hand, when it comes to the probability of selecting the
right dose, hierarchical EMAX model and simple NDLM have a relatively higher probability compared with second order NDLM. And for the probability of selecting the best dose hierarchical EMAX model does the best compared to both simple NDLM and 2nd order NDLM. As for the reason why 2nd order NDLM failed to respond to the nonlinear spikes, it might be because the current state is associated with the previous two states so the current status is more correlated with each other, and this makes a higher NDLM inaccurate when the response curve fluctuates. In conclusion, we have found in the HOBIT trial that hierarchical EMAX works better than the NDLM choices because it has better overall operating characteristics across monotone and nonmonotone cases.

6. References

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Appendix: WinBUGS code

```winbugs
###Control Separately

####hierarchical EMAX model
{

####Difference from Control
y[1]~dbin(P[1],n[1])
logit(P[1])<-theta[1]
thetadiff[1]<-theta[1]-theta[1]
invV<1/pow(.75,2)

####Difference from Control
Pdiff[1]~dbin(P[1],n[1])
logit(P[1])<-theta[1]
thetadiff[1]<-theta[1]-theta[1]

for (d in 2:8)
{

###Active Dose Model
y[d]~dbin(P[d],n[d])
logit(P[d])<-theta[d]
theta[d]<-a[1]+a[2]*nu[d]/(nu[d]+a[3])+psi[d] ## replace "+psi[d]" with "#+psi[d]" to make Emax
##Repace with theta[d]~dnorm(-.41,1) for independent

####Difference from Control
thetadiff[d]<-theta[d]-theta[1]
Pdiff[d]<-P[d]-P[1]
}
a[1]~dnorm(-.41,1)
a[2]~dnorm(0,.04)
a[3]~dnorm(3,.01) I(0,)

### Probably not necessary
psi[1]<-0

for (d in 2:8)
{
psi_adj[d]<-dnorm(0,inva24_adj)
psi[d]<-psi_adj[d]-mean(psi_adj[2:8])
}
inva24_adj<6/7*inva24

inva24~dgamma(.1,.001)
a[4]<-sqrt(1/inva24)

###Probability max relative to control

###
diffMAX[1]<-thetadiff[1] - max(max(max(max(max(max(max(max(thetadiff[2],thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8]))
diffMAX[2]<-thetadiff[2] - max(max(max(max(max(max(max(max(thetadiff[1],thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8]))
diffMAX[3]<-thetadiff[3] - max(max(max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8]))
diffMAX[4]<-thetadiff[4] - max(max(max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8]))
diffMAX[5]<-thetadiff[5] - max(max(max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[6]),thetadiff[7]),thetadiff[8]))
diffMAX[6]<-thetadiff[6] - max(max(max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[7]),thetadiff[8]))
diffMAX[7]<-thetadiff[7] - max(max(max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]))
diffMAX[8]<-thetadiff[8] - max(max(max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]))

for (d in 1:8) {
  pMAX[d]<-step(diffMAX[d])
pPBO[d]<-step(thetadiff[d])
pPBOf[d]<-step(Pdiff[d] - .1)
}

#### Allocation Weights Done in Excel

##### Now do phase III success prediction

ntx<-500
nc<-500
yc~dbin(P[1],nc)
Phatc<-yc/nc

for (d in 1:8) {
  ytx[d]~dbin(P[d],ntx)
  Phattx[d]<-ytx[d]/ntx
  V[d]<-Phatc^*(1-Phatc)/nc+Phattx[d]^*(1-Phattx[d])/ntx
  Z[d]<-(Phatc-Phattx[d])/sqrt(V[d])
pvalue[d]<-phi(Z[d])
PphaseIIIS[d]<-1-step(pvalue[d] - .025)
}

list(inv24=1)

######## For paper (n=200); 20% control, equal elsewhere
#### Large effect
list(
n=c(39, 23, 23, 23, 23, 23, 23),
y=c(16, 8, 10, 11, 12, 14, 16, 18),
nu=c(0, 2.6, 4.17, 5.4, 5.92, 6.2, 7.76, 9.52))

#### NBH only:
list(n=c(39, 23, 23, 23, 23, 23, 23, 23),
y=c(16, 8, 8, 18, 8, 18, 18, 18, 18),
nu=c(0, 2.6, 4.17, 5.4, 5.92, 6.2, 7.76, 9.52))

#### Over dose
list(
n=c(39, 23, 23, 23, 23, 23, 23, 23),
y=c(16, 8, 10, 12, 18, 12, 4, 2),
nu=c(0, 2.6, 4.17, 5.4, 5.92, 6.2, 7.76, 9.52))

model
{

#### simple NDLM

#### Difference from Control

y[1]~dbin(P[1],n[1])
logit(P[1])<-theta[1]
theta[1]<-dnorm(-.41,invV)
invV <- 1/pow(.75, 2)
tau[1] <- invV

### Difference from Control
theta.diff[1] <- -1000000
P.diff[1] <- -1000000

for (d in 2:8)
{
    ### Active Dose Model
    y[d] ~ dbin(P[d], n[d])
    logit(P[d]) <- theta[d]
    theta[d] ~ dnorm(theta[d-1], tau[d-1])

    ### Difference from Control
    theta.diff[d] <- theta[d] - theta[1]
    P.diff[d] <- P[d] - P[1]
}

for (d in 2:7)
{
    tau[d] <- (nu[d+1] - nu[d])*tao
}

tao ~ dgamma(.1, .001)

### Probability max relative to control

diff.MAX[1] <- theta.diff[1] -
  max(max(max(max(max(theta.diff[2], theta.diff[3]), theta.diff[4]), theta.diff[5]), theta.diff[6]),
       theta.diff[7]), theta.diff[8])
diff.MAX[2] <- theta.diff[2] -
  max(max(max(max(max(theta.diff[1], theta.diff[3]), theta.diff[4]), theta.diff[5]), theta.diff[6]),
       theta.diff[7]), theta.diff[8])
diff.MAX[3] <- theta.diff[3] -
  max(max(max(max(max(theta.diff[1], theta.diff[2]), theta.diff[4]), theta.diff[5]), theta.diff[6]),
       theta.diff[7]), theta.diff[8])
diff.MAX[4] <- theta.diff[4] -
  max(max(max(max(max(theta.diff[1], theta.diff[2]), theta.diff[3]), theta.diff[5]), theta.diff[6]),
       theta.diff[7]), theta.diff[8])
diff.MAX[5] <- theta.diff[5] -
  max(max(max(max(max(theta.diff[1], theta.diff[2]), theta.diff[3]), theta.diff[4]), theta.diff[6]),
       theta.diff[7]), theta.diff[8])
diff.MAX[6] <- theta.diff[6] -
  max(max(max(max(max(theta.diff[1], theta.diff[2]), theta.diff[3]), theta.diff[4]), theta.diff[5]),
       theta.diff[7]), theta.diff[8])
diff.MAX[7] <- theta.diff[7] -
  max(max(max(max(max(theta.diff[1], theta.diff[2]), theta.diff[3]), theta.diff[4]), theta.diff[5]),
       theta.diff[6]), theta.diff[8])
diff.MAX[8] <- theta.diff[8] -
  max(max(max(max(max(theta.diff[1], theta.diff[2]), theta.diff[3]), theta.diff[4]), theta.diff[5]),
       theta.diff[6]), theta.diff[7])

for (d in 1:8)
{
    p.MAX[d] <- step(diff.MAX[d])
p.PBO[d] <- step(theta.diff[d])
p.PB.O[d] <- step(P.diff[d] - .1)
}

#### Allocation Weights Done in Excel

#### Now do phase III success prediction
ntx <- 500
nc <- 500
yc ~ dbin(P[1], nc)
Phat.c <- yc/nc

for (d in 1:8)
{
    ytx[d] ~ dbin(P[d], ntx)
    Phat.t[d] <- ytx[d]/ntx
    V[d] <- Phat.c*(1 - Phat.c)/nc + Phat.t[d] *(1 - Phat.t[d])/ntx
    Z[d] <- (Phat.c - Phat.t[d]) / sqrt(V[d])
    p.value[d] <- phi(Z[d])
    P.phase.III[d] <- 1 - step(p.value[d] - .025)
model
{
###second order NDLM
####Difference from Control
y[1]~dbin(P[1],n[1])
logit(P[1])<-theta[1]
theta[1]~dnorm(-.41,invV)
invV<-1/pow(.75,2)
tau[1]<-invV

y[2]~dbin(P[2],n[2])
logit(P[2])<-theta[2]
theta[2]~dnorm(0, invV2)
invV2<-1/pow(.75,2)
tau[2]<-invV2

####Difference from Control
thetadiff[1]<- -1000000
Pdiff[1]<- -1000000
for (d in 3:8)
{
###Active Dose Model
y[d]~dbin(P[d],n[d])
logit(P[d])<-theta[d]
theta[d]<-(((theta[d-1]-theta[d-2])/(nu[d-1]-nu[d-2]))+zeta[d])*(nu[d]-nu[d-1])+theta[d-1]
zeta[d]~dnorm(0,tau2)

####Difference from Control
thetadiff[d]<-theta[d]-theta[1]
Pdiff[d]<-P[d]-P[1]
tau2~dgamma(.1,.001)
}

####Probability max relative to control
diffMAX[1]<-thetadiff[1]
diffMAX[2]<-thetadiff[2]-max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8])
diffMAX[3]<-thetadiff[3]-max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8])
diffMAX[4]<-thetadiff[4]-max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8])
diffMAX[5]<-thetadiff[5]-max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8])
diffMAX[6]<-thetadiff[6]-max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8])
diffMAX[7]<-thetadiff[7]-max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8])
diffMAX[8]<-thetadiff[8]-max(max(max(max(max(max(thetadiff[1],thetadiff[2]),thetadiff[3]),thetadiff[4]),thetadiff[5]),thetadiff[6]),thetadiff[7]),thetadiff[8])
for (d in 1:8)
{
pMAX[d]<-step(diffMAX[d])
}
pPBO[d]<-step(thetadiff[d])
pPBO[d]<-step(Pdiff[d].1)
}

### Allocation Weights Done in Excel

#### Now do phase III success prediction
ntx<-500
nc<-500
yc<-dbin(P[1],nc)
Phatc<-yc/nc

for (d in 1:8)
{
  ytx[d]<-dbin(P[d],ntx)
  Phattx[d]<-ytx[d]/ntx
  V[d]<-Phatc+(1-Phatc)/nc+Phattx[d]*(1-Phattx[d])/ntx
  Z[d]<-(Phatc-Phattx[d])/sqrt(V[d])
  pvalue[d]<-phi(Z[d])
  PphaseIIIS[d]<-1-step(pvalue[d].025)
}

8. Ethics approval and consent to participate

Not applicable.

9. Consent for publication

Not applicable.

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The authors declare that they have no competing interests.

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12. Authors' contributions

XH & BG created the code and ran the simulations as well as drafted the manuscript.

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