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# Designing group dose-response studies in the presence of transmission

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## Abstract

Dose-response studies are used throughout pharmacology, toxicology and in clinical research to determine safe, effective, or hazardous doses of a substance. When involving animals, the subjects are often housed in groups; this is in fact mandatory in many countries for *social animals*, on ethical grounds. An issue that may consequently arise is that of unregulated between-subject dosing (transmission), where a subject may *transmit* the substance to another subject. Transmission will obviously impact the assessment of the dose-response relationship, and will lead to biases if not properly modelled. Here we present a method for determining the optimal design – pertaining to the size of groups, the doses, and the killing times – for such group dose-response experiments, in a Bayesian framework. Our results are of importance to minimising the number of animals required in order to accurately determine dose-response relationships. Furthermore, we additionally consider scenarios in which the estimation of the amount of transmission is also of interest. A particular motivating example is that of *Campylobacter jejuni* in chickens. Code is provided so that practitioners may determine the optimal design for their own studies.

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## 1. Introduction

A group dose-response experiment involves exposing subjects to a range of doses of a substance (for example, an infectious agent, or bacteria or a drug) and measuring their responses (for example, if they became colonised) [2]. These experiments are routinely used to characterise the relationship between the dose of a substance and the response in a subject, known as the *dose-response relationship.*

Studies of this type have been widely used throughout pharmacology [27], toxicology [3] and in clinical trials [1], and methods for characterising the dose-response relationship developed [28]. However, a recent study by Conlan *et al.* noted a potential issue with such analyses when considering infectious agents [7]: in some cases, subjects may *transmit* their dose to other subjects, hence complicating the analysis. The motivating example is of *Campylobacter jejuni* in chickens.

The *Campylobacter* genus of bacteria is the most common cause of food-borne diarrhoeal disease in developed and developing countries – surpassing *Salmonella* and *Shigella* spp. [12]. Group dose-response experiments with *C. jejuni* in chickens are a useful tool in understanding the dose-response and transmission characteristics of the bacteria, allowing sensible measures to be put in place to contain, or eradicate, the infection in livestock used for human consumption. Chickens are social animals, and thus ethically are required to be co-housed [14]. Conlan *et al.* [7] noted that previous statistical analyses of the dose-response characteristics of *C. jejuni* in chickens had neglected the potential for transmission between co-housed subjects – resulting in incorrect estimation of the dose-response relationship.

The presence of transmission in these experiments leads to an "all-or-nothing" response if the subjects are observed too late – that is, once at least one subject is infected within a group, transmission to the initially uninfected chickens leads to

more chickens being colonised than is representative of the administered dose. This yields a lower estimated $ID_{50}$ (i.e., the dose required to infect 50% of the population, on average), and steeper slope-at-half-height – common statistics used to characterise dose-response curves [7]. To limit between-subject dosing, one might attempt to sample the chickens after a very short period of time following initial dosing. However, there exists a latent period between a chicken being challenged and it becoming colonised (i.e., it presenting its response), thus this also provides inaccurate assessment of the number of colonised subjects. Finally, a chicken is "observed" via post-mortem caecal sampling, meaning that only one observation of each subject is possible.

Studies of this form – grouped dose-response experiments with the potential for between-subject dosing – are common, and given the ethical, financial and physical constraints associated with such studies, determining their optimal experimental design in order to obtain the most information about the dose-response relationship is important. One must consider the allocation of the number of subjects to groups, possibly different doses, and the associated time(s) to observe the process, in order to gain the most information about the dose-response relationship. In particular, using these optimal design tools, we can quantify the trade-off in information between allocating many individuals to few groups (doses), or few individuals to many groups (doses). We furthermore give consideration to scenarios in which the estimation of the transmission rate is also of interest – highlighting the potential for these tools to inform design of experiments where the purpose is understanding the transmission dynamics of a pathogen (e.g., avian influenza as in [26]).

We work within a Bayesian framework, allowing for use of prior information concerning the various components of the dose-response study, and transmission dynamics. Our method involves a novel continuous-time Markov chain model for the dynamics within such a study, combined with recently-developed methods for Bayesian optimal experimental design [20, 21]. `MATLAB` code is provided so that

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practitioners may determine the optimal design for their own studies.

## 2. Methodology

### 2.1. Modelling of Group Dose-response Experiments

The first step in determining the optimal experimental design for these experiments is determining suitable models to represent the dynamics amongst a group of subjects. In determining a suitable model, we must ensure we account for the experimental aspects we wish to determine as part of our optimal designs. First and foremost, we are interested in the optimal doses to allocate to subjects in order to gain the most information about the dose-response relationship. Hence, we must represent the dose-response relationships we believe are possible given the substance and subjects being studied. This is achieved by specifying a suitable prior distribution for the model parameters, which results in a range of dose-response curves we believe may eventuate from the experiment (examples given in Section 3).

We must also determine when to observe the process, to measure the response – in this example, we count the number of infectious chickens in each group (i.e., our data is the number of infectious individuals in each group). There are three important considerations when determining the optimal observation time for these group dose-response experiments. First, observation here is assumed to involve killing the subject; hence, we have only one observation for each subject. Second, transmission may occur which may in turn increase the number of colonised subjects we observe for a given dose, thus skewing the dose-response relationship to appear steeper, and reducing the estimate of the $ID_{50}$ [7]. Hence, this suggests we should observe the process early enough in order to mitigate transmission. However, the earlier observation time due to transmission is in direct competition with the third and final consideration: the latent period. That is, there is a delay between exposure to a dose (say via injection, or ingestion) and colonisation. Thus, in determining the optimal observation time, we must allow sufficient time for the subject to pass through this

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latent period, but still observe the process early enough to ensure that there has not been significant amounts of transmission between subjects. With regards to the design, we choose one dose and observation time for all chickens within a group – that is, each chicken within a group receives an identical dose, and is killed at the same time.

In order to cover these three important aspects – the dose-response relationship, a latent period, and transmission – we propose a continuous-time Markov chain model to incorporate each of these stages. We use the beta-Poisson model for the probability of infection, $P_{\text{inf}}$, for a subject given dose $D$. That is,

$$P_{\text{inf}}(D; \alpha, \delta) \approx 1 - \left(1 + \frac{D}{\delta}\right)^{-\alpha}. \tag{1}$$

This follows as the approximation to the hypergeometric model used by [7] – suitable when $\delta >> \max(\alpha, 1)$. Common statistics used to characterise a dose-response relationship are the $\text{ID}_{50}$ and the Slope-at-half-height (SHH). The $\text{ID}_{50}$ represents the dose required to infect 50% of the population, and the slope-at-half-height is a measure of the susceptibility of the host to the pathogen [7]. The $\text{ID}_{50}$ and SHH can be evaluated with respect to $\alpha$ and $\delta$ as follows:

$$\text{ID}_{50} = \delta(2^{1/\alpha} - 1), \qquad \text{and}, \qquad \text{SHH} = \frac{\log(10)}{2}\alpha\left(1 - \left(\frac{1}{2}\right)^{1/\alpha}\right).$$

Note that the slope-at-half-height is independent of $\delta$.

The model we consider takes into account both the latent period of infection, as well as transmission between subjects. We propose a $SE_kI$ Markov chain epidemic model, where: subjects begin the process as healthy; then, the subjects move into either the (first, of $k$) exposed class (with probability $P_{\text{inf}}$, i.e., they are colonised by the design dose), or the susceptible class (with probability $1 - P_{\text{inf}}$) otherwise. We choose to have more than one exposed class ($k > 1$) to allow the distribution of time spent in the latent period to follow an Erlang distribution – a more representative distribution of the latent period than the exponential distribution (e.g., [30, 23]).

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Once a subject has passed through the $k$ exposed classes, they transition into the infectious class. Once a subject is in the infectious class, they may transmit some dose to uncolonised subjects, where $\beta$ is the effective transmission rate. Figure 1 provides a graphical representation of this process. In the example considered herein, we use $k = 2$ and $\gamma = 2$, in order to achieve a mean time between exposure and infectiousness of 1 day (and probability 0.9 of being infectious by day 2) [5], consistent with values reported in [6] on data from [29].
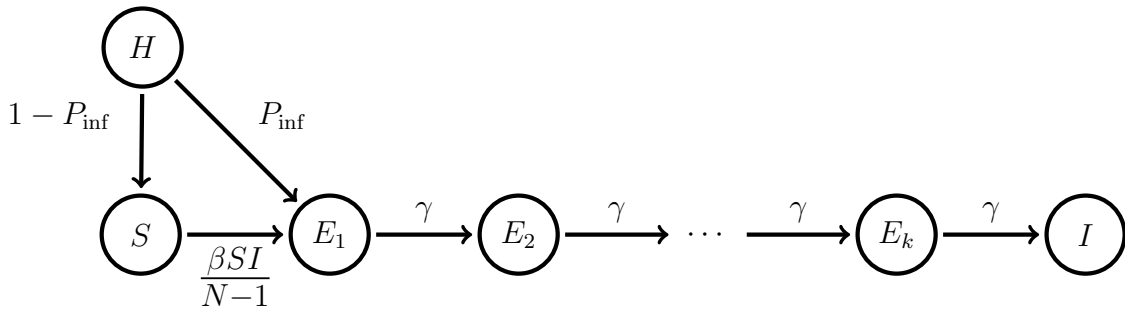


Figure 1: Diagram illustrating the progression of subjects through the complete model. Subjects begin as Healthy ($H$), and after being dosed, move to the first Exposed class ($E_1$) with probability $P_{\text{inf}}$, or otherwise they move to the Susceptible class ($S$). Once exposed, the subjects pass through $k$ exposed classes ($E_1, \ldots, E_k$), each at rate $\gamma$, to reach the Infectious class ($I$). Once in the infectious class, the subject can transmit the infection to subjects in the susceptible class with effective transmission rate $\beta$.

Note that we need to keep track of all but one of the compartments, as we have a fixed population size, $N$; hence, the state corresponding to the infectious class is omitted from our state space and rate description. We define the transition rates for the $SE_kI$ Markov chain model on the state space,

$$\mathcal{S} = \{(s, e_1, \ldots, e_k) : 0 \leq s, e_1, \ldots, e_k, s + e_1 + \cdots + e_k \leq N\}$$

as follows:

$$q_{(s,e_1,\ldots,e_k),(s-1,e_1+1,\ldots,e_k)} = \beta \frac{s(N-s-\sum_{l=1}^{k} e_l)}{N-1},$$

$$q_{(s,\ldots,e_j,e_{j+1},\ldots),(s,\ldots,e_j-1,e_{j+1}+1,\ldots)} = \gamma e_j, \qquad \text{for } j = 1,\ldots,k-1,$$

$$q_{(s,\ldots,e_k),(s,\ldots,e_k-1)} = \gamma e_k.$$

An individual subject begins as 'exposed' with probability $P_{\text{inf}}$. Hence, the probability of having $m$ initially exposed subjects follows a binomial distribution with $N$ trials, and probability of success $P_{\text{inf}}(D; \alpha, \delta)$. That is, the initial state of our process is given by,

$$P(s = N - m, e_1 = m, e_j = 0, \text{for } j = 2,\ldots,k) = \binom{N}{m} P_{\text{inf}}^m (1 - P_{\text{inf}})^{N-m}.$$

The Markov chain model is then initiated from the state $\{s = N - m, e_1 = m, e_2 = 0, \ldots, e_k = 0\}$. We assume that subjects can only be identified as colonised once they enter the infectious class, which is an important assumption when it comes to determining the optimal observation times later.

2.2. Background: Optimal Experimental Design

The aim of optimal experimental design is to determine the best experimental setup in order to maximise some utility of the experiment. To achieve this aim, we specify a utility function $U(\boldsymbol{\theta}, \boldsymbol{x}, d)$, where $d$ is an experimental design chosen from the set of all designs $\mathcal{D}$, $\boldsymbol{\theta}$ is the model parameters and $\boldsymbol{x}$ is the data. This utility function represents how we 'value' a design. We are interested in the expected utility of using design $d$, over the unknown model parameters and data. That is, we wish to evaluate the following,

$$u(d) = E_{\boldsymbol{\theta},\boldsymbol{x}}[U(\boldsymbol{\theta}, \boldsymbol{x}, d)] = \int_{\boldsymbol{x}} \int_{\boldsymbol{\theta}} U(\boldsymbol{\theta}, \boldsymbol{x}, d) p(\boldsymbol{x} \mid \boldsymbol{\theta}, d) p(\boldsymbol{\theta}) d\boldsymbol{\theta} d\boldsymbol{x}, \qquad (2)$$

where $p(\boldsymbol{x} \mid \boldsymbol{\theta}, d)$ is the likelihood function of the unobserved data, under design $d$, and $p(\boldsymbol{\theta})$ is the prior distribution of the model parameters. The optimal design $d^*$

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maximises the expected utility over the design space $\mathcal{D}$,

$$d^* = \operatorname*{argmax}_{d \in \mathcal{D}} u(d).$$

117    The utility function is chosen to represent those aspects of the experiment deemed
118 to be of importance. See [4] and [25] for a review of Bayesian optimal experimental
119 design.

120 *2.3. Choice of Utility*

121    In this work, we investigate two utility functions with the purpose of parameter
122 estimation, namely the Kullback-Leibler divergence (KLD), and the Mean Absolute
123 Percentage Error (MAPE) of a point estimate from the posterior distribution (here,
124 we use the posterior median).

125    The Kullback-Leibler divergence is given by:

$$U(\boldsymbol{x}, d) = \int_{\boldsymbol{\theta}} \log \left( \frac{p(\boldsymbol{\theta} \mid \boldsymbol{x}, d)}{p(\boldsymbol{\theta})} \right) p(\boldsymbol{\theta} \mid \boldsymbol{x}, d) d\boldsymbol{\theta}, \tag{3}$$

126 where $p(\boldsymbol{\theta} \mid \boldsymbol{x}, d)$ is the posterior distribution having observed data $\boldsymbol{x}$ at design
127 $d$. The Kullback-Leibler divergence is the most commonly used utility function
128 when the purpose of the experiment is parameter estimation (e.g., [8], [15], [10],
129 [24], [19], [20]). This is perhaps due to its independence to model parameterisation,
130 or the convenient interpretation: designs which maximise the EKLD maximise the
131 increase in information between the prior and the posterior distributions, which can
132 be interpreted as maximising the amount *learned* from the experiment. However, of
133 concern is the potential for this utility to select designs that maximise the divergence
134 as a consequence of biases in the likelihood that are more likely, or stronger, for those
135 particular designs. As an alternative, we propose the following utility with the aim
136 of estimating model parameters accurately.

137    The Mean Absolute Percentage Error (MAPE) for true (known) parameters $\boldsymbol{\theta} =$
138 $(\theta_1, \theta_2, \ldots \theta_p)$ and estimated parameters $\hat{\boldsymbol{\theta}} = (\hat{\theta}_1, \hat{\theta}_2, \ldots \hat{\theta}_p)$ is given by:

$$U(\boldsymbol{x}, d) = \frac{1}{p} \sum_{j=1}^{p} \frac{|\theta_j - \hat{\theta}_j|}{\theta_j}, \tag{4}$$

where we choose as our parameter estimates $\hat{\boldsymbol{\theta}}$ the median *a posteriori* estimate from the posterior distribution $p(\boldsymbol{\theta} \mid \boldsymbol{x}, d)$. We choose the median over the mode, as evaluating the mode of a high-dimensional distribution can be computationally inefficient and cumbersome (e.g., [10]). In this work, we are only considering experimental design for the purpose of parameter estimation, where it is assumed that the model is known. One could include model uncertainty in this process, or, if the purpose was to best discriminate between a number of competing models, alternative utility functions exist for this purpose (e.g., [9]).

Unfortunately, analytic evaluation of the expected utility function $u(d)$ can rarely be achieved. Hence, we evaluate approximations to equations 3 and 4, and hence the expected utility for each design in equation 2, using the following algorithm [20].

## 2.4. Evaluation of Utility: The ABCdE Algorithm

To evaluate the utility, we take the approach used within the ABCdE algorithm of [20], which has proven beneficial for this type of discrete data problem. The method utilises an Approximate Bayesian Computation (ABC) approach to approximating the posterior distribution, which relies on simulations of the model (e.g., [16]).

Note that the data in this example are the number of infectious individuals in each group, e.g., $\boldsymbol{x}_j = (i_{1j}, i_{2j}, \dots)$, where $i_{kj}$ is the number of infectious individuals in the $j^{th}$ simulation of the $k^{th}$ group for a given design. We provide a brief description below, but direct the reader to the original manuscript for full details.

For each design, we use each set of the pre-simulated data as the "observed datum" one-by-one, and evaluate the utility using all the $N_{pre}$ data as "simulated data". This creates a set of posterior samples having observed every set of simulated data for a particular design. That is, for simulated data $\boldsymbol{x}_1, \boldsymbol{x}_2, \dots, \boldsymbol{x}_{N_{pre}}$ under design $d$, we determine ABC posteriors $[\hat{p}(\boldsymbol{\theta} \mid \boldsymbol{x}_1, d), \hat{p}(\boldsymbol{\theta} \mid \boldsymbol{x}_2, d), \dots, \hat{p}(\boldsymbol{\theta} \mid \boldsymbol{x}_{N_{pre}}, d)]$ using Algorithm 1 (Appendix 6.1). For the current design, we pre-simulate all $N_{pre}$ simulated data sets corresponding to sampled parameter values, and thus we can

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pass pre-simulated data and corresponding parameter values to Algorithm 1 to form the posterior distributions.

We evaluate the utility using each of these $N_{pre}$ posterior distributions under a particular design, and take the average of these $N_{pre}$ values to be our estimate of the expected utility for that design. The optimal design is then the design that returns the largest expected utility. The full algorithm is outlined in Appendix 6.1 (Algorithm 2). We propose that the number of simulations $N_{pre}$ and ABC tolerance $\epsilon$ be chosen in the same way as one would choose the number of simulations and tolerance when using ABC for inference (see, for example, [18]).

For gridded parameter values $\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \ldots, \boldsymbol{\theta}_l$ (allocated prior to running the algorithm, and fixed for all designs), we evaluate a Monte-Carlo approximation to the Expected Kullback-Leibler divergence (EKLD) as:

$$u(d) = \frac{1}{N_{pre}} \sum_{i=1}^{N_{pre}} \sum_{j=1}^{l} \log\left(\frac{p(\boldsymbol{\theta}_j \mid \boldsymbol{x}_i, d)}{p(\boldsymbol{\theta}_j)}\right) p(\boldsymbol{\theta}_j \mid \boldsymbol{x}_i, d). \tag{5}$$

Similarly, the average MAPE for design $d$, where the $i^{th}$ simulation ($i = 1, \ldots, N_{pre}$), $\boldsymbol{x}_i \sim p((\theta_{i1}, \ldots, \theta_{ip}))$, has median *a posteriori* $\hat{\boldsymbol{\theta}}_i = (\hat{\theta}_{i1}, \ldots, \hat{\theta}_{ip})$, is estimated by:

$$u(d) = \frac{1}{p \times N_{pre}} \sum_{i=1}^{N_{pre}} \sum_{j=1}^{p} \frac{|\theta_{ij} - \hat{\theta}_{ij}|}{\theta_{ij}}. \tag{6}$$

Note that inference under a particular design will be identical for the same set of observed data. For this reason, when dealing with discrete data, we evaluate a posterior distribution corresponding to each *unique* data set and use this distribution when evaluating (5) and (6). The frequency of that set of observed datum under the current design is then used to weight the contribution to the expected utility.

*2.5. Design Search: The INSH Algorithm*

The optimisation routine to find the optimal designs is detailed in [21], however we provide a brief description here.

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The Induced Natural Selection Heuristic (INSH) is an optimisation heuristic to efficiently search across a high-dimensional design space and find (near-) optimal designs. At each iteration of the algorithm we consider a number of designs, and through some mechanism, we retain some designs (e.g., top $\rho\%$, or best $r$ designs) – thus, inducing selection. Each of the retained designs then populate the next iteration of the algorithm by sampling $m$ designs around each of them from some distribution. By not combining the accepted samples at each iteration, we are able to efficiently explore multiple regions of the design space simultaneously. Parallel-computing is used to efficiently generate the data and evaluate the utility of each design at each iteration. The initial designs used to start the algorithm can be allocated across a grid, or randomly selected over the design space (e.g., via latin hypercube sampling). Here, prior information regarding regions of the design space with high-utility can be incorporated to allocate these initial designs. The algorithm is outlined in Appendix 6.1 (Algorithm 3). Choices of each component of the algorithm (i.e., initial designs, acceptance criteria, sampling distribution and stopping criteria), are detailed in Section 3.

### 2.6. Case Study

Of particular interest in this paper are group dose-response challenge experiments to monitor the spread of the bacteria *Campylobacter jejuni* amongst chickens. *C. jejuni* is zoonotic, meaning it spreads from animals to humans, and is a common cause of intestinal disease in humans [22]. Incidence of *C. jejuni* infection amongst humans could be dramatically reduced through the prevention of food-borne transmission [31]. Thus, a solid understanding of the dynamics of the bacteria through a flock of chickens, which are to be used for human consumption, is paramount.
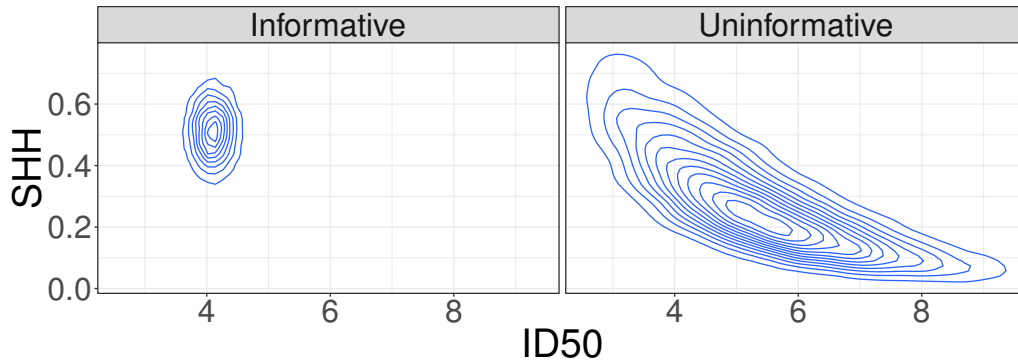
### 2.7. Prior Distributions

In the following examples, we consider two scenarios: 1) where we have a reasonably informative prior distribution, and 2) where we have a relatively uninformative

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prior distribution. In order to more closely represent a practical example, we place prior distributions on the $ID_{50}$ and SHH, rather than $\alpha$ and $\delta$ in the dose-response model. In order to motivate the prior distributions for the $ID_{50}$ and SHH in these examples, we use the estimated distributions of the 2- and 14-day old chicks reported in [7] (specifically, Fig 3a on page 8) – in particular, the prior distributions in the informative scenario represent the estimated distributions for the 2-day old chicks, whereas the prior distributions specified in the uninformative scenario span the reported distributions of both the 2- and 14-day old chicks.

In the informative scenario, we place independent normal prior distributions on each of the $ID_{50}$ and SHH – $N(4.10, 0.225)$, and $N(0.51, 0.08)$, respectively – and a $\log-N(0.7, 0.25)$ prior distribution on $\beta$. In the uninformative scenario, we induce a correlation between the two parameters through a multivariate normal copula, such that the marginal prior distributions of $ID_{50}$ and SHH are Gamma(14.5, 0.35) and Gamma(12, 0.025), respectively, with a correlation of -0.85. The uninformative prior distribution for $\beta$ is $U(1,3)$. When sampling from the prior, lower limits were specified to ensured positive values were sampled, and an upper limit on the slope-at-half-height was enforced at $(1/2)\log(10)\log(2)$, so as to not violate the hypothesis of independent action [7]. The resulting prior distributions for the two scenarios are shown in Figure 2. The experimental design method and all inference examples herein, are with respect to the $ID_{50}$, SHH, and transmission rate $\beta$ (where applicable).

*2.8. Design Space*

Consider a scenario where we are limited by resources – e.g., a fixed number of chickens, doses or maximum time over which we may conduct the experiment. Specifically, assume we are able to dose at most $N = 40$ chickens. We are interested in determining optimal Bayesian experimental designs with respect to the number of groups to allocate the fixed number of subjects to, the dose to allocate to each group, and the time to sample each group. The ranges of these design parameters are presented in Table 1. Note, we are dealing with a social animal, and as such, subjects

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(a) Prior distributions on $ID_{50}$ and Slope-at-half-height (SHH) under both the informative and uninformative scenarios.
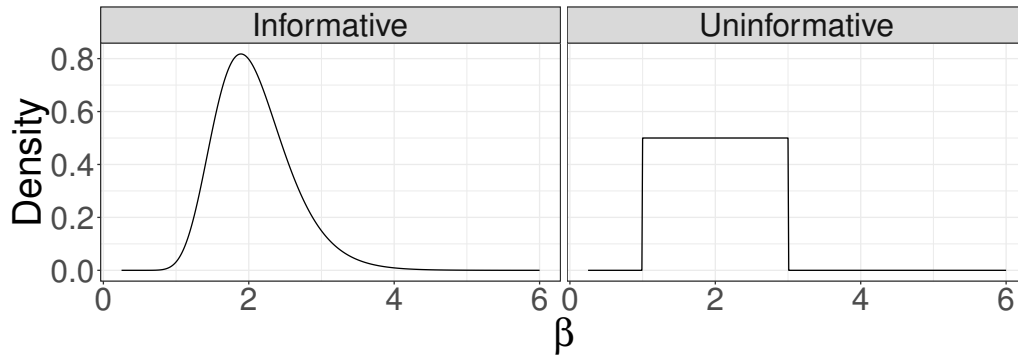


(b) Prior distributions on transmission rate, $\beta$, under both the informative and uninformative scenarios

Figure 2: Prior distributions for $ID_{50}$, SHH and $\beta$ in the informative and uninformative scenarios described above.

must be co-housed. That is, we assume that the chickens are allocated amongst at most five groups. Due to limitations by which one can generate a dose of infectious bacteria (e.g., growing colonies, dilution, etc.), we consider doses in step sizes of $0.5 \log_{10}CFU$ as practically feasible [13]. However, we note that improvements in microfluidics technology will lead to the ability to produce more precise inocula in the future [13], and so we also present results on a finer grid in the Supplementary Material.

Table 1: Typical values of design parameters considered when determining the optimal experimental designs.

| Design aspect | Typical Values |
| --- | --- |
| Number of groups $(G)$ | $\{2,3,4,5\}$ |
| Dose allocation $(A)$ | $\{0.5,1.00,1.50,\ldots,10.00\}$ $\log_{10}$CFU |
| Observation times $(T)$ | $\{0.05,0.10,0.15,\ldots,6.00\}$ days |

We consider only the number of groups $G$, rather than the number of groups and the number of chickens in each group – specifically, we assume that the $N = 40$ chickens are to be divided evenly among two, three, four or five groups (that is, 20, 13, 10 or 8 chickens per group). Note that throughout we refer to the dose in units of $\log_{10}$ colony forming units (CFU), i.e., we refer to a dose of $10^4$ CFU, as a dose of 4. We allow any number of groups to receive the same dose, and each group can have a different observation time – however, each individual within a group has the same dose and observation time.

We note that the Bayesian optimal designs are specific to the prior distributions chosen; hence, the results we provide are not comprehensive. We will provide discussion, where appropriate, to the sensitivity of the optimal designs to the choice of prior distributions, and provide `MATLAB` code for individuals to determine optimal designs for their own experiments.

## 3. Results

Recall, we consider two scenarios: 1) where we have an informative prior distribution on the model parameters, and 2) where we have an uninformative prior distribution. For both scenarios, we consider the optimal designs with respect to both 1) the EKLD, and 2) the MAPE. Furthermore, we also establish the optimal designs when we are interested in either 1) the dose-response parameters only, 2)

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the dose-response and the transmission rate parameter, and 3) the transmission rate parameter only. That is, in total, we consider 12 different sets of results. We present the optimal designs obtained via the INSH algorithm, in each example, and provide figures demonstrating the regions (with respect to the dose and observation time) that each group should be allocated to – akin to sampling windows considered in pharmacokinetic experiments (e.g., [11], [17], [21]). We describe these regions by taking the "top" designs from the INSH algorithm output, and drawing a convex hull around each group – here, we consider the top 0.05% of designs considered by INSH, ranked by their utility (corresponding to approximately 135 designs).

We demonstrate how well each design performs with regards to inference for all parameters. In particular, for 200 simulated experiments, we evaluate the bias (of the posterior median estimate) and variance of the posterior distributions evaluated under each design for each simulated experiment. The posterior distributions were evaluated using a standard ABC-rejection algorithm (Algorithm 1 in Appendix 6.1) with 2,000,000 simulations, and a tolerance of $\epsilon = 0.25 \times G$. Figures illustrating the convergence of the INSH algorithm – with respect to the number of designs of each group size being considered, and the utility of all designs under consideration at each wave – for each scenario are presented in Appendix 6.3.

### 3.1. Optimal Designs from the INSH Algorithm

For this problem, we have a number of different choices for the INSH algorithm. In particular, the allocation of the initial designs, the acceptance criteria, the perturbation kernel (to sample new designs), and the stopping criteria. Steps 3-10 of Algorithm 2 (ABCdE) are used to evaluate the utility for each design, as this approach has proven efficient for discrete data sets as we consider here. We allocate the initial designs according to a uniform distribution across the range of the design variables (given in Table 1), for each number of groups ($G = 2, 3, 4, 5$). We specify the number of initial designs for each group size according to our belief about the location of the optimal design, and the size of the design space within each group size. In each

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example considered herein, we begin with 50, 100, 150, 500 designs for $G = 2, 3, 4, 5$, respectively (a total of 800 designs in the first iteration). At each iteration, we accept the best $r_w = (150, 75, 30)$ designs, and sample $m_w = (3, 6, 15)$ new designs around each accepted design (thus, considering 450 designs at each iteration), for 30, 15 and 15 iterations each (i.e., first 30 iterations are exploring the space, accepting the best 150 designs and sampling three new designs around each accepted design). New designs are sampled according to a truncated-multivariate normal distribution (truncated to the limits of the design space), centred on the retained designs, with standard deviation for the dose allocation (A), $\sigma_w^A = (1.0, 0.75, 0.5)$ and observation time (T), $\sigma_w^T = (0.1, 0.075, 0.05)$, for 30, 15 and 15 iterations, as above. The updating of $r$, $m$, $\sigma^A$ and $\sigma^T$ across each iteration is done in order to reduce exploration and increase exploitation, as the algorithm progresses. Table 2 contains the resulting optimal experimental design for each scenario.

Figures 3 and 4 show the dose and time combination for each group of the designs (i.e., the coloured groups $1, \ldots, G$ represent the $G$ groups in the design). The figures show convex hulls around the top designs with respect to the EKLD and MAPE (respectively). The designs have been jittered slightly so that one can identify where more design points for each group are clustered.

| Scenario | Utility | Target Parameters | G | Optimal Design: A: Dose ($\log_{10}$ CFU); T: Obs. Time (days) |
|---|---|---|---|---|
| 1 | EKLD | $(ID_{50}, SHH)$ | 5 | $A = (0.50, 1.00, 1.50, 2.00, 9.00)$ <br> $T = (1.30, 1.30, 1.15, 1.05, 0.90)$ |
| 1 | MAPE | $(ID_{50}, SHH)$ | 2 | $A = (1.50, 2.00)$ <br> $T = (1.95, 1.90)$ |
| 1 | EKLD | $(ID_{50}, SHH, \beta)$ | 5 | $A = (0.50, 1.00, 2.50, 5.50, 6.00)$ <br> $T = (1.45, 1.30, 0.75, 0.85, 0.85)$ |
| 1 | MAPE | $(ID_{50}, SHH, \beta)$ | 2 | $A = (0.50, 1.00)$ <br> $T = (4.20, 3.70)$ |
| 1 | EKLD | $(\beta)$ | 5 | $A = (0.50, 1.00, 1.50, 3.00, 8.50)$ <br> $T = (1.40, 1.30, 0.95, 0.90, 0.85)$ |
| 1 | MAPE | $(\beta)$ | 2 | $A = (2.40, 2.45)$ <br> $T = (5.00, 4.90)$ |
| 2 | EKLD | $(ID_{50}, SHH)$ | 5 | $A = (0.50, 1.00, 1.50, 3.00, 7.50)$ <br> $T = (1.35, 1.45, 1.50, 0.90, 0.90)$ |
| 2 | MAPE | $(ID_{50}, SHH)$ | 2 | $A = (2.00, 2.50)$ <br> $T = (1.75, 1.80)$ |
| 2 | EKLD | $(ID_{50}, SHH, \beta)$ | 5 | $A = (0.50, 1.00, 1.50, 2.50, 5.00)$ <br> $T = (1.45, 1.55, 1.05, 0.95, 0.95)$ |
| 2 | MAPE | $(ID_{50}, SHH, \beta)$ | 2 | $A = (0.50, 2.50)$ <br> $T = (4.45, 2.05)$ |
| 2 | EKLD | $(\beta)$ | 5 | $A = (0.50, 1.00, 1.50, 2.50, 9.00)$ <br> $T = (1.40, 1.45, 0.95, 0.85, 0.85)$ |
| 2 | MAPE | $(\beta)$ | 2 | $A = (0.50, 1.00)$ <br> $T = (4.15, 4.05)$ |

Table 2: Optimal designs corresponding to two different scenarios ((1) informative and (2) uninformative prior distributions), according to two different utility functions (EKLD and MAPE), where the parameters of interest are either just the dose-response parameters ($ID_{50}$,SHH), both the dose-response and transmission rate parameters ($ID_{50}$,SHH,$\beta$), or the transmission parameter ($\beta$).

(a) Scenario 1, Target (ID$_{50}$, SHH)

(b) Scenario 2, Target (ID$_{50}$, SHH)

(c) Scenario 1, Target (ID$_{50}$, SHH, $\beta$)

(d) Scenario 2, Target (ID$_{50}$, SHH, $\beta$)

(e) Scenario 1, Target ($\beta$)

(f) Scenario 2, Target ($\beta$)

Figure 3: Convex hull plots demonstrating the dose-time pairing for each group, for the best 0.05% of designs according to the EKLD from the INSH algorithm, for Scenarios 1 and 2, when targeting each of (ID$_{50}$,SHH), (ID$_{50}$,SHH,$\beta$), and ($\beta$).

(a) Scenario 1, Target $(ID_{50}, SHH)$

(b) Scenario 2, Target $(ID_{50}, SHH)$

(c) Scenario 1, Target $(ID_{50}, SHH, \beta)$

(d) Scenario 2, Target $(ID_{50}, SHH, \beta)$

(e) Scenario 1, Target $(\beta)$
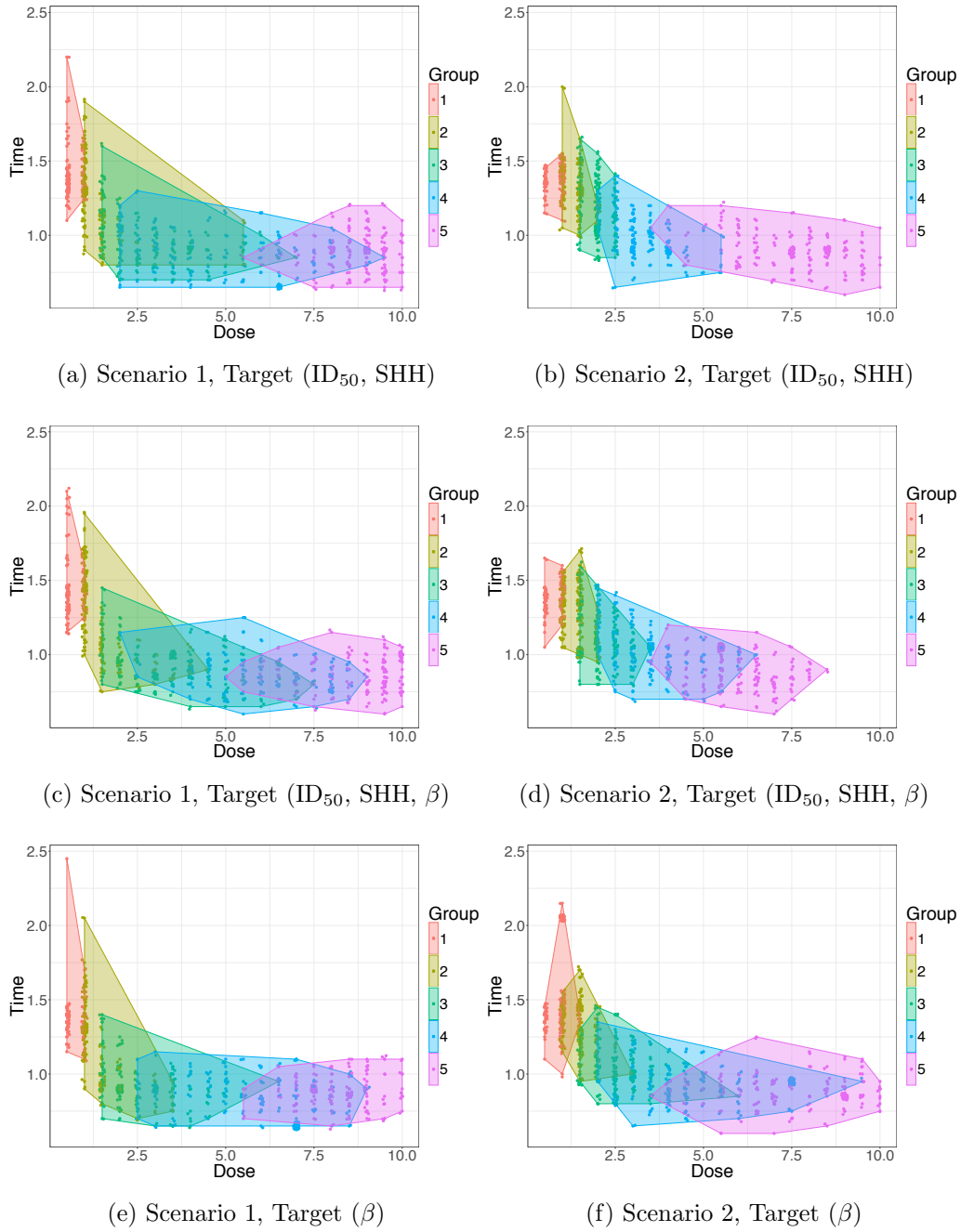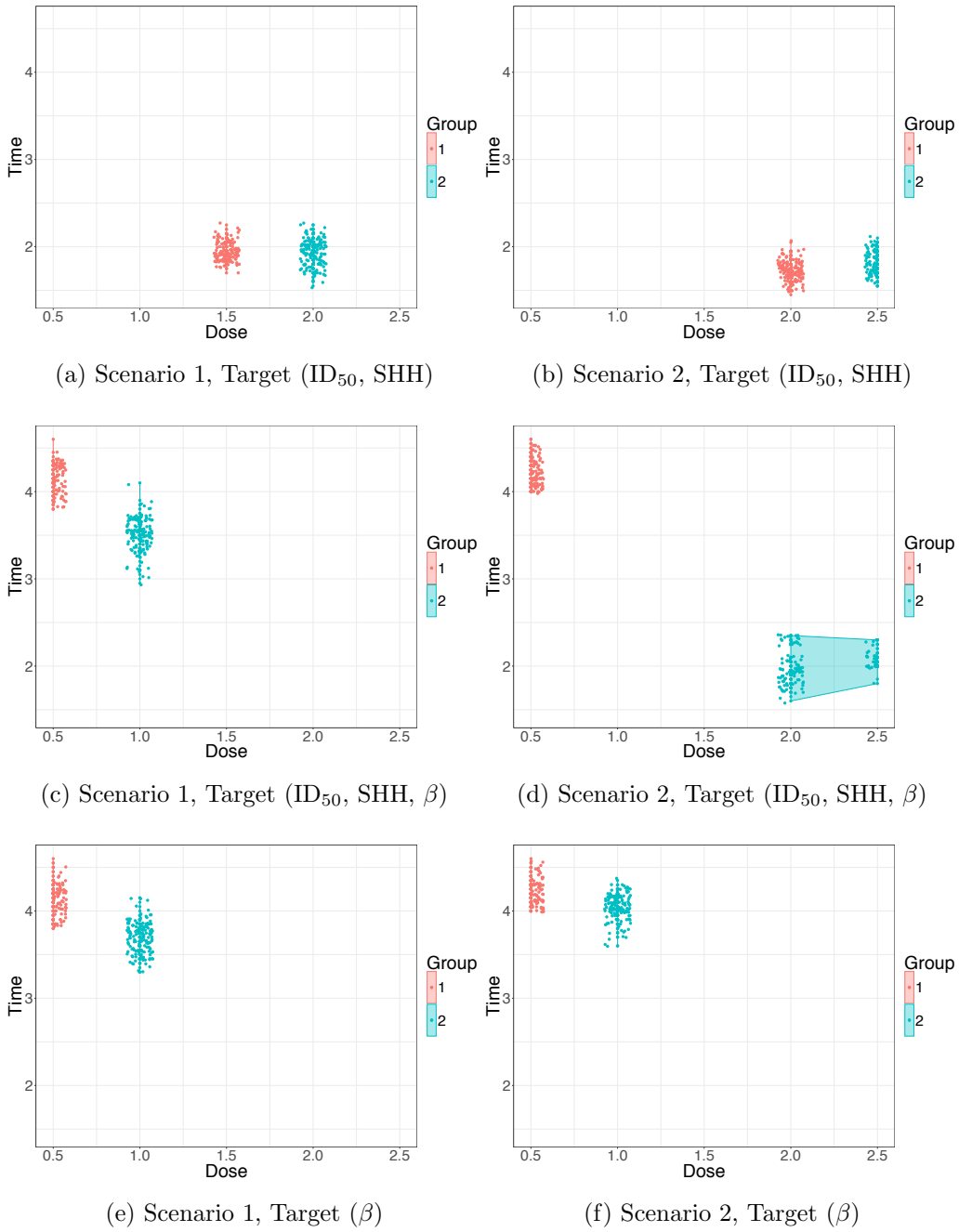
(f) Scenario 2, Target $(\beta)$

Figure 4: Convex hull plots demonstrating the dose-time pairing for each group, for the best 0.05% of designs according to the MAPE from the INSH algorithm, for Scenarios 1 and 2, when targeting each of $(ID_{50}, SHH)$, $(ID_{50}, SHH, \beta)$, and $(\beta)$.

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*3.2. Performance of Optimal Designs*

*3.2.1. Scenario 1: Informative Prior Distributions*

Figures 5 and 6 show the performance of the two optimal designs (i.e., with respect

to the EKLD and MAPE), for targeting the dose-response parameters, dose-response

and transmission parameters, or the transmission parameter only (i.e., $(ID_{50}, SHH)$,

$(ID_{50}, SHH, \beta)$, or $(\beta)$), with informative prior distributions. Performance is assessed

with respect to the bias in the median of the posterior distribution (i.e., posterior

median - known parameter value used to simulate the experiment), and the posterior

variance, of 200 simulated experiments.



Figure 5: Scenario 1 (informative prior distributions). Boxplots of the posterior distribution median bias in estimates of each of $ID_{50}$, SHH and $\beta$ (rows), corresponding to 200 simulated experiments, calculated at each of the optimal designs evaluated with respect to the EKLD and MAPE, when targeting each of the dose-response parameters, $(ID_{50}, SHH)$, transmission rate and dose-response parameters, $(ID_{50}, SHH, \beta)$, or only the transmission rate parameter $(\beta)$ (columns).

Figure 6: Scenario 1 (informative prior distributions). Boxplots of the variance of the posterior distribution of each of $ID_{50}$, SHH and $\beta$ (rows), corresponding to 200 simulated experiments, calculated at each of the optimal designs evaluated with respect to the EKLD and MAPE, when targeting each of the dose-response parameters, ($ID_{50}$, SHH), transmission rate and dose-response parameters, ($ID_{50}$, SHH, $\beta$), or only the transmission rate parameter ($\beta$) (columns). The horizontal line in each figure corresponds to the prior variance.

### 3.2.2. Scenario 2: Uninformative Prior Distributions

Figures 7 and 8 show the performance of the two optimal designs (i.e., with respect to the EKLD and MAPE), for targeting the dose-response parameters, dose-response and transmission parameters, or the transmission parameter only (i.e., ($ID_{50}$, SHH), ($ID_{50}$, SHH, $\beta$), or ($\beta$)), with uninformative prior distributions. Performance is assessed with respect to the bias in the median of the posterior distribution (i.e., posterior median - known parameter value used to simulate the experiment), and the posterior variance, of 200 simulated experiments.
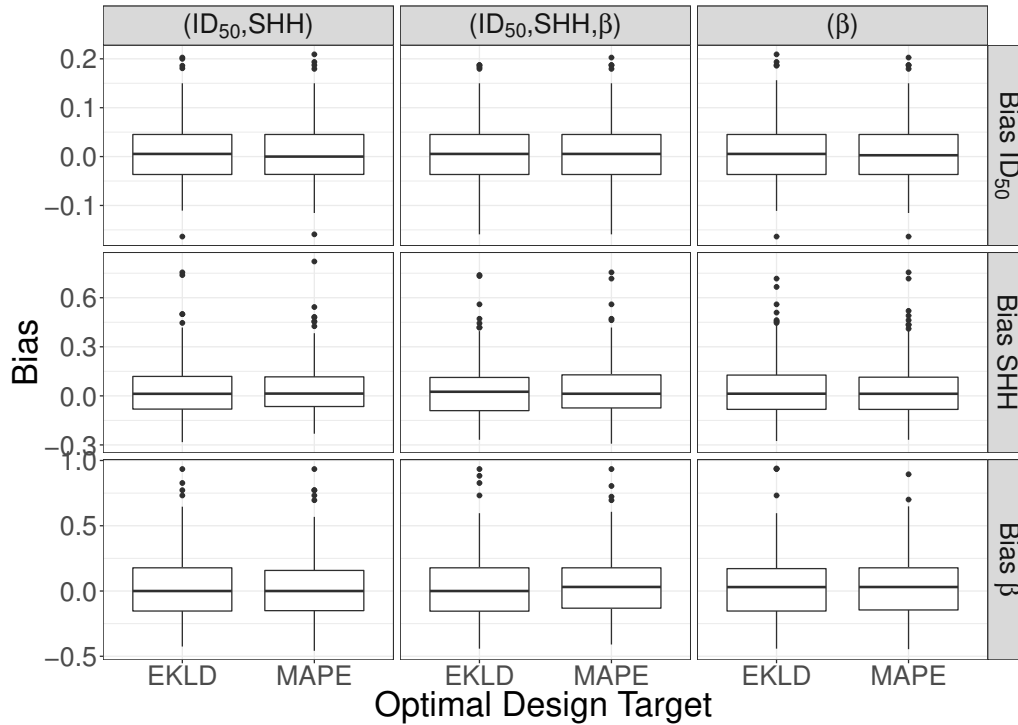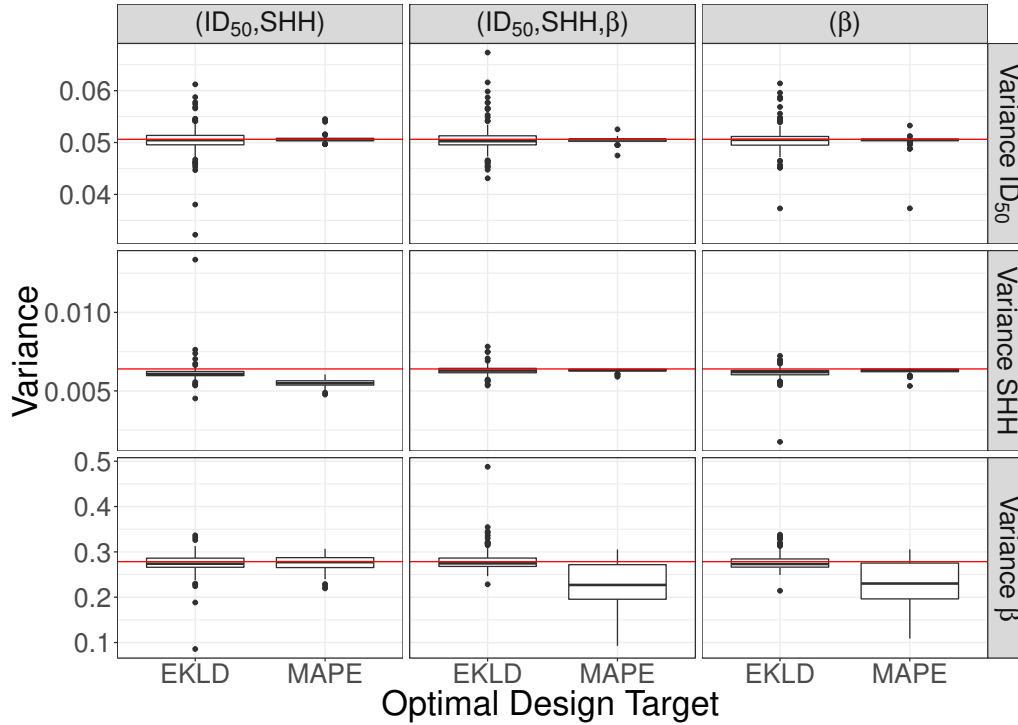
21
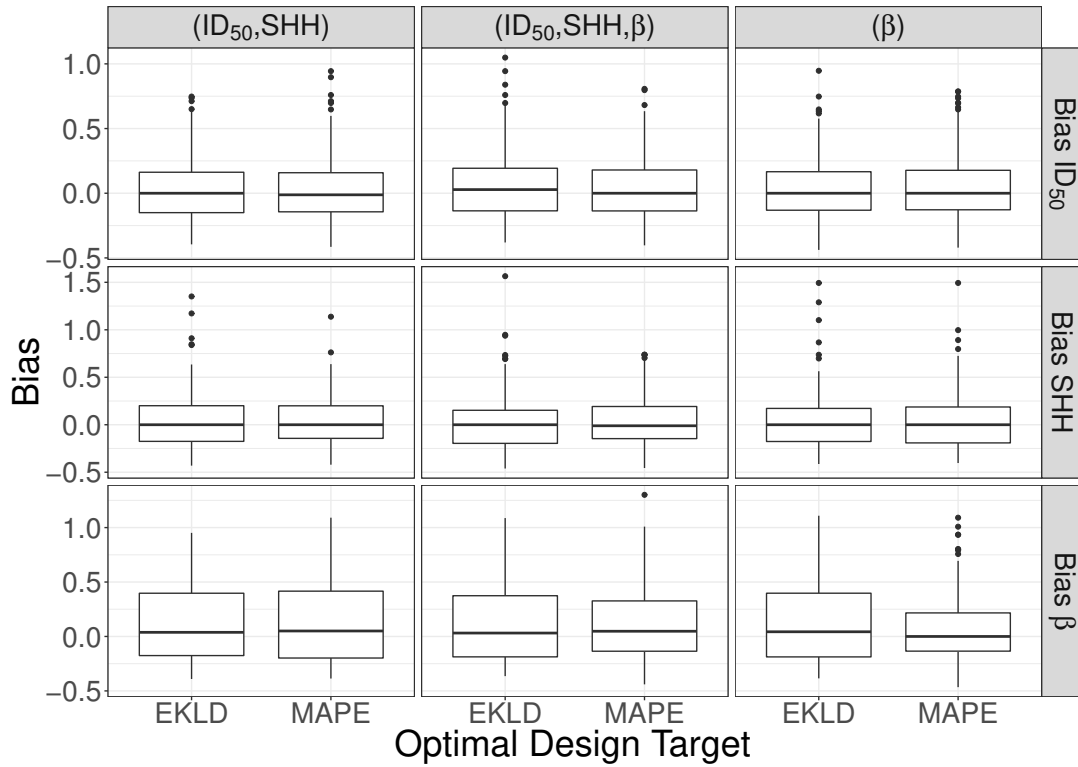
Figure 7: Scenario 2 (uninformative prior distributions). Boxplots of the posterior distribution median bias in estimates of each of $ID_{50}$, SHH and $\beta$ (rows), corresponding to 200 simulated experiments, calculated at each of the optimal designs evaluated with respect to the EKLD and MAPE, when targeting each of the dose-response parameters, ($ID_{50}$, SHH), transmission rate and dose-response parameters, ($ID_{50}$, SHH, $\beta$), or only the transmission rate parameter ($\beta$) (columns).
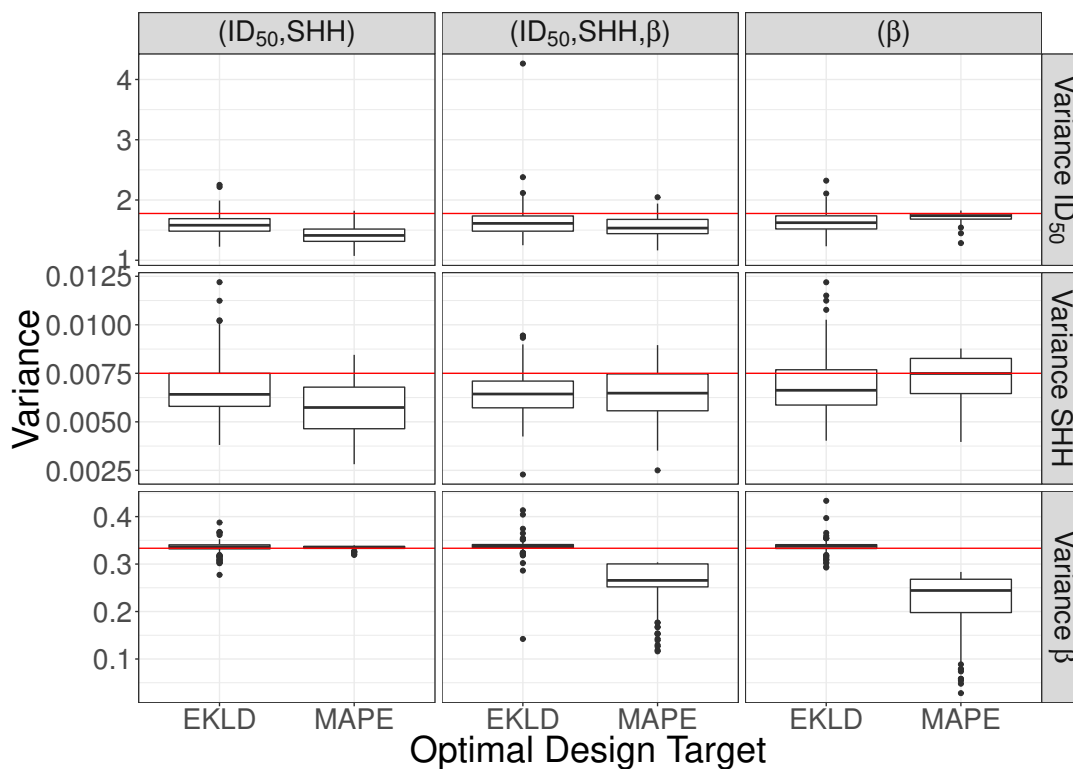
Figure 8: Scenario 2 (uninformative prior distributions). Boxplots of the variance of the posterior distribution of each of $ID_{50}$, SHH and $\beta$ (rows), corresponding to 200 simulated experiments, calculated at each of the optimal designs evaluated with respect to the EKLD and MAPE, when targeting each of the dose-response parameters, ($ID_{50}$, SHH), transmission rate and dose-response parameters, $(\alpha, \delta, \beta)$, or only the transmission rate parameter ($\beta$) (columns). The horizontal line in each figure corresponds to the prior variance.

## 4. Discussion

First of all, we wish to reiterate that the results here are prior-specific, and therefore different trends may be apparent when considering other prior distributions than those we have considered here.

The designs returned under the two different utility functions in Figures 3 and 4 show distinct differences. In particular, the EKLD designs consistently prefer more groups (with less replicates in each), whereas the MAPE designs prefer more repli-

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cates within less groups. The designs under the EKLD each show a similar pattern, with low-dose groups being observed at a marginally later observation time (around 1.5-2 days post-inoculation), while groups that receive a larger dose are observed earlier (around 0.85-1.25 days post-inoculation). The marginally later observation time in the low-dose groups is indicative of the smaller probability of colonisation in these groups, thus, suggesting it is beneficial to wait marginally longer than the mean time to progress through the exposed classes ($\approx 1$ day), in order to successfully observe the colonised chickens. The groups receiving larger doses can feasibly be observed earlier, as there are a greater number of chickens that will be colonised (and so we will have a negligible probability of observing no colonised chickens), while also avoiding the possibility of transmission occurring.

In contrast, the MAPE designs are all preferentially allocating chickens to only two groups, and show obvious differences depending on which parameter combinations are of interest. Designs considering only the dose-response relationship (i.e., $ID_{50}$ and SHH) are allocated to relatively small doses, and observed at later observation times (note that with the Erlang(2,2) distribution of time to pass through the exposed classes, there is approximately a 90% chance of having progressed to the infectious class by 2 days post-inoculation). When considering only the transmission rate parameter, $\beta$, the designs are vastly different – with lower doses and later observation times, allowing the potential for more transmission events to occur and sufficient time to observe a second-wave of infectious chickens that would likely be due to transmission. Finally, when considering both the dose-response relationship and transmission dynamics, the designs attempt to balance the two previous extremes. Under this example of informative prior distributions, the design resembles that of considering only the transmission rate parameter, suggesting that more information can be obtained about $\beta$ than could be obtained for the $ID_{50}$ or SHH. This can be observed in the posterior variances in Figure 8, where the variance for these dose-response parameters resembles both that of the EKLD designs, and the

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prior variance, however there is a considerable improvement in the posterior variance for $\beta$ compared to both the EKLD and prior variance. Note that there are no distinct differences in the posterior bias estimates under the designs from the two utility functions. Under the uninformative prior distribution however, we can see that the optimal design is to actually allocate our resources between these two regions – one group with a low-dose and late observation time in order to learn about the transmission dynamics, and a second group with an earlier observation time and a higher-dose in order to learn about the dose-response parameters.

Figures 6 and 8 demonstrate the posterior variance for each parameter, having conducted the experiment under each of the different optimal designs, compared to the variances of the prior distribution. Again, it appears as though the MAPE designs outperform the EKLD designs – that is, the posterior distributions have smaller variance, on average. In fact, in some cases, the posterior variance under the EKLD designs appears marginally worse than that of the prior distribution – suggesting that this allocation of resources provides no further information about the system than was achievable under the prior distribution. The only instances that the EKLD designs out-perform the MAPE designs appear to be with regards to the slope-at-half-height of the dose-response relationship. Under the uninformative prior distributions, the posterior variance of SHH is worse under the MAPE design than the corresponding EKLD design, once consideration is also given to the transmission rate parameter $\beta$ (a marginal difference for (ID$_{50}$,SHH,$\beta$), however more notable when considering only ($\beta$)). Furthermore, the EKLD design appears to outperform the MAPE design with respect to the posterior variance of ID$_{50}$ when considering *only* $\beta$ – however, this is not unexpected as the MAPE design is targeting only $\beta$. Note that each case where EKLD outperforms the MAPE, is where MAPE is not targeting the parameter which has a larger posterior variance. The larger variances in each case are made up by considerably reduced variance for the parameter of interest, compared to the EKLD design. This suggests that the MAPE utility is clearly prioritising the

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parameter of direct interest, and sacrifices estimating other parameters well in order to gain improved accuracy for those parameters under consideration. Conversely, the posterior variances evaluated at the EKLD designs do not appear to change considerably when targeting different parameter combinations – not surprising, since the designs returned under various scenarios for the EKLD utility were all very similar. Thus, if only a subset of the model parameters are of interest, it appears as though these can be more accurately targeted using the MAPE utility, rather than the EKLD utility. Similar patterns exist in the informative scenarios, but to a lesser degree (as there is a smaller margin for improvement) – in particular, note the improved posterior variances for $\beta$ under the MAPE designs, in the scenarios where $\beta$ is targeted, compared to the EKLD designs.

## 5. Conclusion

Group dose-response challenge experiments are routinely used to assess safe, effective, or hazardous doses of a substance. However, the possibility for transmission can lead to incorrect estimation of the dose-response relationship. Here, we have utilised optimal experimental design theory to demonstrate how to pre-determine a suitable experimental design in order to target different aspects of the dose-response relationship, or transmission dynamics.

Within the experimental design framework, the Mean Absolute Percentage Error (MAPE) appears to be a suitable alternative to the Expected Kullback-Leibler Divergence (EKLD) as a choice of utility, in some situations, when evaluating optimal designs for the purpose of parameter inference. The designs evaluated under the EKLD and MAPE have quite distinct features, most notably in the number of preferred groups, which appears to correlate with better estimation of targeted parameters under the MAPE designs. It appears as though by allocating all subjects to only two groups, we obtain more certain estimates of the dose-response relationship at those doses, by reducing the uncertainty within each group. However, this

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often comes at the cost of reduced information about other parameters that were not directly being targeted – thus careful consideration needs to be given at the design stage to the dynamics that are of interest when using the MAPE utility.

With regards to the MAPE designs, if there is interest in the transmission rate as well as the dose-response relationship, then resources are directly allocated to estimating the transmission rate. However, the amount of resources that should be used to estimate the transmission rate parameter is governed by the level of prior information that is available for the parameters. If we have informative prior distributions for the dose-response parameters, then all resources are allocated to estimating the transmission rate parameter (i.e., lower doses and late observation times). Inherently, some information will still be available on the dose-response relationship from this design, however the quantity of information that can be obtained about the transmission rate parameter is greater than that regarding the dose-response relationship. Conversely, if we have less-informative prior distributions on each parameter, then the resources are allocated between the two regions – targeting the transmission rate parameter (low dose and late observation time), or the dose-response parameters (higher dose and an earlier observation time), with a trade-off between the information gain for each aspect of the underlying dynamic.

Here, we have used state-of-the-art experimental design methodology to provide a tool to design group dose-response challenge experiments in the presence of transmission. Code to implement this method in `MATLAB` is available as Supplementary Material.

**Author Contributions**

DJP produced code and results, and drafted the manuscript. NGB, JVR and JT conceived the study, and helped draft the manuscript. All authors gave final approval for publication.

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## Acknowledgements

# 6. Appendix

*6.1. Algorithms*

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**Algorithm 1** ABC Algorithm: Fixed tolerance

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**Input:** Observed data $\boldsymbol{x}$, simulated data $\boldsymbol{y} = (\boldsymbol{y}^1, \dots, \boldsymbol{y}^N)$, corresponding parameter

values $\boldsymbol{\theta}^i, i = 1, \dots, N$, and tolerance $\epsilon$.

1: Evaluate discrepancies $\rho^i = \rho(\boldsymbol{y}, \boldsymbol{x}^i)$, creating particles $\{\boldsymbol{\theta}^i, \rho^i\}$ for $i = 1, \dots, N$.

2: Using the posterior sample of parameters $\boldsymbol{\theta}^i$ such that $\rho^i < \epsilon$, evaluate utility.

**Output:** Utility for current design, having observed $\boldsymbol{x}$, $U(d, \boldsymbol{x})$.

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**Algorithm 2** ABCdE Algorithm
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1: Choose grid over the parameter space for the discrete estimate of the utility, number of simulations $N_{pre}$, and tolerance $\epsilon$.

2: Sample $N_{pre}$ parameters $\boldsymbol{\theta}$ from $p(\boldsymbol{\theta})$.

3: For each of the $N_{pre}$ parameters, and under every design $d$ in the design space $\mathcal{D}$, simulate process and store $X_{N_{pre} \times |\mathcal{D}|}(\boldsymbol{\theta}, d)$.

4: **for** $i = 1$ to $|\mathcal{D}|$ **do**

5:     Consider the unique rows of data $Y(\boldsymbol{\theta}, d^i) = \text{unique}(X(\boldsymbol{\theta}, d^i))$.

   *Note: We let $K^i$ be the number of such unique data, and $n_{k^i}$ be the number of repetitions of the $k^{i^{th}}$ unique data, for $k^i = 1, \dots, K^i$.*

6:     **for** $k^i = 1$ to $K^i$ **do**

7:         Pass 'observed data' $\boldsymbol{y}^{k^i} = [Y(\boldsymbol{\theta}, d^i)]_{k^i}$, 'simulated data' $X(\boldsymbol{\theta}, d^i)$, $N_{pre}$ sampled parameters, and tolerance $\epsilon$ to Algorithm 1, and return contribution $U(\boldsymbol{y}^{k^i}, d^i)$ to the expected utility, for $k^{i^{th}}$ unique datum ('observed data') and $i^{th}$ design.

8:     **end for**

9:     Store $u(d^i) = \frac{1}{N} \sum_{k^i} n_{k^i} U(\boldsymbol{y}^{k^i}, d^i)$; the average utility over all parameters and data for design $d^i$.

10: **end for**

**Output:** The optimal design $d^* = \underset{d \in \mathcal{D}}{\text{argmax}}(u(d))$.
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**Algorithm 3** INSH Algorithm

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1: Choose an initial set of designs. $D$ (e.g., a coarse grid of design points across the design space, or randomly sample).

2: Specify the number of generations (iterations) of the algorithm $W$, a perturbation function $f(d \mid d')$, and the acceptance criteria.

3: **for** $w = 1$ to $W$ **do**

4:     For each design $d^i \in D$, sample parameters $\boldsymbol{\theta} \sim p(\boldsymbol{\theta})$, and simulate data $\boldsymbol{x}^i$ from the model.

5:     Evaluate utility $u(d^i)$, for each design $d^i \in D$.

6:     Set $D'$ to be the designs which satisfy the acceptance criteria, and the current optimal design $d^*$ (even if it occurred in a previous generation).

7:     Sample $m$ designs from $f(d \mid d')$, for each $d' \in D'$. Set $D$ to be these newly sampled designs.

8: **end for**

**Output:** Set of designs $d$, and corresponding utilities $u(d)$ (and hence, the optimal design $d^* = \underset{d \in \mathcal{D}}{\operatorname{argmax}}(u(d))$).

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456   *6.2. Derivation of $P_{inf}$ Approximation.*

Consider the confluent hypergeometric function,

$$_1F_1(\alpha, \alpha + \delta, -D) = \int_0^1 e^{-Dt} \frac{\Gamma(\alpha + \delta)}{\Gamma(\alpha)\Gamma(\delta)} t^{\alpha-1}(1-t)^{\delta-1}dt.$$

Let $t = y/\delta$, and hence $dt = dy/\delta$. Then we have,

$$_1F_1(\alpha, \alpha + \delta, -D) = \int_0^\delta e^{-yD/\delta} \frac{\Gamma(\alpha + \delta)}{\Gamma(\alpha)\Gamma(\delta)} \left(\frac{y}{\delta}\right)^{\alpha-1} \left(1 - \left(\frac{y}{\delta}\right)\right)^{\delta-1} \frac{dy}{\delta}.$$

For large $\delta$, $\left(1 - \left(\frac{y}{\delta}\right)\right)^{\delta-1}$ is approximately equal to $e^{-y}$. Hence we have,

$$_1F_1(\alpha, \alpha + \delta, -D) \approx \int_0^\delta e^{-yD/\delta} \left[\frac{\Gamma(\alpha + \delta)}{\delta^\alpha \Gamma(\delta)}\right] \left(\frac{y^{\alpha-1}}{\Gamma(\alpha)}\right) e^{-y}dy.$$

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Employing Stirling's approximation to the expression inside the square brackets, we get,

$$\frac{\Gamma(\alpha + \delta)}{\delta^\alpha \Gamma(\delta)} \approx \frac{\sqrt{2\pi}(\alpha + \delta)^{\alpha + \delta - 1/2} e^{-\alpha - \delta}}{\sqrt{2\pi}(\delta)^{\delta - 1/2} e^{-\delta}} \times \frac{1}{\delta^\alpha}$$

$$= \frac{(\alpha + \delta)^{\alpha + \delta - 1/2} e^{-\alpha}}{(\delta)^{\alpha + \delta - 1/2}}$$

$$= e^{-\alpha} \left(1 + \frac{\alpha}{\delta}\right)^{\alpha + \delta - 1/2}$$

$$= 1,$$

since $\left(1 + \frac{\alpha}{\delta}\right)^{\alpha + \delta - 1/2}$ is approximately equal to $e^\alpha$ for large $\delta$, and small $\alpha$ relative to $\delta$.

Note, Stirling's Approximation for the gamma function is: $\Gamma(z) = \sqrt{(2\pi/z)}(z/e)^z(1 + \mathcal{O}(1/z))$. The error of order $1/z$ is ignored since we consider large $\beta$.

Hence, we have,

$$_1F_1(\alpha, \alpha + \delta, -D) \approx \int_0^\delta e^{-yD/\delta} \left(\frac{y^{\alpha - 1}}{\Gamma(\alpha)}\right) e^{-y} dy$$

$$= \int_0^\delta e^{-y(1 + D/\delta)} \left(\frac{y^{\alpha - 1}}{\Gamma(\alpha)}\right) dy.$$

Let $u = y\left(1 + \frac{D}{\delta}\right)$, and hence $dy = \left(1 + \frac{D}{\delta}\right)^{-1} du$. Then, we have,

$$_1F_1(\alpha, \alpha + \delta, -D) \approx \int_0^{\delta + D} \left(\frac{u}{\left(1 + \frac{D}{\delta}\right)}\right)^{\alpha - 1} \frac{e^{-u}}{\Gamma(\alpha)} \frac{du}{\left(1 + \frac{D}{\delta}\right)}$$

$$= \left(1 + \frac{D}{\delta}\right)^{-\alpha} \int_0^{\delta + D} \frac{e^{-u} u^{\alpha - 1}}{\Gamma(\alpha)} du.$$

Since $\frac{e^{-u} u^{\alpha - 1}}{\Gamma(\alpha)}$ is the pdf for a random variable with a Gamma($\alpha$,1) distribution, and for large $\delta$,

$$\int_0^{\delta + D} \frac{e^{-u} u^{\alpha - 1}}{\Gamma(\alpha)} du \approx \int_0^\infty \frac{e^{-u} u^{\alpha - 1}}{\Gamma(\alpha)} du = 1,$$

we get that,

$$_1F_1(\alpha, \alpha + \delta, -D) \approx \left(1 + \frac{D}{\delta}\right)^{-\alpha}.$$

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<sub>461</sub> Hence, given dose $D$, and model parameters $\alpha$ and $\delta$, we can write the probability
<sub>462</sub> of infection as,

$$P_{\text{inf}}(D; \alpha, \delta) \approx 1 - \left(1 + \frac{D}{\delta}\right)^{-\alpha}. \tag{7}$$

<sub>463</sub> *6.3. Results: INSH Algorithm*

<sub>464</sub> Figures 9 and 10 shows the progression of the INSH algorithm towards regions
<sub>465</sub> of the design space of high-utility, for each of the four scenarios for both the EKLD
<sub>466</sub> and (negative) MAPE.

(a) Scenario 1, Target ($ID_{50}$, SHH)

(b) Scenario 2, Target ($ID_{50}$, SHH)

(c) Scenario 1, Target ($ID_{50}$, SHH, $\beta$)

(d) Scenario 2, Target ($ID_{50}$, SHH, $\beta$)

(e) Scenario 1, Target ($\beta$)

(f) Scenario 2, Target ($\beta$)

Figure 9: Estimated utility (EKLD) of designs considered at each wave of the INSH algorithm, for Scenarios 1 and 2, when targeting each of ($ID_{50}$,SHH),($ID_{50}$,SHH,$\beta$), and $\beta$, respectively.

(a) Scenario 1, Target ($ID_{50}$, SHH)

(b) Scenario 2, Target ($ID_{50}$, SHH)

(c) Scenario 1, Target ($ID_{50}$, SHH, $\beta$)

(d) Scenario 2, Target ($ID_{50}$, SHH, $\beta$)

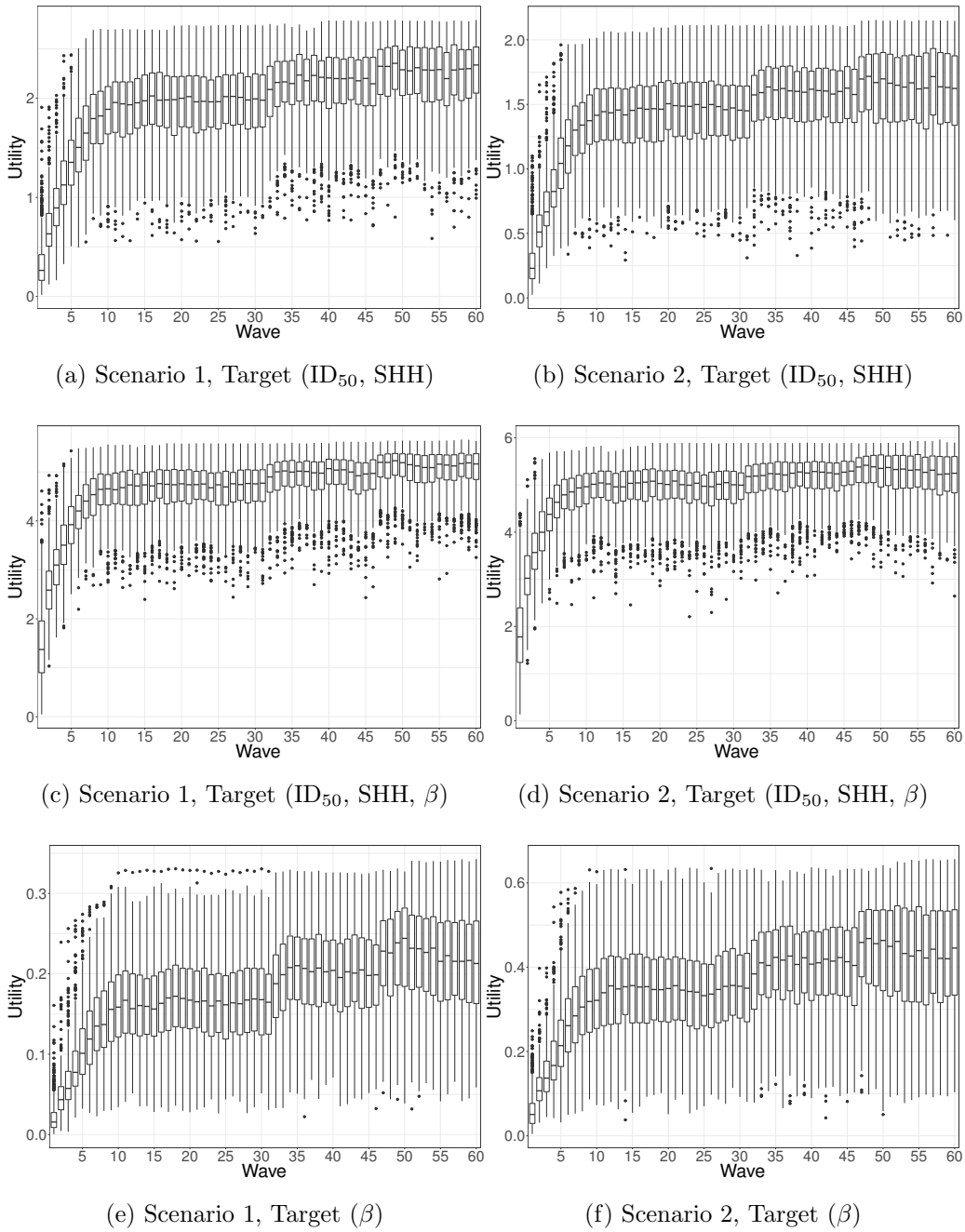(e) Scenario 1, Target ($\beta$)

(f) Scenario 2, Target ($\beta$)
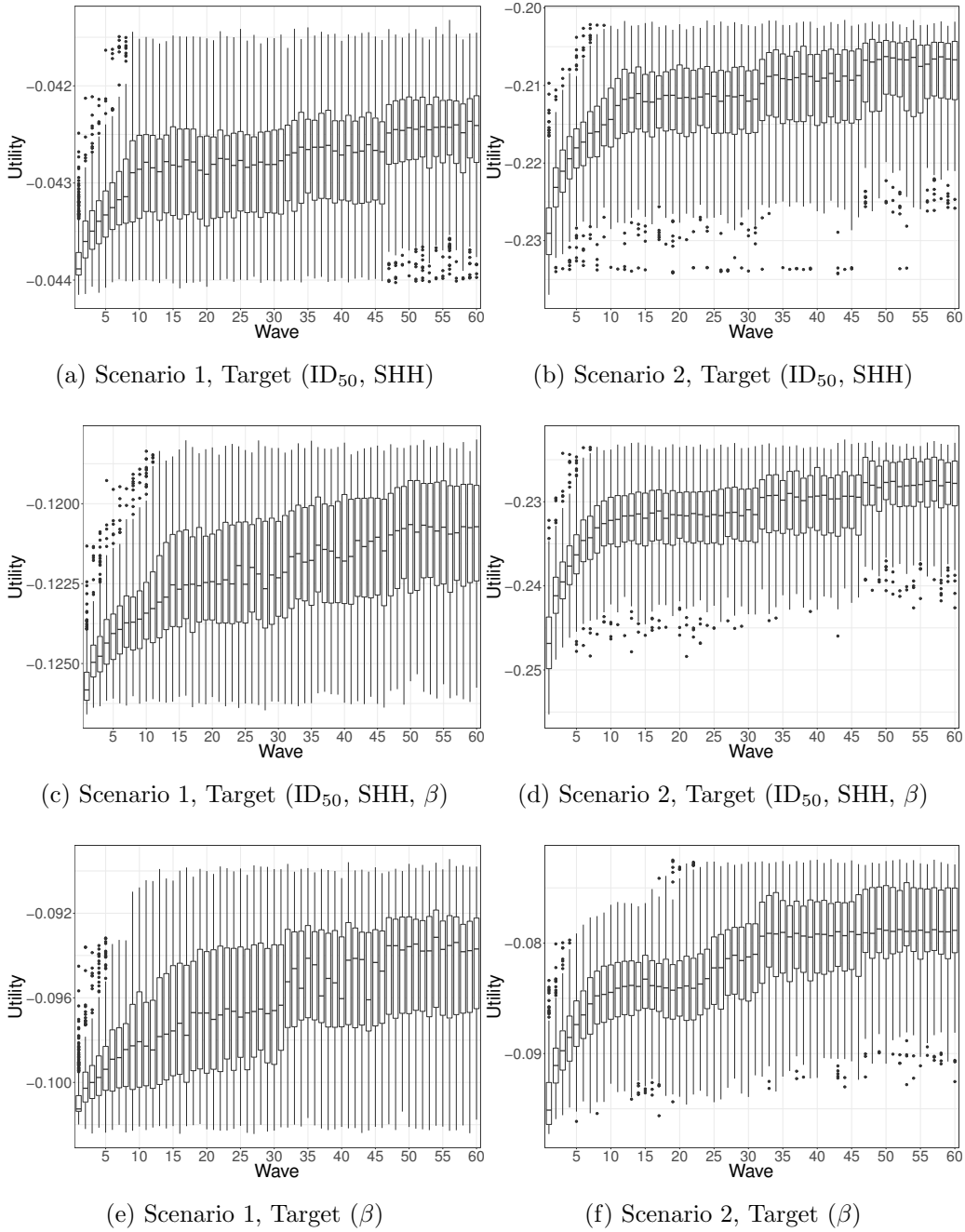
Figure 10: Estimated utility (MAPE) of designs considered at each wave of the INSH algorithm, for Scenarios 1 and 2, when targeting each of ($ID_{50}$,SHH), ($ID_{50}$,SHH,$\beta$), and $\beta$, respectively.

467    Figures 11 and 12 show the proportion of the total designs considered that are

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made up of each of $G = 2, 3, 4, 5$ groups, across each wave of the INSH algorithm.

(a) Scenario 1, Target ($ID_{50}$, SHH)

(b) Scenario 2, Target ($ID_{50}$, SHH)

(c) Scenario 1, Target ($ID_{50}$, SHH, $\beta$)

(d) Scenario 2, Target ($ID_{50}$, SHH, $\beta$)

(e) Scenario 1, Target ($\beta$)

(f) Scenario 2, Target ($\beta$)

Figure 11: Proportion of the designs being considered at each wave of the INSH algorithm (EKLD), coloured by how many groups in each design, for Scenarios 1 and 2, when targeting each of ($ID_{50}$,SHH), ($ID_{50}$,SHH,$\beta$), and $\beta$, respectively.
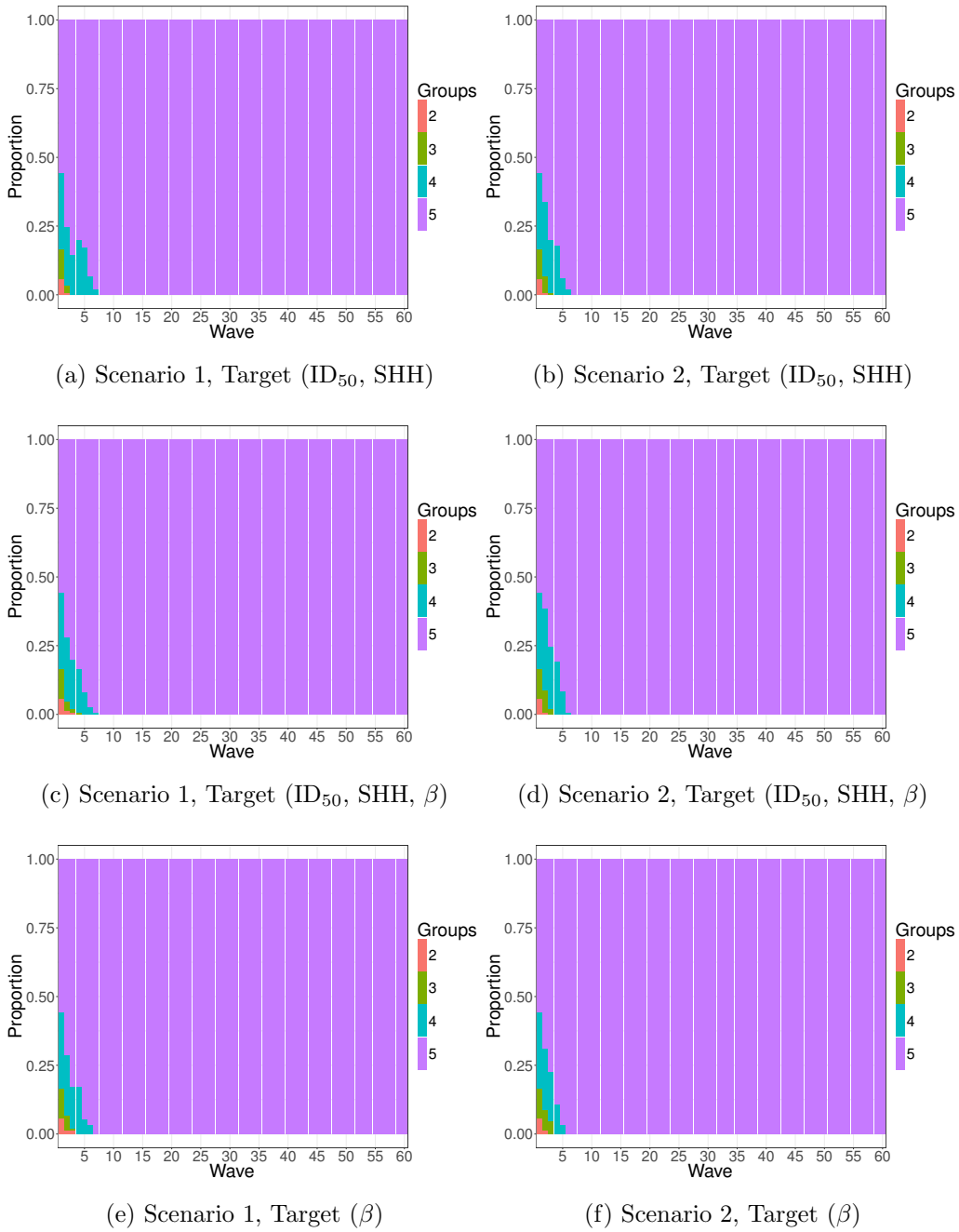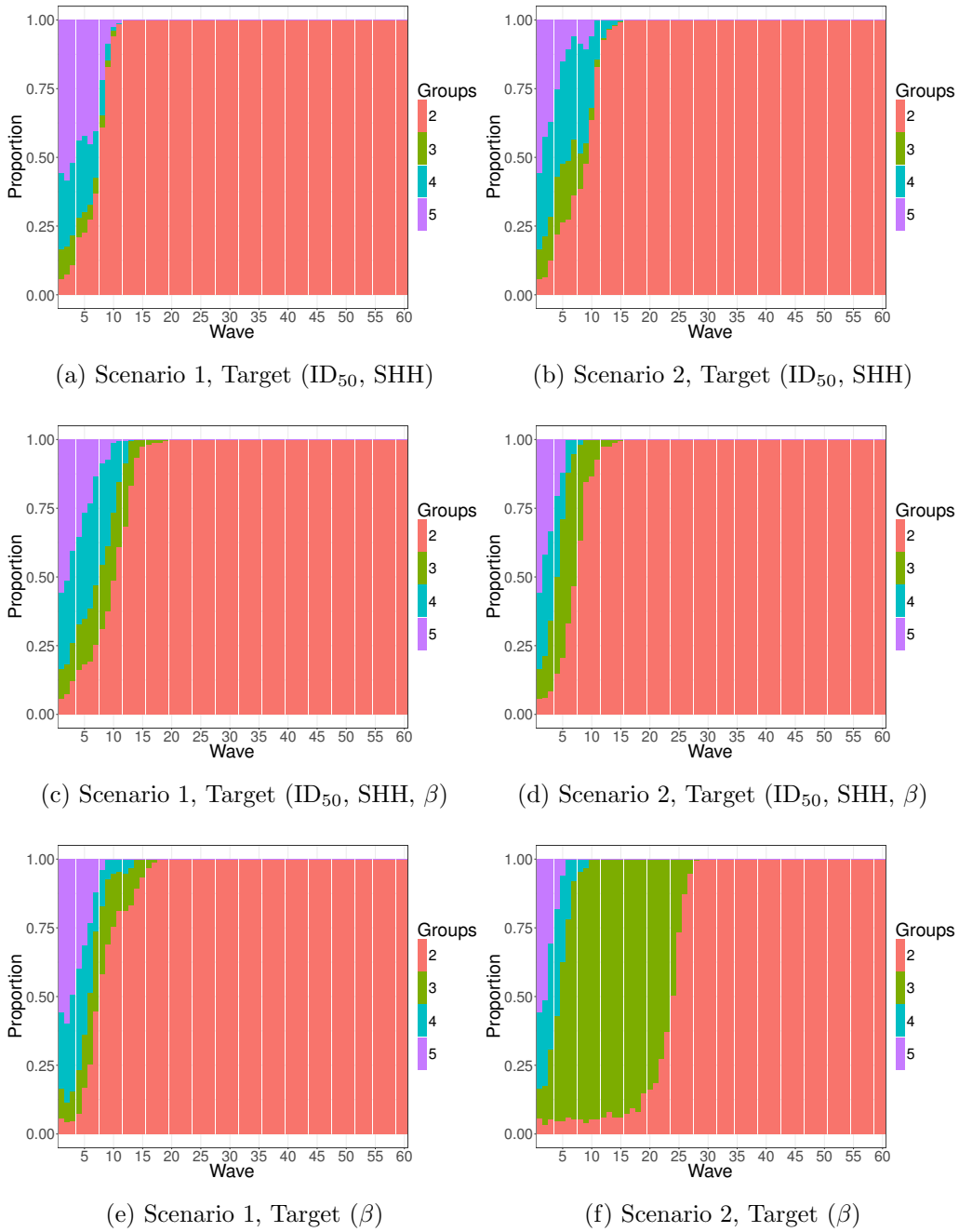
Figure 12: Proportion of the designs being considered at each wave of the INSH algorithm (MAPE), coloured by how many groups in each design, for Scenarios 1 and 2, when targeting each of $(ID_{50}, SHH)$, $(ID_{50}, SHH, \beta)$, and $\beta$, respectively.

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# Supplementary Material for Designing group dose-response studies in the presence of transmission

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## 1. Supplementary Results: Finer grid on dose-allocation

These supplementary results mirror those presented in the manuscript, however, here we consider both prior distributions placed on the parameters $\alpha$ and $\beta$ directly, and a finer grid across the dose-allocation, in order to demonstrate the results that we can obtain should we be able to feasibly derive doses to this precision.

### 1.1. Prior Distributions

In the following examples, we consider two scenarios: 1) where we have a reasonably informative prior distribution, and 2) where we have a relatively uninformative prior distribution. Table S1 contains the choice of prior distribution for each parameter, in the two scenarios.

Table S1: Choice of prior distributions for dose-response model parameters, $(\alpha, \delta)$ and transmission parameter $\beta$.

| Scenario | $\alpha$ | $\delta$ | $\beta$ |
|:---:|:---:|:---:|:---:|
| | | Parameter | |
| 1 | $U(0.15, 0.25)$ | $\log\text{-}N(4.825, 0.25)$ | $\log\text{-}N(0.7, 0.25)$ |
| 2 | $U(0.10, 0.70)$ | $U(75, 250)$ | $U(1, 3)$ |

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Figures S1a and S1b demonstrate the resulting dose-response curves under the specified prior distributions for $(\alpha, \delta)$. The viable curves are demonstrated using the end points of the prior distribution for uniformly distributed parameters, and the $(0.025, 0.975)$-quantiles of the prior distribution otherwise.
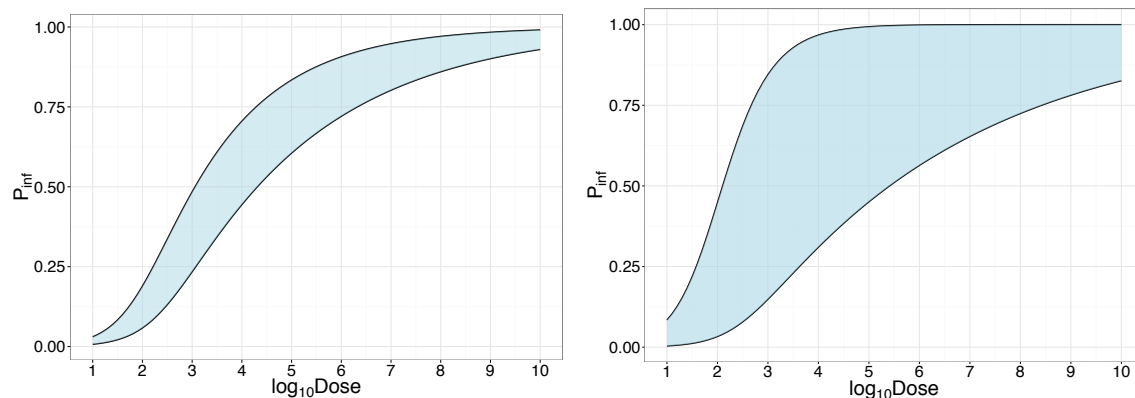


(a) Dose-response relationship under informative prior distributions.

(b) Dose-response relationship under uninformative prior distributions.

Figure S1: The shaded region demonstrates the prior-predictive dose-response relationship under (a) informative, or (b) uninformative prior distributions.

*1.2. Design Space*

Consider a scenario where we are limited by resources – e.g., a fixed number of chickens, doses or maximum time over which we may conduct the experiment. Specifically, assume we are able to dose at most $N = 40$ chickens. We are interested in determining optimal Bayesian experimental designs with respect to the number of groups to allocate the fixed number of subjects to, the dose to allocate to each group, and the time to sample each group. The ranges of these design parameters are presented in Table S2. Note, we are dealing with a social animal, and as such, subjects must be co-housed. That is, we assume that the chickens are allocated amongst at most five groups.

Table S2: Typical values of design parameters considered when determining the optimal experimental designs.

| Design aspect | Typical Values |
|---|---|
| Number of groups $(G)$ | {2,3,4,5} |
| Dose allocation $(A)$ | {0.05,0.10,0.15,...,8.00} $\log_{10}$CFU |
| Observation times $(T)$ | {0.05,0.10,0.15,...,6.00} days |

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We consider only the number of groups $G$, rather than the number of groups and the number of chickens in each group – specifically, we assume that the $N = 40$ chickens are to be divided evenly among two, three, four or five groups (that is, 20, 13, 10 or 8 chickens per group). Note that throughout we refer to the dose in units of $\log_{10}$ colony forming units (CFU), i.e., we refer to a dose of $10^4$ CFU, as a dose of 4. We allow any number of groups to receive the same dose, and each group can have a different observation time – note that each individual within a group has the same dose and observation time.

## 2. Results

In the following, we consider two scenarios: 1) where we have an informative prior distribution on the model parameters, and 2) where we have an uninformative prior distribution. For both scenarios, we consider the optimal designs with respect to both 1) the EKLD, and 2) the MAPE. Furthermore, we also establish the optimal designs when we are interested in either 1) the dose-response parameters only, 2) the transmission rate parameter only, and 3) the dose-response and the transmission rate parameter. That is, in total, we consider 12 different sets of results. We present the optimal designs obtained via the INSH algorithm, in each example, and provide figures demonstrating the regions (with respect to the dose and observation time) that each group should be allocated to – akin to sampling windows considered in pharmacokinetic experiments (e.g., [1], [2], [3]). We describe these regions by taking the top $n$ designs from the INSH algorithm output, and drawing a convex hull around each group (here, $n = 35$).

We demonstrate how well each design performs with regards to inference for all parameters. In particular, for 200 simulated experiments, we evaluate the bias (of the posterior median estimate) and variance of the posterior distributions evaluated under each design for each simulated experiment. The posterior distributions were evaluated using a standard ABC-rejection algorithm with 1,500,000 simulations, and a tolerance of $\epsilon = 0.25 \times G$.

Figures illustrating the convergence of the INSH algorithm – with respect to the number of designs of each group size being considered, and the utility of all designs under consideration at each wave – for each scenario are presented in Appendix 4.1.

### 2.1. Optimal Designs from the INSH Algorithm

The same setup for the INSH algorithm is used in these examples, as those reported in the main results.

Table S3 contains the resulting optimal experimental design for each scenario.

| Scenario | Utility | Target Parameters | G | Optimal Design: A: Dose ($\log_{10}$ CFU); T: Obs. Time (days) |
|---|---|---|---|---|
| 1 | EKLD | $(\alpha, \delta)$ | 5 | $A = (3.50, 3.95, 4.20, 4.25, 4.30)$ <br> $T = (1.30, 1.40, 1.80, 1.55, 1.60)$ |
| 1 | MAPE | $(\alpha, \delta)$ | 5 | $A = (3.60, 4.00, 4.20, 4.30, 4.65)$ <br> $T = (1.35, 1.45, 1.90, 1.45, 1.55)$ |
| 1 | EKLD | $(\alpha, \delta, \beta)$ | 5 | $A = (3.75, 3.90, 4.15, 4.20, 4.25)$ <br> $T = (1.25, 1.35, 1.50, 1.70, 1.65)$ |
| 1 | MAPE | $(\alpha, \delta, \beta)$ | 2 | $A = (2.50, 2.55)$ <br> $T = (4.50, 4.25)$ |
| 1 | EKLD | $(\beta)$ | 5 | $A = (4.00, 4.10, 4.25, 4.30, 4.35)$ <br> $T = (1.35, 1.50, 1.80, 1.60, 1.40)$ |
| 1 | MAPE | $(\beta)$ | 2 | $A = (2.40, 2.45)$ <br> $T = (5.00, 4.90)$ |
| 2 | EKLD | $(\alpha, \delta)$ | 5 | $A = (4.20, 4.45, 4.70, 5.05, 6.55)$ <br> $T = (0.95, 0.95, 1.15, 1.10, 0.90)$ |
| 2 | MAPE | $(\alpha, \delta)$ | 2 | $A = (3.25, 3.40)$ <br> $T = (1.55, 1.75)$ |
| 2 | EKLD | $(\alpha, \delta, \beta)$ | 5 | $A = (4.55, 4.65, 4.75, 5.00, 5.15)$ <br> $T = (1.10, 1.05, 1.00, 0.95, 0.85)$ |
| 2 | MAPE | $(\alpha, \delta, \beta)$ | 5 | $A = (2.20, 2.25, 3.25, 3.40, 3.50)$ <br> $T = (3.05, 3.55, 1.70, 1.90, 1.70)$ |
| 2 | EKLD | $(\beta)$ | 5 | $A = (4.45, 4.70, 4.85, 5.10, 6.25)$ <br> $T = (1.05, 1.15, 1.10, 1.10, 0.85)$ |
| 2 | MAPE | $(\beta)$ | 2 | $A = (1.95, 2.00)$ <br> $T = (5.25, 5.00)$ |

Table S3: Optimal designs corresponding to two different scenarios ((1) informative and (2) uninformative prior distributions), according to two different utility functions (EKLD and MAPE), where the parameters of interest are either just the dose-response parameters $(\alpha, \delta)$, the transmission parameter $(\beta)$, or both the dose-response and transmission rate parameters $(\alpha, \delta, \beta)$.

Figures S2 and S3 show the dose and time combination for each group of the designs (i.e., the coloured groups $1 - G$ represent the $G$ groups in the design). The figures show convex hulls around the "best" 35 designs with respect to the EKLD and MAPE (respectively). The designs have been jittered slightly so that one can identify where more design points for each group are clustered.

(a) Scenario 1, Target $(\alpha, \delta)$

(b) Scenario 2, Target $(\alpha, \delta)$

(c) Scenario 1, Target $(\alpha, \delta, \beta)$

(d) Scenario 2, Target $(\alpha, \delta, \beta)$

(e) Scenario 1, Target $(\beta)$

(f) Scenario 2, Target $(\beta)$

Figure S2: Convex hulls demonstrating the dose-time pairing for each group, for the 35 "best" designs according to the EKLD from the INSH algorithm, for Scenarios 1 and 2, when targeting each of $(\alpha, \delta)$, $(\alpha, \delta, \beta)$, and $(\beta)$.

(a) Scenario 1, Target $(\alpha, \delta)$

(b) Scenario 2, Target $(\alpha, \delta)$

(c) Scenario 1, Target $(\alpha, \delta, \beta)$

(d) Scenario 2, Target $(\alpha, \delta, \beta)$

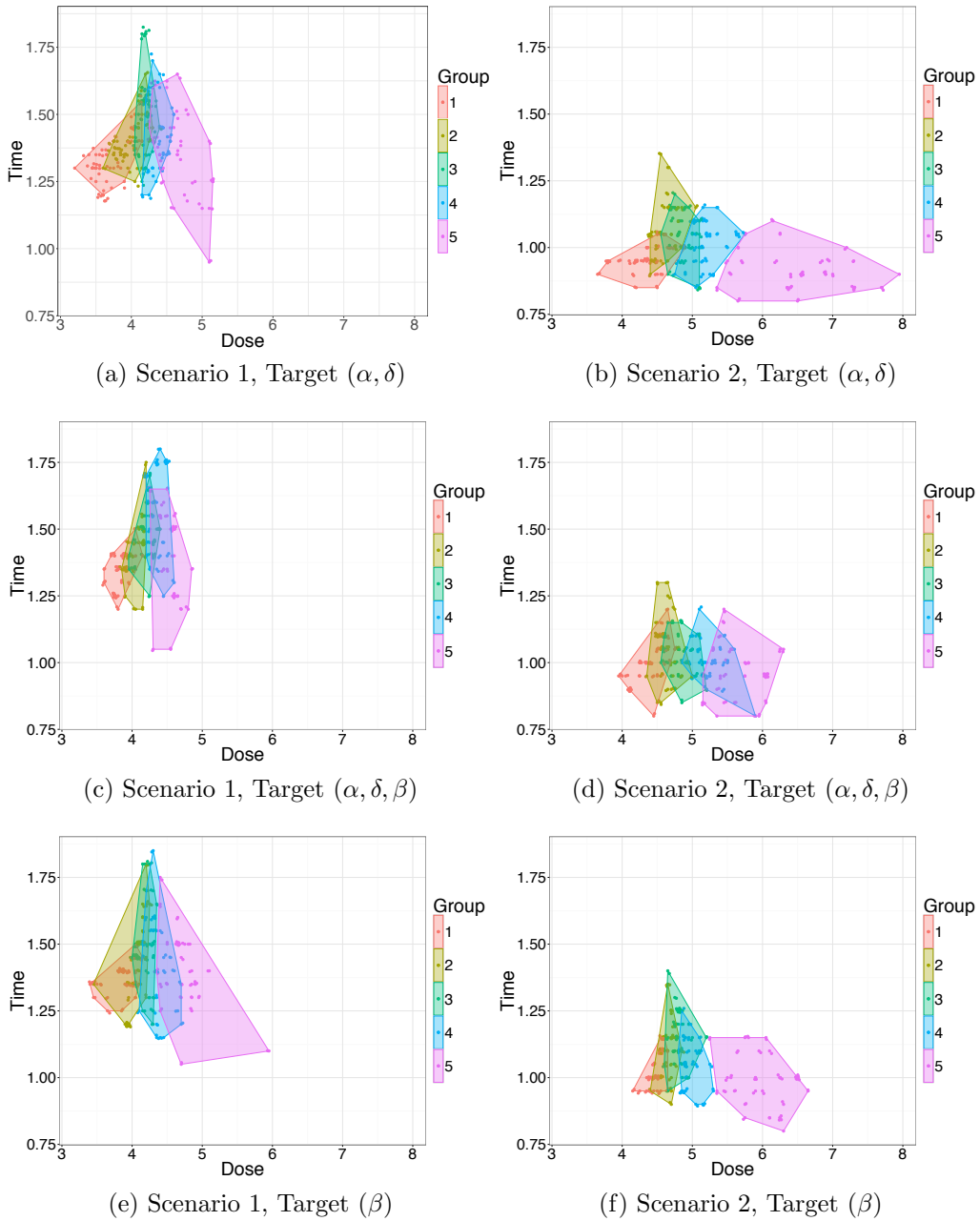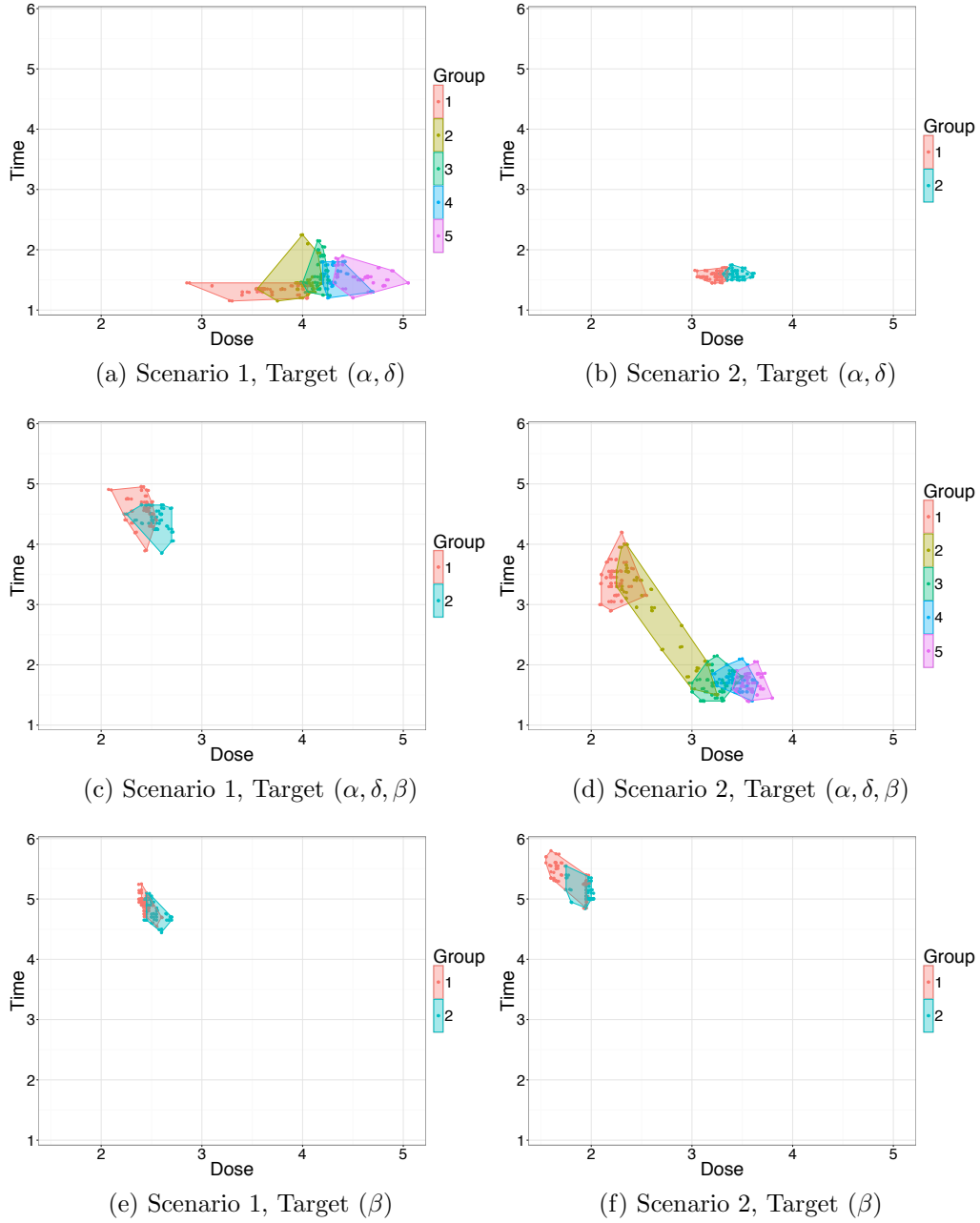(e) Scenario 1, Target $(\beta)$

(f) Scenario 2, Target $(\beta)$

Figure S3: Convex hulls demonstrating the dose-time pairing for each group, for the 35 "best" designs according to the MAPE from the INSH algorithm, for Scenarios 1 and 2, when targeting each of $(\alpha, \delta)$, $(\alpha, \delta, \beta)$, and $(\beta)$.

## 2.2. Performance of Optimal Designs

### 2.2.1. Scenario 1: Informative Prior Distributions

Figures S4 and S5 show the performance of the two optimal designs (i.e., with respect to the EKLD and MAPE), for targeting the dose-response parameters, dose-response and transmission parameters, or the transmission parameter only (i.e., $(\alpha, \delta)$, $(\alpha, \delta, \beta)$, or $(\beta)$), with informative prior distributions. Performance is assessed with respect to the bias in the median of the posterior distribution (i.e., posterior median - known parameter value used to simulate the experiment), and the posterior variance, of 200 simulated experiments.
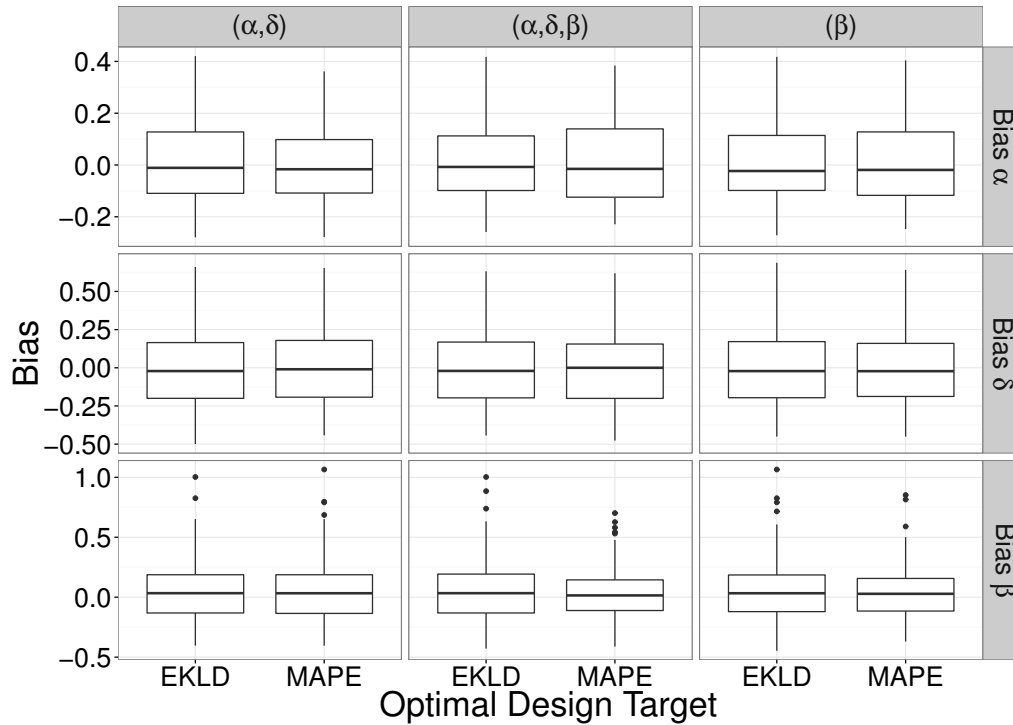


Figure S4: Scenario 1 (informative prior distributions). Boxplots of the posterior distribution median bias in estimates of each of $\alpha$, $\delta$ and $\beta$ (rows), corresponding to 200 simulated experiments, calculated at each of the optimal designs evaluated with respect to the EKLD and MAPE, when targeting each of the dose-response parameters, $(\alpha, \delta)$, transmission rate and dose-response parameters, $(\alpha, \delta, \beta)$, or only the transmission rate parameter $(\beta)$ (columns).
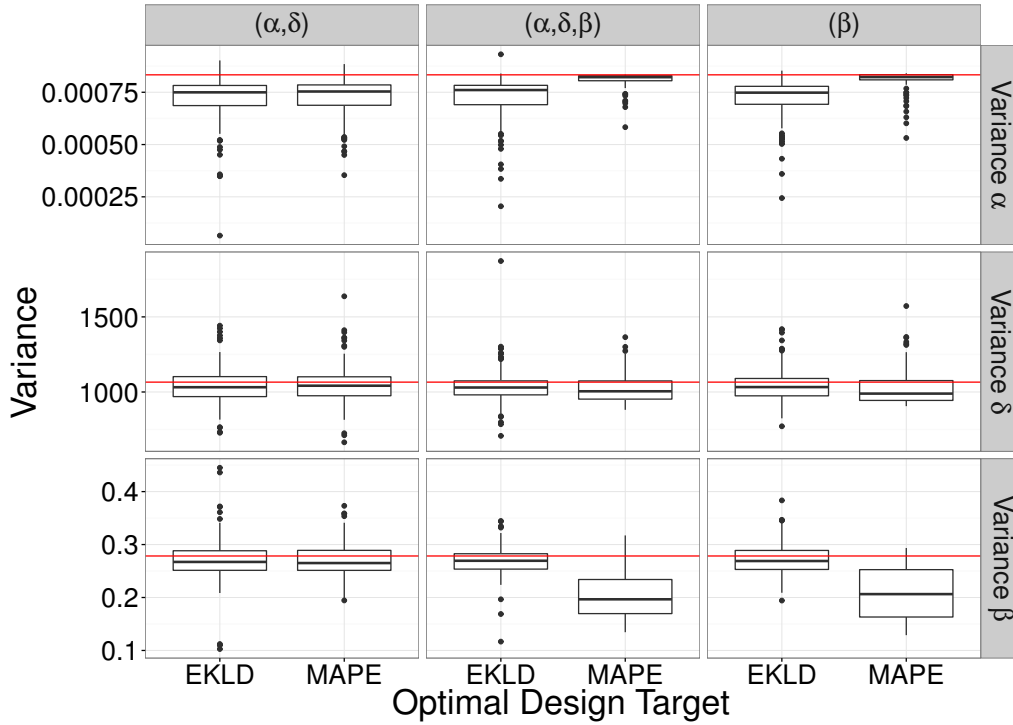
Figure S5: Scenario 1 (informative prior distributions). Boxplots of the variance of the posterior distribution of each of $\alpha$, $\delta$ and $\beta$ (rows), corresponding to 200 simulated experiments, calculated at each of the optimal designs evaluated with respect to the EKLD and MAPE, when targeting each of the dose-response parameters, $(\alpha, \delta)$, transmission rate and dose-response parameters, $(\alpha, \delta, \beta)$, or only the transmission rate parameter $(\beta)$ (columns). The horizontal line in each figure corresponds to the prior variance.

*2.2.2. Scenario 2: Uninformative Prior Distributions*

Figures S6 and S7 show the performance of the two optimal designs (i.e., with respect to the EKLD and MAPE), for targeting the dose-response parameters, dose-response and transmission parameters, or the transmission parameter only (i.e., $(\alpha, \delta)$, $(\alpha, \delta, \beta)$, or $(\beta)$), with uninformative prior distributions. Performance is assessed with respect to the bias in the median of the posterior distribution (i.e., posterior median - known parameter value used to simulate the experiment), and the posterior variance, of 200 simulated experiments.
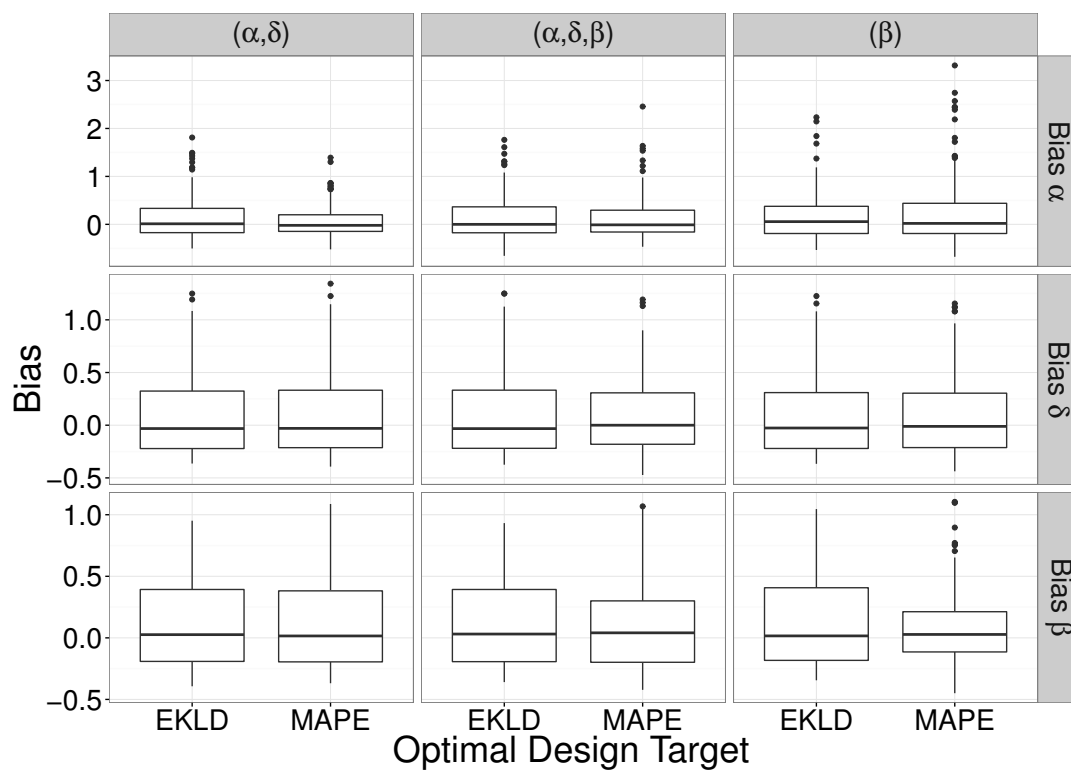
Figure S6: Scenario 2 (uninformative prior distributions). Boxplots of the posterior distribution median bias in estimates of each of $\alpha$, $\delta$ and $\beta$ (rows), corresponding to 200 simulated experiments, calculated at each of the optimal designs evaluated with respect to the EKLD and MAPE, when targeting each of the dose-response parameters, $(\alpha, \delta)$, transmission rate and dose-response parameters, $(\alpha, \delta, \beta)$, or only the transmission rate parameter $(\beta)$ (columns).
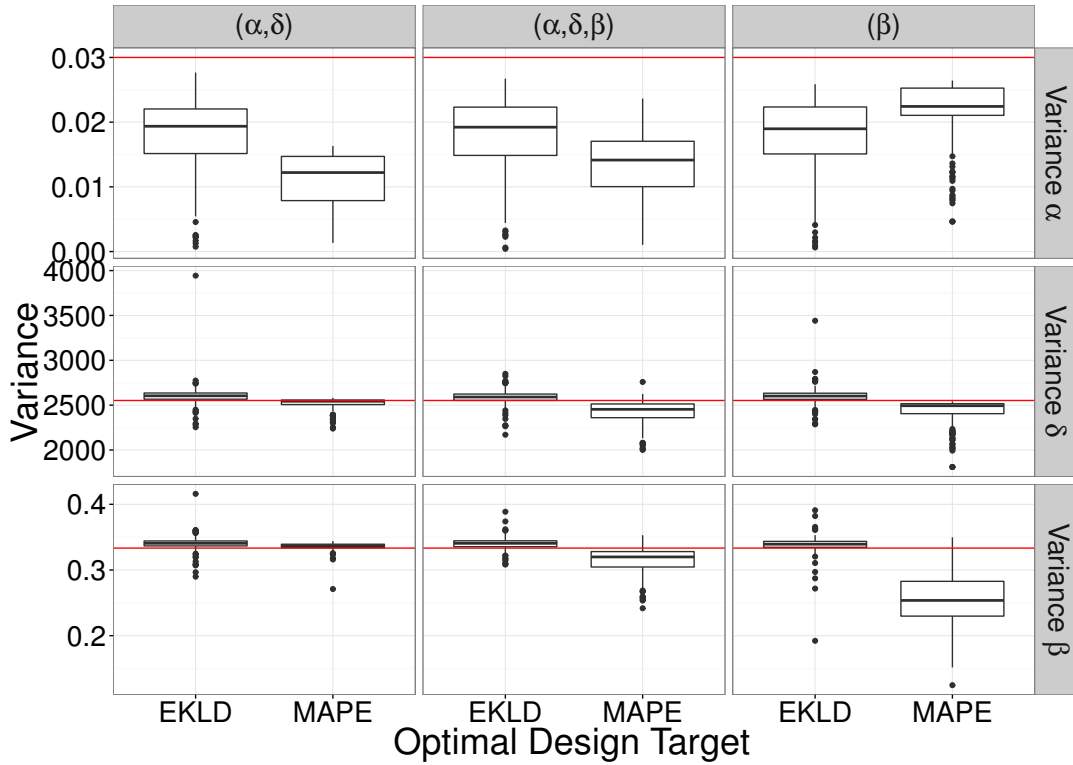
Figure S7: Scenario 2 (uninformative prior distributions). Boxplots of the variance of the posterior distribution of each of $\alpha$, $\delta$ and $\beta$ (rows), corresponding to 200 simulated experiments, calculated at each of the optimal designs evaluated with respect to the EKLD and MAPE, when targeting each of the dose-response parameters, $(\alpha, \delta)$, transmission rate and dose-response parameters, $(\alpha, \delta, \beta)$, or only the transmission rate parameter $(\beta)$ (columns). The horizontal line in each figure corresponds to the prior variance.

## 3. Discussion

The designs that are obtained under the EKLD utility are demonstrated in Figure S2. In each case, the EKLD utility appears to suggest allocating the chickens amongst five groups, with doses that correspond to the prior $\text{ID}_{50}$. Note that the doses under the informative prior distribution are allocated across a narrower range compared to those for the uninformative prior distribution, corresponding to the increased prior belief in the location of the dose-response relationship. In Scenario 1 (informative prior distribution), the optimal observation times for each group are marginally later than those corresponding to Scenario 2 (uninformative prior distribution). This is perhaps due to the increased confidence in the dose-response relationship, meaning that we can confidently wait longer without the potential for all chickens in a group to appear infectious following a single (or few) transmission event(s) (i.e., if the dose corresponds to a very high probability of infection).

The designs obtained under the MAPE utility are interesting. Under an informative prior distribution, targeting only the dose-response parameters results in a similar design to that obtained under the EKLD – five groups with observation times of roughly 1.5 (marginally after the mean time to pass through the latent-period), and doses allocated near to the $ID_{50}$. However, once consideration is also given to the transmission rate parameter, $\beta$, the optimal designs are those that allocate all chickens to only two groups, with lower doses (i.e., less initially exposed chickens), and later observation times (i.e., allow more transmission events to occur).

Under an uninformative prior distribution, the optimal design corresponding to only the dose-response parameters is to allocate all individuals to only two groups at the middle of the doses which could correspond to the $ID_{50}$ (see Figure S1b). However, once again, considering the transmission parameter $\beta$ changes the optimal designs. In particular, consideration of *only* the transmission parameter corresponds to low dose and late observation time – similar to under the informative prior distribution – however, when considering both the dose-response parameters and transmission rate parameter, the optimal design allocates five groups amongst these two distinct regions. Moreover, the second group is allocated between targeting the transmission rate parameter (small dose, late observation time), and the dose-response parameters (higher dose, earlier observation time) – highlighting the obvious trade-off between better estimation of the dose-response parameters, or the transmission parameter.

In each case, it appears as though the designs found using the MAPE utility out-perform the corresponding designs under the EKLD utility. The bias in each parameter estimate is not considerably different under the different designs (EKLD vs. MAPE). As the simulation studies are conducted using parameters sampled from the prior distribution, it is not unexpected that each posterior distribution is centred on the correct value on average, as a random sample from the prior distribution would also achieve this. Where we can observe a difference in the bias between the designs resulting from the two different utilities is when we have uninformative prior distributions. In particular, the MAPE designs appear to have a smaller bias, on average, for the dose-response parameter $\alpha$, when the designs were evaluated to target $(\alpha, \delta)$, or $(\alpha, \delta, \beta)$, and for $\beta$ when the designs were evaluated to target $(\alpha, \delta, \beta)$ or $(\beta)$ (Figure S6).

Figures S5 and S7 demonstrate the reduction in variance for each parameter, having conducted the experiment under each of the different optimal designs, compared to the variances of the prior distribution. Again, it appears as though the MAPE designs outperform the EKLD designs – that is, the posterior distributions have smaller variance, on average. In fact, the posterior variance under the EKLD designs is marginally worse than that of the prior distribution – suggesting that this allocation of resources provides no further information about the system than was achievable under the prior distribution. The only instance that the EKLD designs out-perform

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the MAPE designs appear to be with regards to the dose-response parameter $\alpha$. Under the informative prior distributions, the posterior variance of $\alpha$ is worse under the MAPE design than the corresponding EKLD design, once consideration is also given to the transmission rate parameter $\beta$ (i.e., considering $(\alpha, \delta, \beta)$ or $(\beta)$). Note also that in the case where $(\alpha, \delta, \beta)$ are being considered, the less-improved variance for $\alpha$ is made up by considerably reduced variance for $\beta$, compared to the EKLD design. Under the uninformative prior distributions, the EKLD design only appears to outperform the MAPE design with respect to the posterior variance of $\alpha$ when considering *only* $\beta$ – that is, when not considering $\alpha$ at all. This appears reasonable, as the MAPE design is clearly targeting only those parameters of interest, and thus loses accuracy about $\alpha$ in order to improve accuracy about the other parameters. Conversely, the posterior variances evaluated at the EKLD designs do not appear to change considerably when targeting different parameter combinations. Thus, if only a subset of the model parameters are of interest, it appears as though these can be more accurately targeted using the MAPE utility, rather than the EKLD utility.

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## 4. Appendix

### 4.1. Results: INSH Algorithm

Figures S8 and S9 shows the progression of the INSH algorithm towards regions of the design space of high-utility, for each of the four scenarios for both the EKLD and (negative) MAPE.
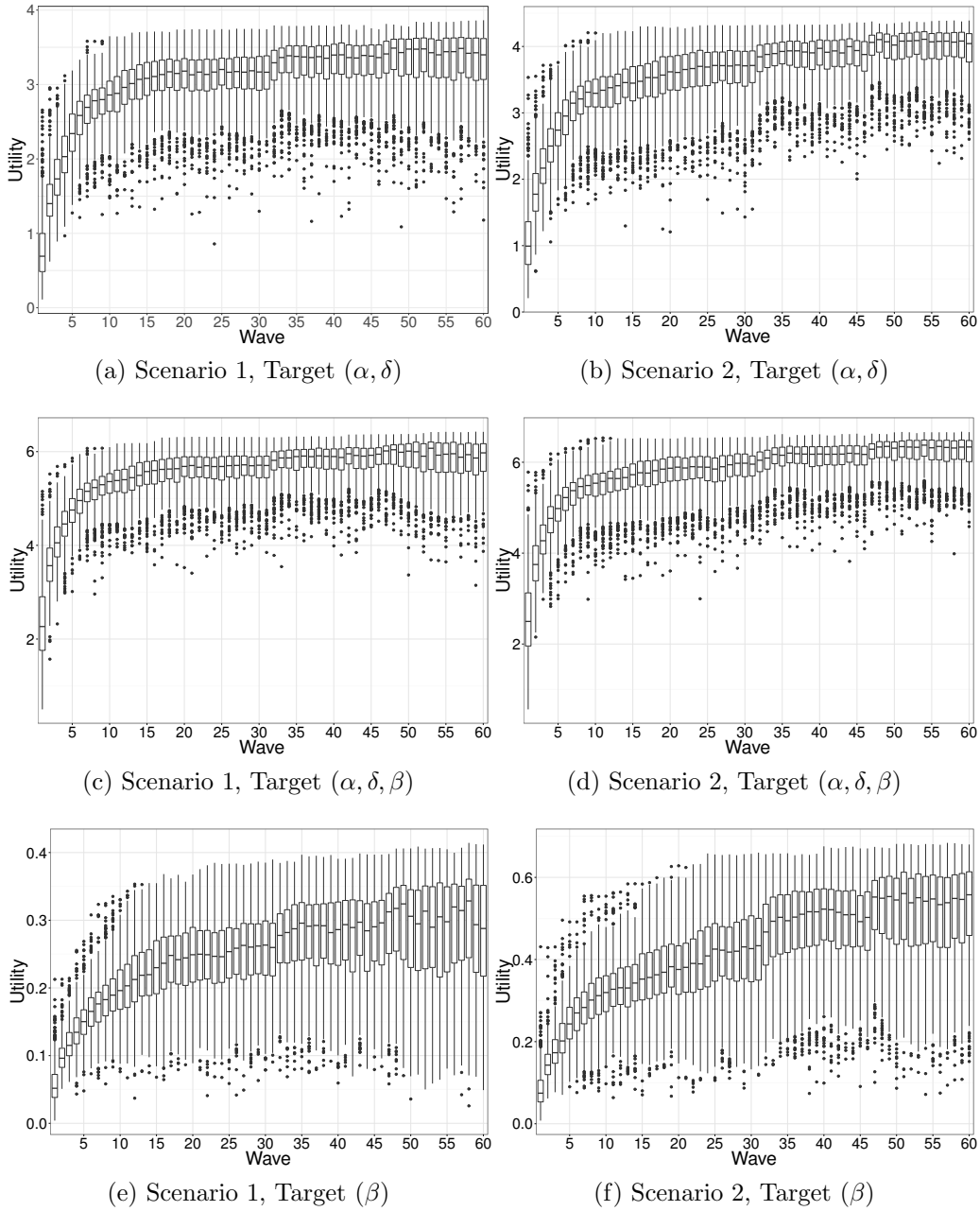
(a) Scenario 1, Target $(\alpha, \delta)$

(b) Scenario 2, Target $(\alpha, \delta)$

(c) Scenario 1, Target $(\alpha, \delta, \beta)$

(d) Scenario 2, Target $(\alpha, \delta, \beta)$

(e) Scenario 1, Target $(\beta)$

(f) Scenario 2, Target $(\beta)$

Figure S8: Estimated utility (EKLD) of designs considered at each wave of the INSH algorithm, for Scenarios 1 and 2, when targeting each of $(\alpha, \delta)$, $(\alpha, \delta, \beta)$, and $\beta$, respectively.

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(a) Scenario 1, Target $(\alpha, \delta)$

(b) Scenario 2, Target $(\alpha, \delta)$

(c) Scenario 1, Target $(\alpha, \delta, \beta)$

(d) Scenario 2, Target $(\alpha, \delta, \beta)$

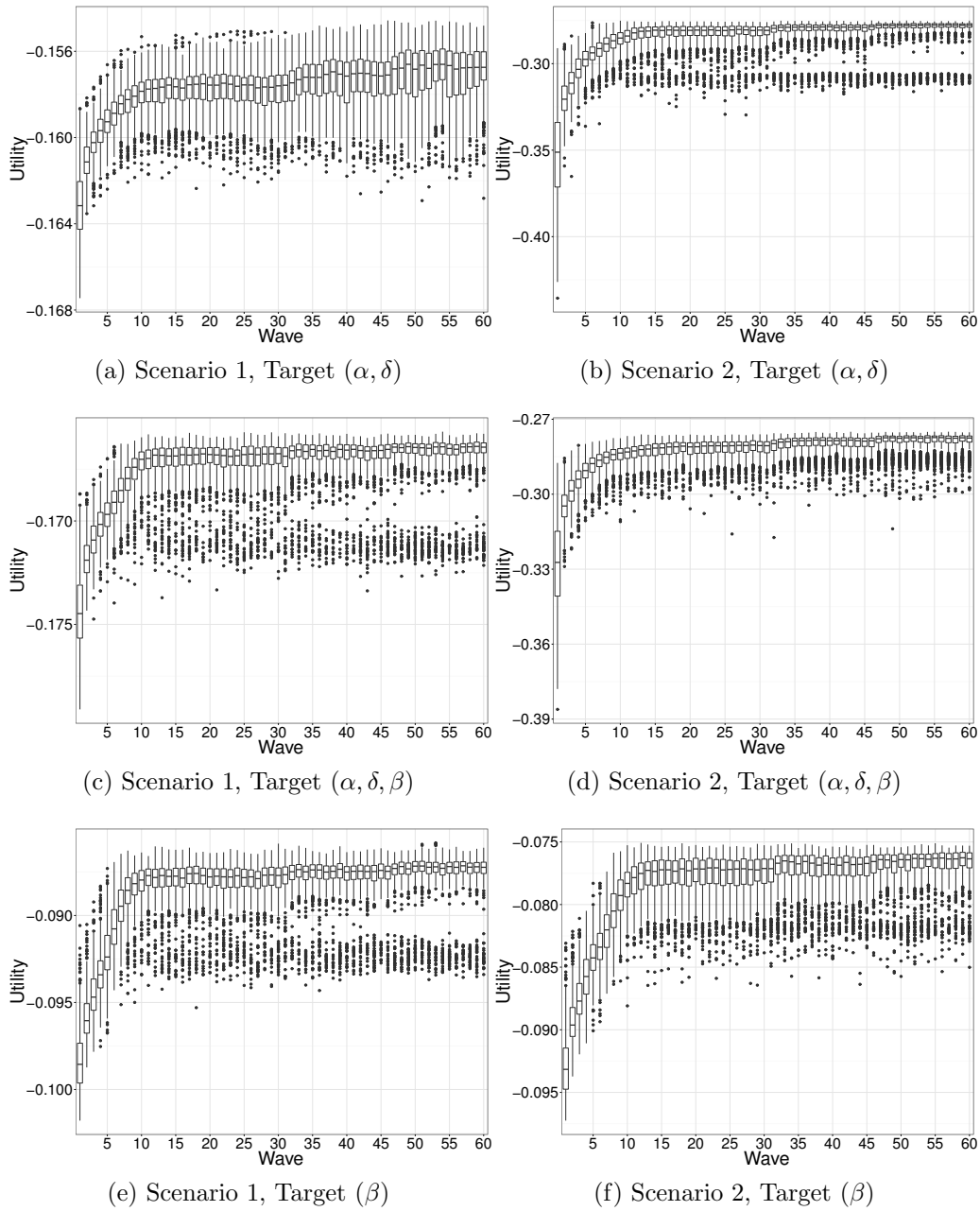(e) Scenario 1, Target $(\beta)$

(f) Scenario 2, Target $(\beta)$

Figure S9: Estimated utility (MAPE) of designs considered at each wave of the INSH algorithm, for Scenarios 1 and 2, when targeting each of $(\alpha, \delta)$, $(\alpha, \delta, \beta)$, and $\beta$, respectively.

Figures S10 and S11 show the proportion of the total designs considered that are made up of each of $G = 2, 3, 4, 5$ groups, across each wave of the INSH algorithm.

(a) Scenario 1, Target $(\alpha, \delta)$

(b) Scenario 2, Target $(\alpha, \delta)$

(c) Scenario 1, Target $(\alpha, \delta, \beta)$

(d) Scenario 2, Target $(\alpha, \delta, \beta)$

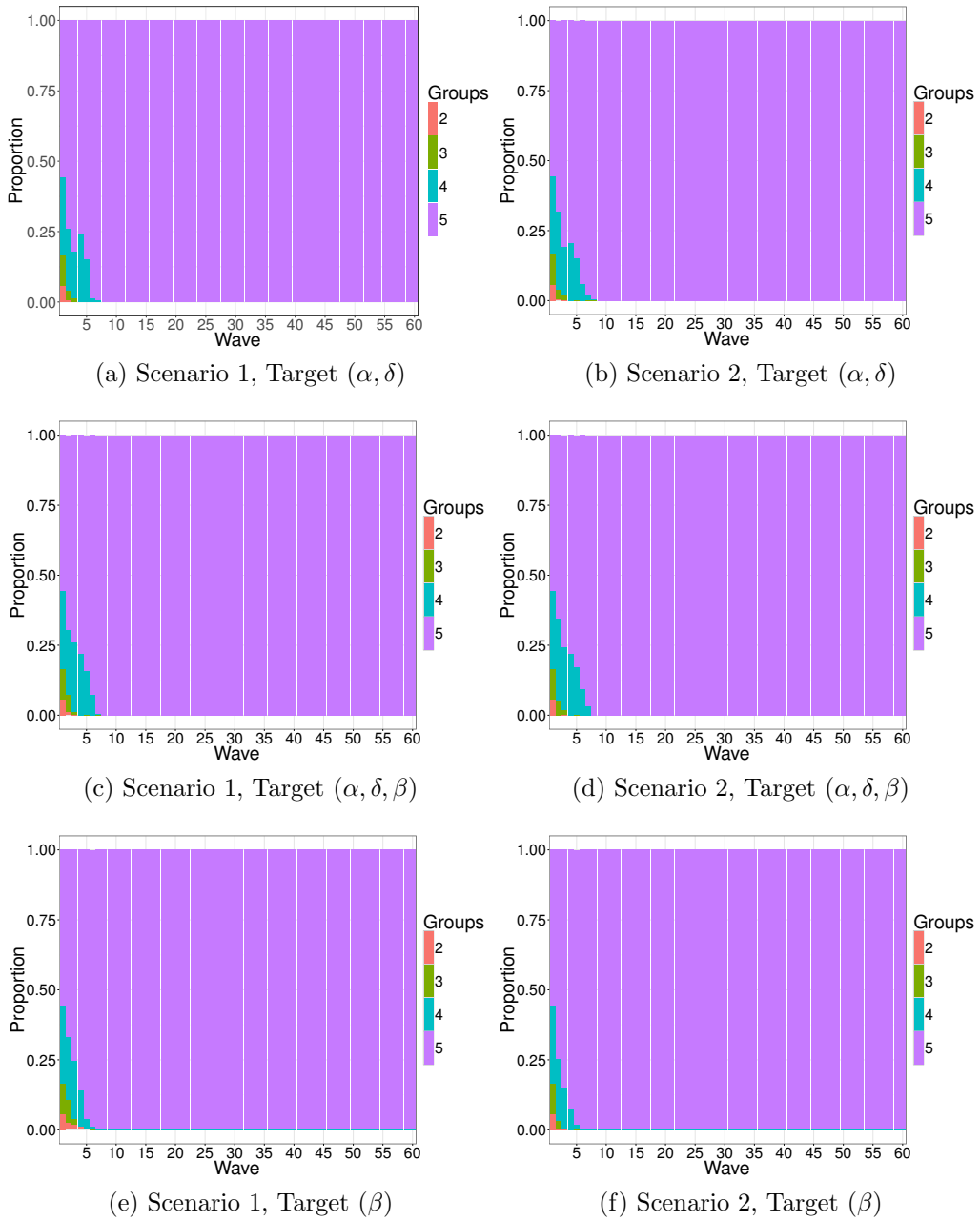(e) Scenario 1, Target $(\beta)$

(f) Scenario 2, Target $(\beta)$

Figure S10: Proportion of the designs being considered at each wave of the INSH algorithm (EKLD), coloured by how many groups in each design, for Scenarios 1 and 2, when targeting each of $(\alpha, \delta)$, $(\alpha, \delta, \beta)$, and $\beta$, respectively.
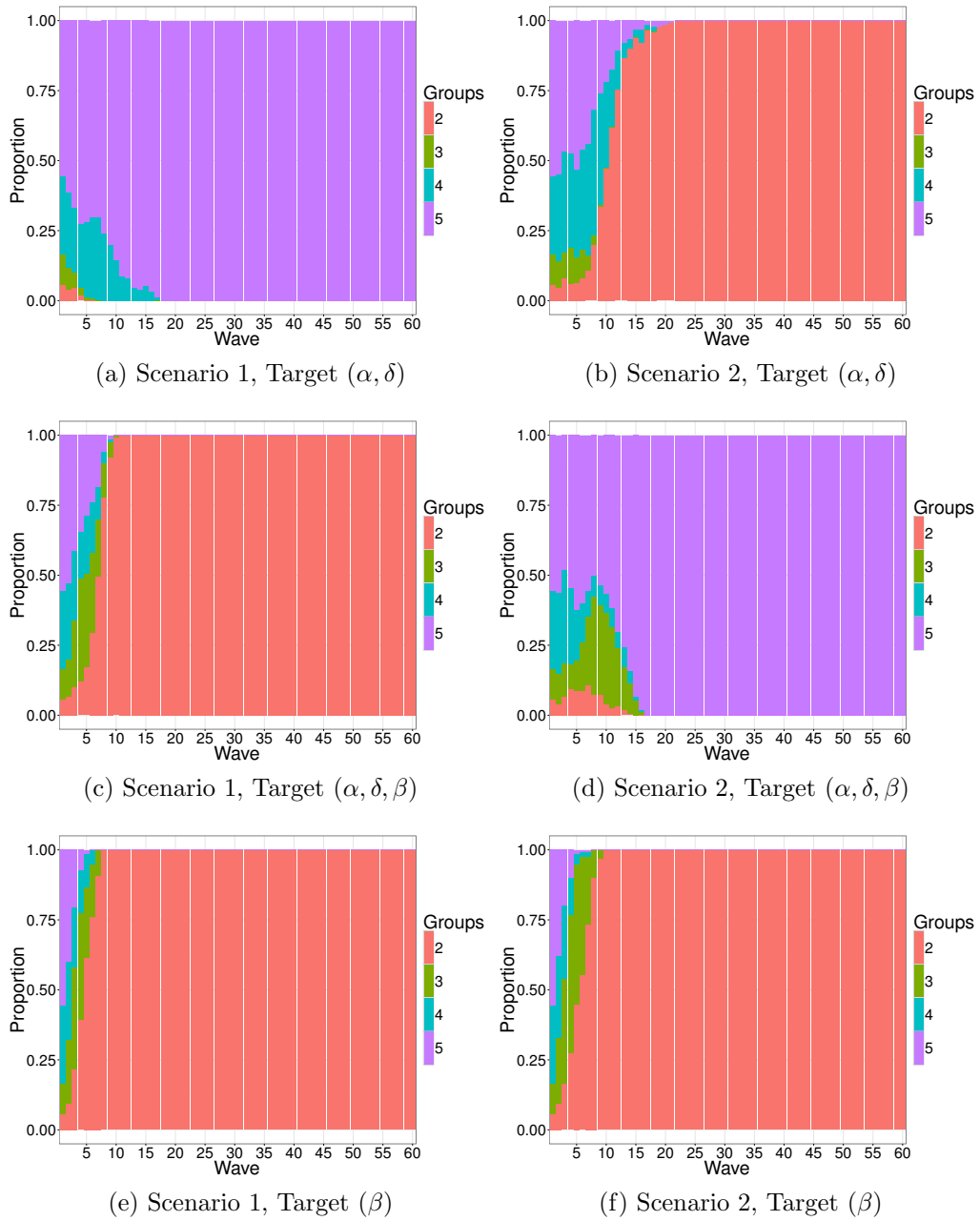
Figure S11: Proportion of the designs being considered at each wave of the INSH algorithm (MAPE), coloured by how many groups in each design, for Scenarios 1 and 2, when targeting each of $(\alpha, \delta)$, $(\alpha, \delta, \beta)$, and $\beta$, respectively.