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Optimal experimental design for predator–prey functional response experiments

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Functional response models are important in understanding predator–prey interactions. The development of functional response methodology has progressed from mechanistic models to more statistically motivated models that can account for variance and the over-dispersion commonly seen in the datasets collected from functional response experiments. However, little information seems to be available for those wishing to prepare optimal parameter estimation designs for functional response experiments. It is worth noting that optimally designed experiments may require smaller sample sizes to achieve the same statistical outcomes as non-optimally designed experiments. In this paper, we develop a model-based approach to optimal experimental design for functional response experiments in the presence of parameter uncertainty (also known as a robust optimal design approach). Further, we develop and compare new utility functions which better focus on the statistical efficiency of the designs; these utilities are generally applicable for robust optimal design in other applications (not just in functional response). The methods are illustrated using a beta-binomial functional response model for two published datasets: an experiment involving the freshwater predator *Notonecta glauca* (an aquatic insect) preying on *Asellus aquaticus* (a small crustacean), and another experiment involving a ladybird beetle (*Propylea quatuordecimpunctata* L.) preying on the black bean aphid (*Aphis fabae* Scopoli). As a by-product, we also derive necessary quantities to perform optimal design for beta-binomial regression models, which may be useful in other applications.

1. Introduction

Models of predator–prey interactions where the rate of predation varies according to the availability of prey are termed functional response models. Typical models deal with single predator, multiple prey scenarios (usually over a finite area), and the aim is to predict the number of prey attacked or consumed as a function of the number of prey available (prey density). Such models are important as they form 'one of the cornerstones of prey–predator interactions' [1], which in turn underpins almost all ecological systems.

The study of functional responses is an active area of research, determining the dynamics and stability of predator–prey systems [2]. Moreover, ecologists often utilize functional response models in order to test several hypotheses. A selection of recent examples include: a study of the predatory behaviour of wolves (*Canis lupus*) against a managed population of moose (*Aleces alces*) in Scandinavia [3]; an examination of the impact of predator and prey size on

the functional response in mosquito–predator systems [4]; a study to better understand predator–prey systems in the ocean via computer simulation of functional response [5]; a study of how the spatial arrangement of prey affects the functional response [6]; and an investigation on the effect of mutual interference on the predation behavior of ladybird beetles [7]. In addition, the importance of functional response in invasion ecology has been recently highlighted [8]. Given these points, an accurate estimation of functional response parameters and outcome is highly desirable for ecologists.

In functional response experiments, the number of prey N used for each observation in the experiment is often controlled. This is biologically feasible as ecologists are usually approximately aware of the predation ability of the selected terrestrial or aquatic species, based on observations on their laboratory cultures and/or preliminary experiments. Fenlon & Faddy [9] give an excellent account of the development of statistical models to account for the variability of data collected from functional response experiments. Some of the seminal work in this area include [1,10]. Fenlon & Faddy [9] themselves compare several models with a variety of equations modelling the mean, and use either binomial or beta-binomial modelling of the variance for each value of N.

However, despite the development of more statistically-driven models and the substantial amount of research activity in the general area of functional response experiments hitherto, there has been little attention given to optimally designing such experiments for the purpose of efficient parameter estimation. To the best of our knowledge, there are no published functional response experiments that express any statistical methodology behind the design points chosen. Our contribution is significant since functional response experiments can by their nature be expensive and/or difficult to conduct [11]; optimally designed experiments are advantageous in that they allow model parameters to be estimated with maximum efficiency and precision, potentially reducing the number of experimental runs necessary. In this paper, we develop an optimal design method for the efficient estimation of model parameters in functional response experiments, using a case study based on an experiment conducted by Hassell *et al.* [12]. The same methods are applied to an additional dataset from [13] to demonstrate the efficacy of our approach.

The optimal design for non-linear models depends on the assumed true parameter value of the model. Such designs are referred to as locally optimal designs. However, there is often uncertainty in the parameter values of the model being designed for, and it is important for experimental designs to be robust, i.e. to perform reasonably well under a variety of parameter configurations that might be plausible. Such designs are referred to as robust designs in the literature [14–16]. The uncertainty in the model parameter can be characterized with a probability, or 'prior', distribution, from which a finite sample of parameter values can be drawn. A common approach to obtaining robust designs is the pseudo-Bayesian method [14], where the utility to be optimized is an average over the utilities for different parameter values. The maximin approach (e.g. [17]) maximizes the lowest utility over the parameter set.

In this paper we also develop some new utilities for robust designs. These novel utilities consider (i) the variability in the utility values, and (ii) maximizing the efficiency (utility value divided by the utility of the locally optimal design for some parameter configuration) rather than the raw utility values, to help mitigate scaling problems for different parameter configurations.

A markedly different approach to obtaining robust designs is suggested by Dror & Steinberg [18]. They first calculate locally optimal designs for each parameter value, and then perform a clustering analysis to obtain a robust design, without needing to optimize over a robust utility. These methods are computationally more efficient, but their clustering analysis is only applicable to continuous design spaces. In this paper, we also develop an analogous approach for integer-valued designs, which is straightforward to implement and provides an additional robust design (generated using a non-utility based method) to compare with.

The case study that we consider involves a beta-binomial regression model, so we derive the necessary quantities required to perform optimal design for such models, which may be useful in other applications.

The paper is outlined as follows. Section 2.1 describes a motivating case study. Utility functions often used for parameter estimation are detailed in §2.2, which includes some new approaches to robust design. The method we use to efficiently maximize a chosen utility function is described in §2.3. The results for the two case studies results are presented in §3. Finally, §4 concludes with a discussion.

2. Material and methods

2.1. Case study

To demonstrate the methods highlighted in this paper, we consider re-designing two published functional response experiments. In this section, we first give some background to functional response and define the design problem. To illustrate the ideas and concepts laid out in this section, we use the first case study (case study I) as a running example. In §3 we present results for case study I and case study II.

In the development of functional response theory, early models focused on mechanistic equations featuring parameters that were readily translated into physical phenomenon. An important and well-known example is Holling's disc equation [19]:

$$n = \frac{rNT}{1 + rT_{\mathrm{h}}N}, \tag{2.1}$$

where n is the number of prey consumed/attacked, N is the available number of prey (in a given area), T is the total duration of the experiment, which is always fixed and predefined such that the interpretation of the model estimated parameters is consistent across the experiment, T_{h} is the handling time per prey attacked and r reflects the *per capita* prey consumption in low prey densities, which determines the initial slope of the functional response curve. When prey are depleted during the experiment, the differential form of the disc equation (see, [13] for more details) is to be used. The parameters of interest are T_{h} and r.

In order to learn about a particular predator–prey interaction, experiments are conducted where varying numbers of prey (the design variable) are made available to a predator, with the number of prey attacked or consumed in a finite period of time recorded as the response variable. We assume that K observations of the predator–prey system are to be obtained and we denote the number of prey to use for observation i as N_i and the vector of prey numbers for all observations as $\boldsymbol{N} = (N_1, \ldots, N_K)$. The corresponding observed number of predated prey for the ith observation is denoted n_i and the full dataset as $\boldsymbol{n} = (n_1, \ldots, n_K)$. An example dataset from a typical functional response experiment is shown in figure 1. The original data were collected by

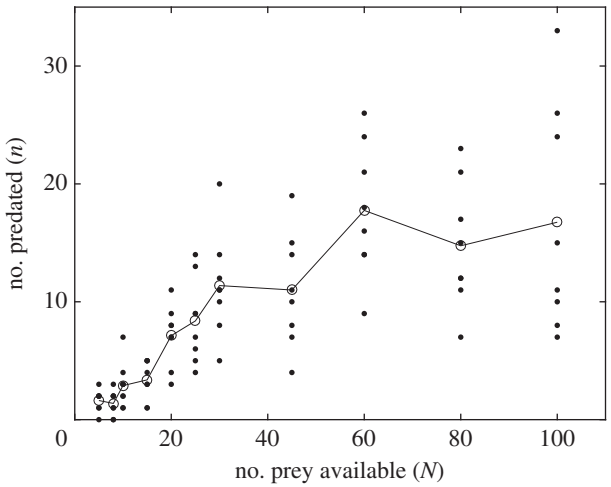

Figure 1. Original data from Hassell *et al.* [12]: individual sample values (•), sample means (○—○—○) for each value of *N*. See Trexler *et al.* [10] and Casas & Hulliger [1] for the raw data values.

Hassell *et al*. [12] from an experiment involving the freshwater predator *Notonecta glauca* (an aquatic insect) preying on *Asellus aquaticus* (a small crustacean resembling a woodlouse).

The Hassell *et al*. [12] experiment features several replicates performed at each value of N (number of *Asellus aquaticus* available). A typical approach then in classical functional response studies is to fit an equation like Holling's disc equation (2.1) through the mean responses n (number of *Asellus aquaticus* predated), and to then use least squares regression to estimate the parameters r and T_h. Crucially though, this approach ignores the obvious variability in the data that occurs at each value of N, as well as the increased variability in the response for higher values of N. This lack of statistical rigour can lead to poor estimation of parameters and inaccurate models, which can have a significant impact on the predictive reliability of models derived in such a manner.

Indeed, it is worth noting that while models with mechanistic parameters are more readily interpretable from a biological perspective, this does not necessarily make them more valid. For example, the assumptions of Holling's disc equation are often violated in practice, as functional response experiments are usually run over long periods of time (e.g. 24 h); this means that digestion should be considered along with the handling time [20,21]. Therefore, even mechanistic parameters (especially the handling time) may not have a suitable biological interpretation in the majority of functional response experiments, and a stochastic model may be more suitable.

Fenlon & Faddy [9] note that the data from the Hassell *et al*. [12] experiment can be well modelled using a modified Gompertz equation for the mean response:

$$\mathsf{E}[n] = a(e^{-b\exp(-cN)} - e^{-b}), \tag{2.2}$$

where n is the number of prey consumed in a single experiment and (a, b, c) are model parameters. Fenlon & Faddy [9] also capture the variability in the data with a beta-binomial model. The probability mass function for a single observation is given by

$$p(n; N, \alpha, \beta) = \binom{N}{n} \frac{B(n+\alpha, N-n+\beta)}{B(\alpha, \beta)}, \tag{2.3}$$

where $B(\cdot, \cdot)$ is the beta function, and α and β are the two parameters of the beta-binomial distribution. The mean for the beta-binomial model is

$$\mathsf{E}[n] = \frac{N\alpha}{\alpha+\beta}. \tag{2.4}$$

This allows the beta-binomial function (2.3) to be linked with the Gompertz equation (2.2) via a convenient reparametrization:

$$\mu = \frac{\alpha}{\alpha+\beta} = \frac{a}{N}(e^{-b\exp(-cN)} - e^{-b}) \quad \text{and}$$
$$\lambda = \frac{1}{\alpha+\beta},$$

where λ is referred to as the overdispersion parameter. One potential source of overdispersion is the between-predator variability resulting from the use of different predators for each experimental observation. We define this model as the beta-binomial-Gompertz (BBG) model.

We acknowledge that in general there could be considerable uncertainty in the model for the mean response (2.2); it would be possible to take this into account but we defer further discussion to §4 and leave it for future research.

For our case study, we consider an experimentalist wishing to re-design the Hassell *et al*. [12] experiment, with accurate estimation of the four parameters $\boldsymbol{\theta} = \{a, b, c, \lambda\}$ of the BBG model as the objective.

The Hassell *et al*. [12] experiment features design points (number of *Asellus aquaticus* available) arranged in a loosely geometric manner: $N = \{5, 8, 10, 15, 20, 25, 30, 45, 60, 80, 100\}$ with eight or nine replicates at each point. A more recent example from Weterings *et al*. [4] set up prey numbers at simple arithmetic intervals: $N = \{10, 20, 30, 40, 50, 60\}$, with two to four replicates of each design point set according to the availability of prey. Both these examples highlight experimental designs that seem reasonably sensible, but may not be optimal for precisely estimating the parameters that are desired.

2.2. Utility functions for optimal design

Optimal experimental design involves selecting design points systematically in such a way as to optimize the inferential abilities of an experiment with respect to a specific hypothetical model or models. Such designs typically maximize some utility function, which encodes the goal of the experiment. Of interest in this paper is the precise estimation of functional response model parameter values. In this section we outline utility functions that may be used for parameter estimation, which include some new robust utility functions that we develop. The majority of the utility functions we describe here are generally applicable to all design problems.

2.2.1. Locally D-optimal designs

As mentioned earlier, our design variable of interest is $\boldsymbol{N} \in \mathcal{N} \subset \mathbb{N}_1^K$, which is a vector of positive integers of length K. We denote the model parameter of interest as $\boldsymbol{\theta} \in \boldsymbol{\Theta} \subseteq \mathbb{R}^p$ where p is the number of parameters. We define a scalar function $u: \mathcal{N} \times \boldsymbol{\Theta} \to \mathbb{R}$ which is called the utility function. The utility function encodes the goal of the experiment. If precise parameter estimation is the experimental objective, a common choice for the utility function $u(\boldsymbol{N}, \boldsymbol{\theta})$ is some scalar function of the Fisher information matrix (FIM). If we denote the log-likelihood function of some potential dataset $\boldsymbol{n}$ as $\ell(\boldsymbol{n}; \boldsymbol{\theta}, \boldsymbol{N})$, the (i, j)th component of the observed information matrix (OIM) is given by

$$\mathcal{O}(\boldsymbol{n}; \boldsymbol{\theta}, \boldsymbol{N})_{i,j} = -\frac{\partial^2 \ell(\boldsymbol{n}; \boldsymbol{\theta}, \boldsymbol{N})}{\partial\theta_i \partial\theta_j},$$

where θ_i is the ith component of $\boldsymbol{\theta}$. After substituting in the parameters $\boldsymbol{\theta}$, design points $\boldsymbol{N}$ and data $\boldsymbol{n}$, the components of the OIM provide information about the curvature of the log-likelihood surface (as a function of $\boldsymbol{\theta}$) evaluated at those values. Since the experimental design phase occurs before the data collection phase, a common approach is to average the OIM with respect to datasets that may be generated under the chosen

model and design $\boldsymbol{N}$, when the parameter value is $\boldsymbol{\theta}$. The FIM is given by

$$\mathcal{I}(\boldsymbol{\theta}, \boldsymbol{N})_{i,j} = -\mathsf{E}\left[\frac{\partial^2 \ell(\boldsymbol{n}; \boldsymbol{\theta}, \boldsymbol{N})}{\partial \theta_i \partial \theta_j}; \boldsymbol{\theta}, \boldsymbol{N}\right]. \tag{2.5}$$

The FIM for the beta-binomial model of interest defined in §2.1 is developed in the appendix.

In this paper we consider so-called D-optimal designs [22, p. 81], where the utility is given by the determinant of the FIM

$$u(\boldsymbol{\theta}, \boldsymbol{N}) = \det[\mathcal{I}(\boldsymbol{\theta}, \boldsymbol{N})]. \tag{2.6}$$

Another approach called A-optimality seeks to minimize the trace of the inverse of the FIM. The ideas in this paper are applicable to any choice of the utility function.

We seek the design that maximizes the utility function

$$\boldsymbol{N}^*_{\boldsymbol{\theta}} = \arg\max_{N \in \mathcal{N}} u(\boldsymbol{\theta}, \boldsymbol{N}), \tag{2.7}$$

where we explicitly denote that the optimal design will depend on the chosen $\boldsymbol{\theta}$. This is often referred to as a locally optimal design.

2.2.2. Robust design approaches

It should be noted that since the calculation of locally optimal designs requires the input of model parameter values, any designs obtained are parameter-dependent. If a specific set of parameter values are used, perhaps based on a previous experiment or from expert opinion, the experimental design obtained is truly optimal only if those parameter values are exactly correct. If the $\boldsymbol{\theta}$ selected is not close to the true parameter value then the locally optimal design may be inefficient.

We suggest that a robust optimal design should be tolerant to a range or distribution of parameter values; as long as the 'true' underlying parameter value for the model lies within the specified range, a robust optimal design will still allow relatively accurate parameter estimation. The uncertainty about the parameter may be encapsulated by a probability distribution $p(\boldsymbol{\theta})$. This distribution could be thought of as a 'prior' distribution as it might incorporate knowledge from experts or from previous similar experiments. However, it is not a prior distribution in the Bayesian sense as the approach assumes that $p(\boldsymbol{\theta})$ will be discarded upon data collection. There is a fully Bayesian approach to optimal design (see [23,24]) where the utility function is some posterior functional, but we do not consider this here. The aim is to obtain a design that is likely to be relatively efficient for a variety of $\boldsymbol{\theta}$ values.

It is generally intractable to accommodate the full density $p(\boldsymbol{\theta})$, so a discrete sample $\{\boldsymbol{\theta}_j\}_{j=1}^J \sim p(\boldsymbol{\theta})$ is often generated instead. If $p(\boldsymbol{\theta})$ has a simple parametric form such as a normal distribution then the $\boldsymbol{\theta}$ samples can be drawn directly. In our case study, we use Markov chain Monte Carlo (MCMC) methods to generate from the posterior distribution conditional on some pilot data of the experiment, $(\boldsymbol{n}_{\mathbf{p}}, \boldsymbol{N}_{\mathbf{p}})$, for some initially chosen design $\boldsymbol{N}_{\mathbf{p}}$. We then use this posterior distribution as the 'prior' distribution for the rest of the experiment. To obtain a roughly independent sample from this 'prior' the MCMC output needs to be thinned using a suitably large thinning factor.

The most common approach to robust design is the pseudo-Bayesian approach [14], which considers the average utility over the prior sample

$$u_{\mathrm{p}}(\boldsymbol{N}) = \frac{1}{J}\sum_{j=1}^{J} \log u(\boldsymbol{N}, \boldsymbol{\theta}^j), \tag{2.8}$$

where the log is used to help avoid different scales of the utilities for different parameter values. Another interpretation is that this approach results in optimizing the geometric mean of the utility values.

Another method for generating a robust design is the maximin approach (e.g. [17]). First, we define the efficiency of design $\boldsymbol{N}$ as $E(\boldsymbol{N}, \boldsymbol{\theta}) = u(\boldsymbol{N}, \boldsymbol{\theta})/u(\boldsymbol{N}^*_{\boldsymbol{\theta}}, \boldsymbol{\theta})$ where $u(\boldsymbol{N}^*_{\boldsymbol{\theta}}, \boldsymbol{\theta})$ is the maximum local utility value based on the parameter $\boldsymbol{\theta}$. The maximin utility is then given by

$$u_m(\boldsymbol{N}) = \min_{j=1,\ldots,J} E(\boldsymbol{N}, \boldsymbol{\theta}_j).$$

Thus the objective is to maximize the lowest efficiency over the prior samples.

These approaches inspired us to develop two new robust utility functions that directly incorporate efficiency values, and is based on the fact that different designs are often compared in terms of their efficiency values (e.g. [15,18]). The additional benefit is that the efficiency values for different θ will be on the same scale, hence mitigating scaling problems for different parameter configurations. Thus we consider maximizing the average efficiency

$$u_{pe}(\boldsymbol{N}) = \frac{1}{J}\sum_{j=1}^{J} E(\boldsymbol{N}, \boldsymbol{\theta}_j).$$

Given that this is how designs are often compared, it is surprising that this type of utility is yet to appear in the literature.

The above utility maximizes the average efficiency but does not guard against several potentially low efficiencies, while the maximin approach optimizes the worst case scenario and somewhat neglects other parameter configurations. In order to balance the best of both approaches, we consider a new utility that attempts to maximize the average efficiency but simultaneously reduces the standard deviation of the efficiencies.

$$u_{pes}(\boldsymbol{N}) = u_{pe}(\boldsymbol{N}) - \sqrt{\frac{1}{J}\sum_{j=1}^{J} (E(\boldsymbol{N}, \boldsymbol{\theta}_j) - u_{pe}(\boldsymbol{N}))^2}. \tag{2.9}$$

This utility falls under the framework of compound design criteria (e.g. [25]).

Regardless of which robust utility is used, the robust optimal design is defined as:

$$\boldsymbol{N}^* = \arg\max_{\boldsymbol{N}} u(\boldsymbol{N}). \tag{2.10}$$

A distinctly different robust design approach developed by Dror & Steinberg [18] firstly constructs locally optimal designs for each $\boldsymbol{\theta}_j$ for $j = 1, \ldots, J$. Then, a clustering approach is applied to the collection of locally optimal designs to form a robust design with the desired number of observations. A limitation of this approach is that it is only applicable for continuous design spaces. Here, we develop an analogous approach for integer-valued design spaces. Denote the concatenation (sorted from smallest to largest) of all the J locally optimal designs as $\boldsymbol{N}_c = \mathrm{sort}(\boldsymbol{N}^*_{\boldsymbol{\theta}_1}, \ldots, \boldsymbol{N}^*_{\boldsymbol{\theta}_J})$ which is of length $M = J \times K$. Then, we construct our robust design of K observations by systematically resampling K values from $\boldsymbol{N}_c$. This is shown in algorithm 1.

In addition to offering an alternative approach to obtaining a robust optimal design, this 'clustering' technique can be computationally advantageous in situations where the robust utilities require lengthy calculations; the systematic resampling algorithm is trivial to run, once all of the locally optimal designs have been generated for the prior samples.

It is important to note that the optimal robust designs generated will be dependent on the collection $\{\boldsymbol{\theta}_j\}_{j=1}^J$. We suggest that the performance of the optimal robust designs should be compared and evaluated using a fresh batch of samples from the prior, which should be generated using a different random seed.

Algorithm 1. Systematic resampling algorithm to obtain a robust design.

Sample $v \sim \mathcal{U}(0,1)$
  for k in 1 to K **do**
    Find index i such that $(i-1)/M \leq v < i/M$
    Extract the ith component from $\boldsymbol{N}_c$ and add it to the robust design
    Set $v = v + 1/K$
    if $v > 1$ **then**
      Set $v = v - 1$
    end if
  end for

We suggest that the best robust design choice will be problem dependent and therefore it is important to have a variety of robust design approaches in the toolbox. As we demonstrate in §3, the robust design approaches can be assessed and compared prior to data collection. We expect that the performance of each method will vary with the specific problem, and it is recommended that the entire suite of methods be used to generate various optimal design options. Additionally, even when assessing the same set of options, different experimentalists may select different robust designs depending on their internal opinion on what 'robust' means to them, further reinforcing the need to have a variety of methods available.

2.3. Design optimization algorithm

In the previous section, we defined utility functions for both local and robust designs. What is left is to derive an optimization algorithm that can find the $\boldsymbol{N}$ to maximize the chosen utility. It is worth noting that even our systematic resampling method requires an optimization algorithm to determine the local design for each sample from the prior. A common approach to solve integer-valued design optimization problems is the so-called exchange algorithm [26]. In this section we give details about the exchange algorithm we use for design optimization, which is particularly suited to discrete-valued design spaces.

The exchange algorithm updates a single or pair of design variables at a time by trialling potential values from a predefined set and updating the design if any proposed utility value is greater than the current highest utility value. The exchange algorithm for our integer design optimization problem is shown in algorithm 2. In the algorithm, $\boldsymbol{\Xi}$ denotes the allowable integer values for each design point N_i, $i = 1, \ldots, K$. For the BBG case study, we set $\boldsymbol{\Xi} = \{1, 2, \ldots, 150\}$.

Design optimization can be computationally intensive when K (the number of observations in the experimental study) is large. For our application, we develop a pre-computing approach for massively reducing the required computational cost. Here we pre-compute and store all of the required sub-Fisher information matrices for single design points and each $\boldsymbol{\theta}$ drawn from the prior, $\mathcal{I}(\boldsymbol{\theta}^j, N_i)$ for all $N_i \in \boldsymbol{\Xi}$ and $j = 1, \ldots, J$. When a particular design $\boldsymbol{N}$ is proposed in the optimization algorithm, the Fisher information matrix for some parameter $\boldsymbol{\theta}$ can be conveniently computed by summing the relevant pre-computed sub-Fisher information matrices. For the two case studies, the pre-computing part takes several minutes on a standard laptop computer. The subsequent optimization for a robust utility function described in the previous section takes around 1 minute only. Without the pre-computing, the robust optimization procedure takes over 100 hours even utilizing multiple cores on a desktop computer.

Algorithm 2. Exchange algorithm for integer design $\boldsymbol{N}$.

1: Generate a random initial design $\boldsymbol{N}$.
2: For N_1, replace with the value from the search grid $\boldsymbol{\Xi}$ that maximizes the utility function, while holding all other values in the search parameter $\boldsymbol{N}$ constant.
3: Repeat Step 2 for all other N_i, $i = 2, \ldots, K$.
4: Repeat Steps 2 and 3 multiple times until no, or only a very minimal, increase in utility can be achieved.

It is important to note that the exchange algorithm is not guaranteed to converge to the optimal design. A common approach is to run the algorithm independently from multiple random starting values.

3. Results

3.1. Case study 1

In the experiment of Hassell *et al.* [12], 89 observations were taken with each observation having one of the following initial number of prey, $\boldsymbol{N}_\mathbf{p} = (5, 8, 10, 15, 20, 25, 30, 45, 60, 80, 100)$. We consider instead designing this experiment using the optimal design methods discussed earlier. We assume that a pilot experiment is conducted with one observation taken at each of the prey levels. We assume that the observed number of prey attacked was $\boldsymbol{n}_\mathbf{p} = (2, 1, 3, 5, 9, 13, 11, 10, 14, 12, 24)$ (this is obtained by randomly sampling a single observation for each prey level from the actual dataset), and we use this pilot data to inform the prior distribution that we use for the optimal design method. Such a pilot study could be designed by an expert in the field, but we stress that there are other ways to construct the prior distributions for optimal design purposes if performing a pilot study is not feasible, such as expert knowledge, historical studies or the use of weakly informative priors. We assume the following prior distribution for the parameters before pilot data collection

$$p(a, b, c, \lambda | \boldsymbol{N}_\mathrm{p}) \propto \mathbb{1}(0 < a < 30) \times \mathbb{1}(0 < b < 30) \times \mathbb{1}(0 < c < 1) \times \mathbb{1}(0 < \lambda < 1) \times \mathbb{1}(0 < \mu < 1 \text{ for all } N \in \boldsymbol{N}_\mathrm{p}),$$

where $\mathbb{1}(\cdot)$ denotes the indicator function that is 1 if the argument is true and 0 otherwise. The upper limits for a, b and c may be informed by experts so that these parameters do not take on unrealistically large values. The final constraint ensures that the model produces a proportion μ, which is a function of a, b and c, between 0 and 1 for any prey level in $\boldsymbol{N}_\mathbf{p}$. Thus the prior, as a function of a, b, c and λ, is uniform on a constrained space. We estimate the posterior distribution of $\boldsymbol{\theta}$ conditional on the pilot data using MCMC methods. We start the chain at a value with relatively large likelihood based on the pilot data (thus we do not use a burn-in) and run the chain for 100 K iterations. We use a thinning factor of 1000 to obtain 100 roughly independent samples from the posterior distribution, which we use as the prior samples for the optimal design method. We refer to this as prior sample A. We repeat this process with a different random seed to generate prior sample B, which we use to compare the various robust optimal designs obtained.

Marginal histograms of the two sets of prior samples are shown in figure 2. The approximate prior predictive median

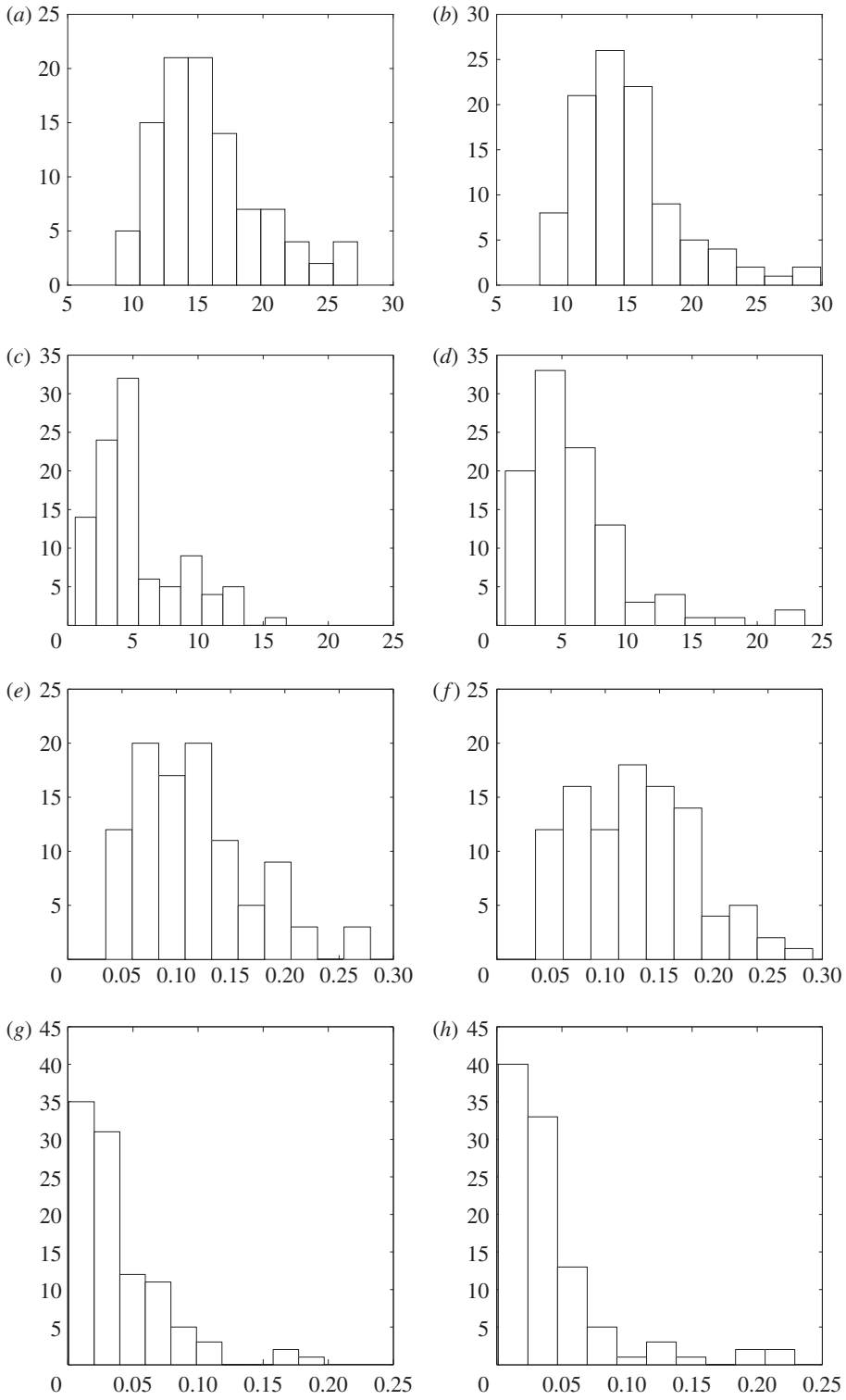

Figure 2. Histograms of the prior samples with prior samples A in the left column and prior samples B in the right column. (*a*) A *a*, (*b*) B *a*, (*c*) A *b*, (*d*) B *b*, (*e*) A *c*, (*f*) B *c*, (*g*) A λ and (*h*) B λ.

and 95% interval of the number of prey predated from the BBG model are shown in figure 3.

With the prior samples in hand, we perform our robust optimal design procedure for the remaining 78 observations in the experiment. To avoid any problems with local optima, we run our exchange method on each utility function 50 times, with each run using a different random seed. To assess the quality of the optimal robust designs we compare the results with: (i) the original design of Hassell *et al.* [12] (proportionally sampled for a 78-point design); (ii) a locally optimal design using the MLE based on the pilot data; and (iii) a random design that involves taking 78 prey levels from the vector $(1, 2, \ldots, 150)$ with replacement. We use shorthand notation for each of the design approaches, which are detailed in table 1.

Comparing the various designs in figure 4, we can see substantial differences, especially when compared with the Original design of Hassell *et al.* [12]. Firstly, the Local design only has three support points (at 6, 21 and 150 prey), with a high number of replicates (20, 20 and 38 respectively). Pseudo, PseudoEff and StdEff exhibit designs typically clustered around 5 or 6 support points, with a higher

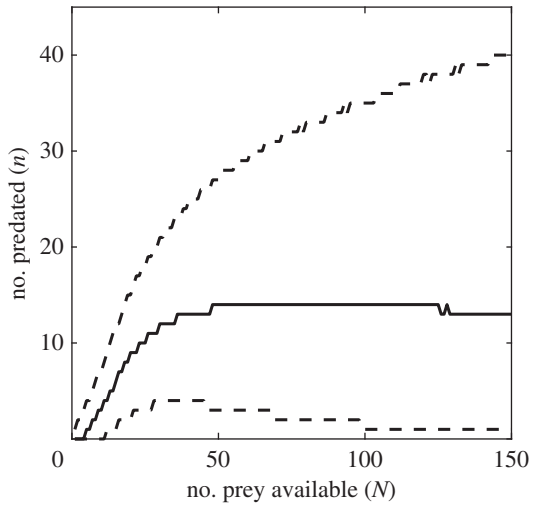

Figure 3. Prior predictive distribution of the response variable (number of prey predated) for the BBG model. The solid line is the approximate prior predictive median whilst the dashed lines represent the approximate 95% prior predictive interval.

Table 1. Details for the shorthand notation that we use for each the design approaches.

shorthand	details
Original	the design used in the original experiment
Random	randomly selected design from the values 1, 2, . . ., 150 with replacement
Local	locally optimal design based on the MLE from the pilot data
Pseudo	the standard pseudo-Bayesian design
PseudoEff	the same utility as Pseudo but applied to the efficiencies rather than the raw utility values
StdEff	the pseudo-Bayesian design applied to efficiencies rather than raw utility values, and also taking into account the standard deviation of the efficiencies
Maximin	the standard maximin design approach applied to the efficiencies
Systematic	the design formed by applying systematic resampling to the collection of all locally optimal designs for each parameter value in the prior set

concentration on the lower end (between 1 to 40 prey). The replicates for these three utility methods top out at 16. Maximin and Systematic look quite different, with a much larger spread of design points with far fewer replicates each (there are many design points with just a single replicate allocated), although there is still a heavy concentration on the lower end (between 1 to 40 prey).

Figure 5 shows boxplots of the D-efficiencies obtained for different designs based on prior samples A (figure 5*a*) and prior samples B (figure 5*b*). From both figures it is clear that the random design performs poorly, so some thought about the experimental design, either through the use of experts, or the methods described here, or both, is very important.

It is evident that the local design is not robust to different parameter configurations, but the design selected for the original experiment in Hassell *et al*. [12] was chosen sensibly, as evidenced by their respective spreads in efficiency under different parameter configurations. Figure 5*a* also shows that all of the robust utilities offer some general improvement in the efficiencies. In particular, the StdEff method seems to perform well given that it has the smallest interquartile range and that its median value is close to the highest median value. The systematic approach also appears to perform reasonably well (with results being similar to the Pseudo utility) given that it is relatively easy to calculate.

However, the efficiencies from the robust design approaches may be biased upwards since they are being assessed on the same parameter values used to obtain the designs. Thus, in figure 5*b*, we reassess the robust designs on the fresh prior samples B. It is evident that the interquartile ranges of the robust design boxplots are wider than figure 5*a*, suggesting that it is not reasonable to assess the designs based on the same parameter values used to generate them (as expected). Despite this, the results are qualitatively similar. The StdEff utility still performs well here and so does the Systematic approach relative to computational effort. The gain of using the optimal design methods over the Original design is in the order of 10–15% increase in the median efficiency value, with some designs (such as StdEff) also offering a tighter interquartile range.

Datasets drawn from the beta-binomial can exhibit significant variability and thus the data can be generally less informative than binomial data. Such variability might make it difficult to discriminate between the performance of the different robust approaches. To investigate this further, we also applied the same optimal design methods to the binomial-Gompertz (BG) functional response model equation [9]. From figure 6, we can see that there is a more noticeable difference now between the various methods. Examining the sample B box plot in particular, StdEff exhibits a very tight interquartile range, as well as the best 'worst case' scenario (lowest efficiency value). Maximin offers a similarly tight interquartile range, but unfortunately with a much lower median efficiency. PseudoEff offers much higher efficiency values than Original in general, although its performance is more variable. Systematic also shows a steady 10% increase in median efficiency compared to the Original method, with a similar spread. In this model, we suggest that StdEff and Pseudo offer compelling alternatives to the Original design, depending on whether the experimenter is interested in higher or more reliable efficiency outcomes.

In terms of the new robust utilities, we find that PseudoEff leads to a less robust design than Pseudo as it generally has a larger interquartile range of efficiencies. In the BG model, StdEff has the tightest interquartile range by far (being noticeably tighter than the equivalent utility applied in the BBG model), with a relatively efficient 'worst case' scenario. Systematic offers consistent gains over the Original approach, without the more obvious pros and cons of the other two. Generally though, these findings are all specific to this application and model. Our suggestion is to have an arsenal of robust design methods in the toolbox; this allows

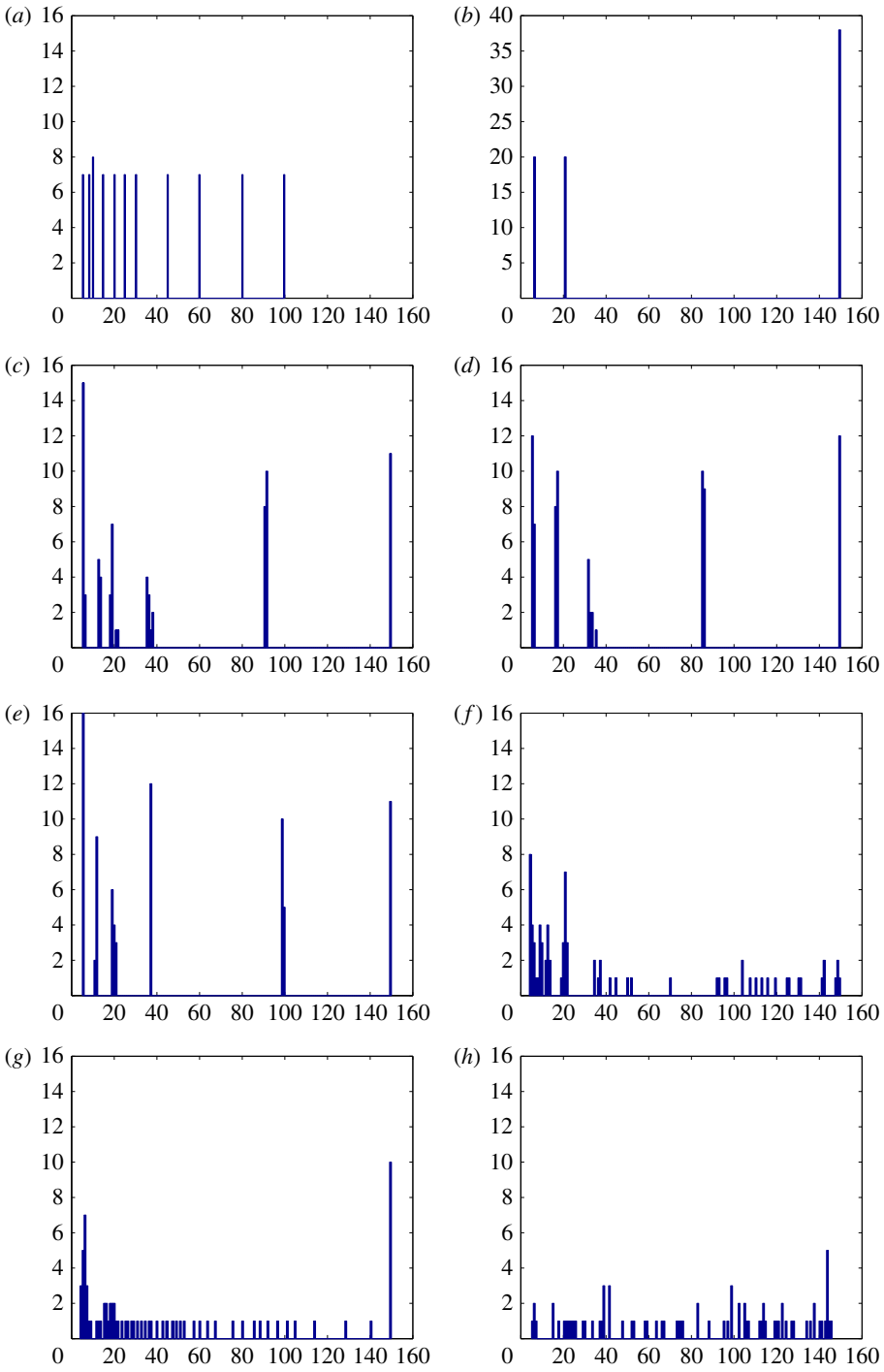

Figure 4. Histograms of the various designs used for comparisons in the BBG model. The x-axis shows the prey number and the y-axis is the number of replicates. (*a*) Original, (*b*) Local, (*c*) Pseudo, (*d*) PseudoEff, (*e*) StdEff, (*f*) Maximin, (*g*) Systematic and (*h*) Random. (Online version in colour.)

a variety of designs to be assessed and compared (prior to data collection) in a similar way to what we have done for this application.

3.2. Case study II

In this section we consider the experiment of Papanikolaou *et al.* [13], which was concerned with the functional response of a widespread ladybird beetle (*Propylea quatuordecimpunctata* L.) to its insect prey (*Aphis fabae* Scopoli). For details on the experimental conditions, see Papanikolaou *et al.* [13]. Sixty observations were taken with each observation having one of the following initial number of prey, $N = \{4, 8, 16, 32, 64, 128\}$. Similarly to the previous case study, we consider an experimentalist wishing to re-design this experiment where the primary objective is to accurately estimate the parameters of the following model:

(i) population dynamics are modelled using Holling's disc equation in which it is assumed that there is no prey depletion (i.e. setting $N = N_0$ in 2.1). This assumption produces an expected number of prey attacked given by

$$\mathsf{E}[n] = \frac{N - \{N - [rNT/(1 + rT_{\mathrm{h}}N)]\}}{N},$$

where $T = 24$ h for this experiment.

(ii) the variability in the data is captured using a beta-binomial model as in (2.3). The model parameter is thus

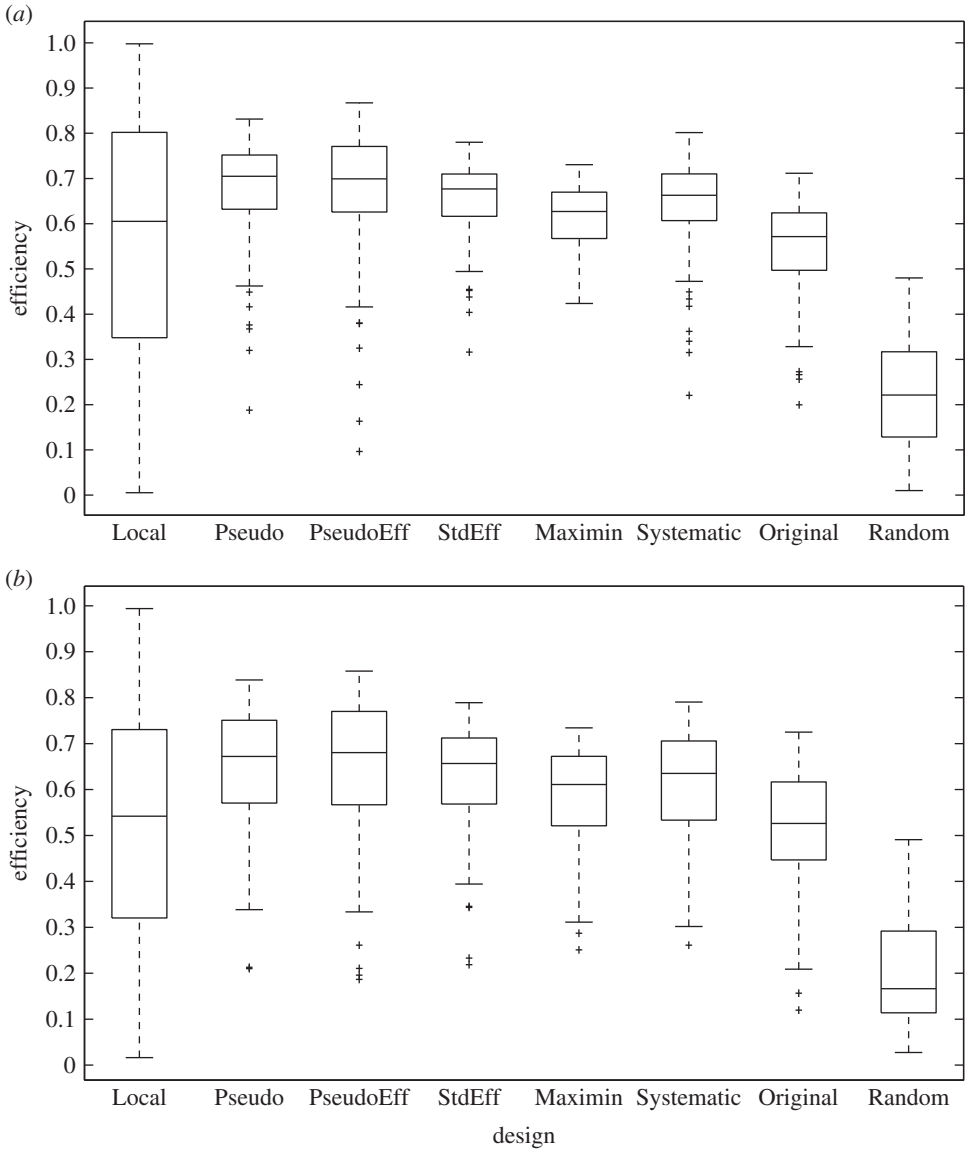

Figure 5. Boxplots of the D-efficiencies obtained for different designs based on (*a*) prior samples A and (*b*) prior samples B. The results are based on the BBG model.

$\boldsymbol{\theta} = \{r, T_h, \lambda\}$. We refer to this as the beta-binomial-Holling (BBH) model.

For this example, the pilot data consists of two observations taken randomly from the dataset at each prey level. The prior distribution on each of the parameters before pilot data collection is set to an exponential distribution with mean 100, with all parameters independent *a priori*. We run 100 000 iterations of MCMC from a suitable starting value and thin the chain by a factor of 1000, producing 100 roughly independent samples from the posterior conditional on the pilot data. We then use these as prior distribution samples to form an optimal robust design for the remaining 48 observations.

Efficiency boxplots (based on a fresh set of prior samples not used in the optimal design procedure) for all the robust design approaches outlined in this paper are shown in figure 7, along with a random design, the original design, and a local MLE design for comparison purposes. Each design is illustrated in the histograms in figure 8. The BBH efficiency plots in figure 7 are qualitatively similar to the BBG and BG model results: StdEff and Maximin have produced the smallest interquartile range whilst still having higher median values than the original design, and all the robust design approaches offer clear improvements relative to the original design.

4. Discussion

In this paper, we have demonstrated the application of optimal design methodology to functional response experiments. In the process, we have developed some additional approaches for determining designs that are robust to parameter uncertainty, which could be applied in other design problems.

We found that our systematic approach to obtaining a robust design produced results that were competitive with other robust utilities. This provides additional support that the clustering idea of Dror & Steinberg [18] is useful, especially since it is more computationally efficient. It would also be straightforward to extend the idea to cases where there is model uncertainty. This would involve taking prior parameter samples from each of the models, and then performing a local optimal design for each parameter value. After concatenating all local optimal designs,

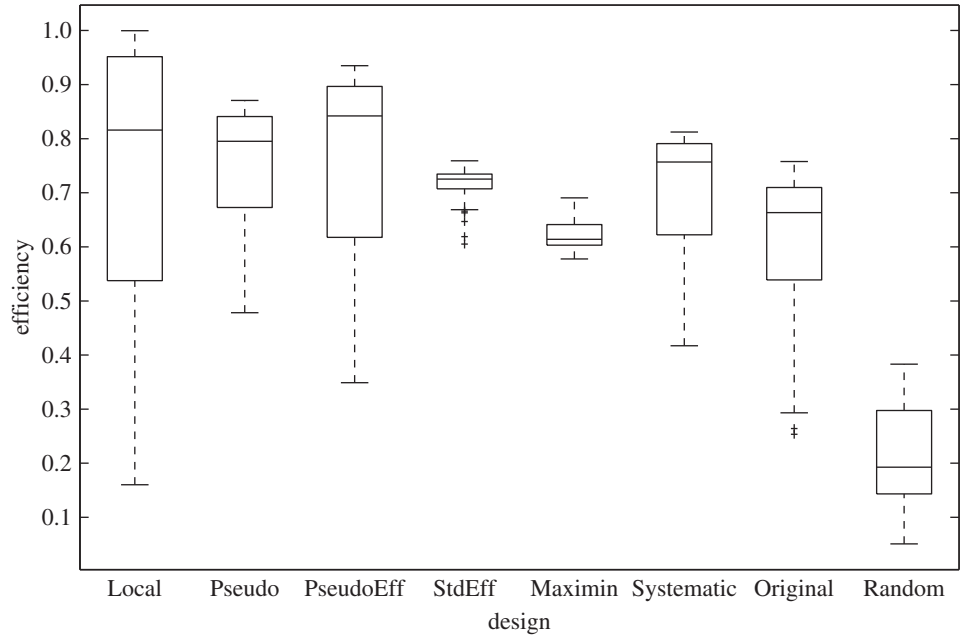

Figure 6. Boxplots of the D-efficiencies obtained for different designs based on prior samples B. The results are based on the BG model.

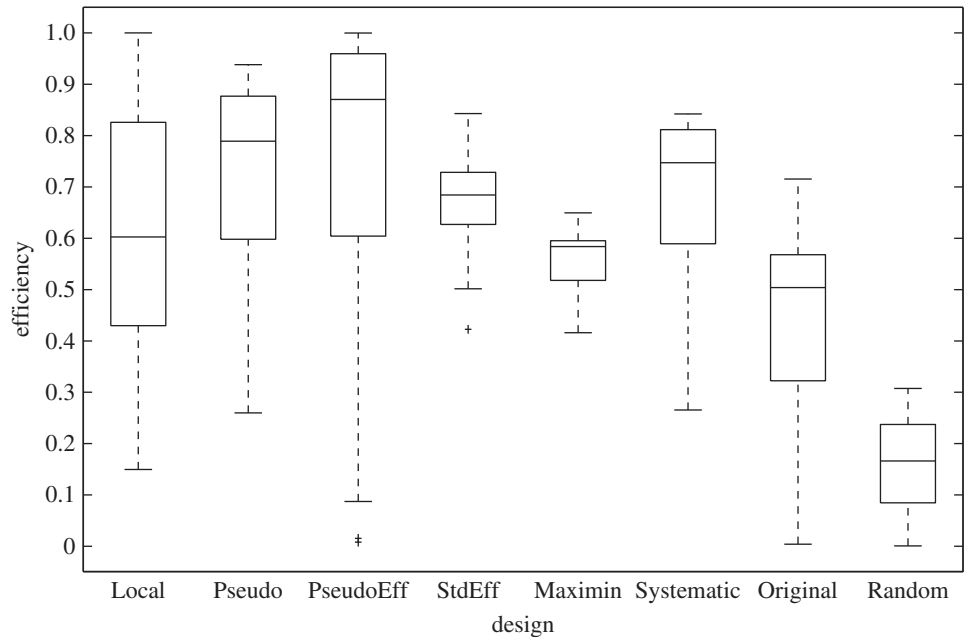

Figure 7. Boxplots of the D-efficiencies obtained for different designs based on prior samples B. The results are based on the BBH model.

a design that is robust to model and parameter uncertainty can be obtained by performing an appropriate clustering of the concatenation.

Furthermore, the clustering idea could be used in fully Bayesian design. Whilst in classical design the utility function is often a functional of the FIM, in Bayesian design the utility is often a functional of the posterior distributed computed from future datasets that might arise from the proposed experimental design. An advantage of the Bayesian approach is that its utility is based on a posterior functional, and so does not rely on an asymptotic approximation that the FIM-based utility does. In a Bayesian optimal design procedure, the posterior distribution needs to be computed many times leading to a high computational cost (see [27] for the computational challenges in Bayesian design). Thus methods for reducing computation are sought. We plan to investigate the clustering approach for fully Bayesian design in further research.

Here we focussed on optimizing the prey levels for a fixed number of experimental observations. However, our optimization method could be modified to handle the constraint where the total number of prey available for the experiment is fixed instead.

An alternative approach to determining designs that are robust to parameter and model uncertainty are sequential design methods (e.g. [28]). After each observation is collected, the information about the model(s) is updated, which can then be used to make a better decision about the prey level to take for the next observation. This can be incorporated with stopping criteria, to stop the experiment once certain criteria are met (instead of fixing the total number of samples up front). The drawback of the sequential design process

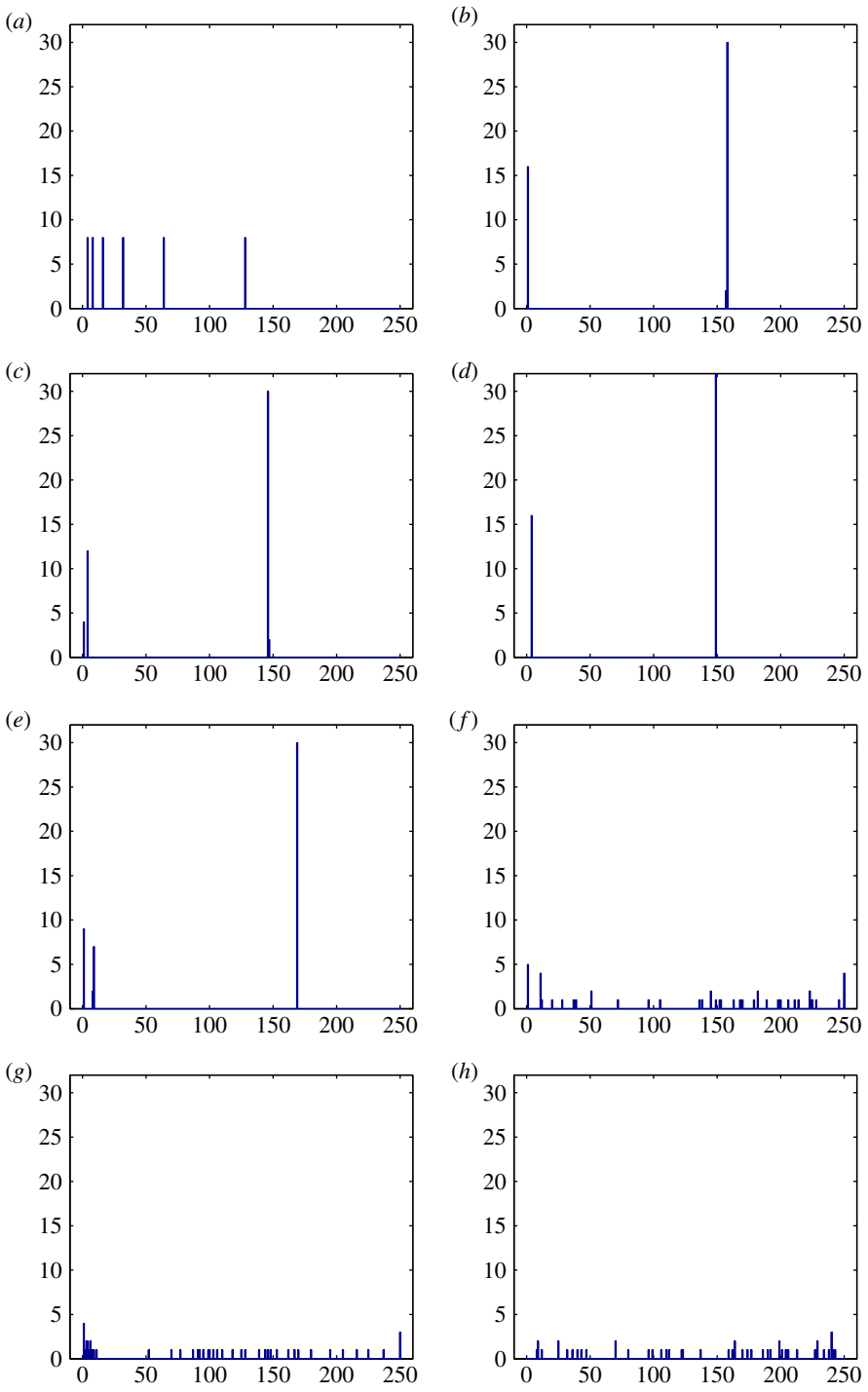

Figure 8. Histograms of the various designs used for comparisons in the BBH model. The *x*-axis shows the prey number and the *y*-axis is the number of replicates. (*a*) Original, (*b*) Local, (*c*) Pseudo, (*d*) PseudoEff, (*e*) StdEff, (*f*) Maximin, (*g*) Systematic and (*h*) Random. (Online version in colour.)

is that it takes a longer time to conduct the experiment. However, we suggest that it is worth considering depending on the logistics of the experiment.

In conclusion, we have developed effective robust optimal design methods for integer-based experimental scenarios. We successfully applied the methods to a novel application in functional response experiments.

Data accessibility. Matlab code and data to implement our methods for the first case study are available at http://www.runmycode.org/companion/view/2708.

Authors' contributions. C.C.D. designed the study. J.F.Z. and C.C.D. developed the methods, wrote the computer code, performed the analysis, interpreted results and drafted the paper. N.E.P. provided expertise on the case studies and critically reviewed the paper. T.K. provided expertise on the statistical modelling and critically reviewed the paper.

Competing interests. We declare we have no competing interests.

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Appendix A

For simplicity we only provide instructions on how to obtain the expression for the first diagonal element of the FIM. The process for the other elements follows in a similar way.

Further, this is only shown for a single design variable N since the FIM for a potential design $\boldsymbol{N}$ can be obtained by summing the FIMs for the individual observations. The log-likelihood for a single observation is given by

$$l(n; N, \alpha, \beta) = \log \binom{N}{n} + \log \Gamma(n+\alpha) + \log \Gamma(N-n+\beta) - \log \Gamma(N+\alpha+\beta) - \log \Gamma(\alpha) - \log \Gamma(\beta) + \log \Gamma(\alpha+\beta). \quad (A\,1)$$

Recall that

$$\mu = \frac{\alpha}{\alpha+\beta} = \frac{a}{N}(e^{-b\exp(-cN)} - e^{-b}) \quad \text{and}$$

$$\lambda = \frac{1}{\alpha+\beta},$$

so that $\alpha = \mu/\lambda$ and $\beta = (1-\mu)/\lambda$. Take, for example, the term $\log\Gamma(N+\alpha+\beta)$. Differentiating this with respect to a gives

$$\frac{\partial}{\partial a}\log\Gamma(N+\alpha+\beta) = \psi^{(0)}(N+\alpha+\beta)\left(\frac{\partial\alpha}{\partial a} + \frac{\partial\beta}{\partial a}\right),$$

where

$$\frac{\partial\alpha}{\partial a} = \frac{\partial\alpha}{\partial\mu}\frac{\partial\mu}{\partial a} \quad \text{and}$$

$$\frac{\partial\beta}{\partial a} = \frac{\partial\beta}{\partial\mu}\frac{\partial\mu}{\partial a}.$$

The partial derivatives on the right hand side of the above are easy to obtain. A similar process needs to be repeated for each of the $\log\Gamma(\cdot)$ terms in (A 1). The second derivative of $\log\Gamma(N+\alpha+\beta)$ involves the use of the product rule, repeated application of the chain rule and also the polygamma function of order 1, $\psi^{(1)}(\cdot)$.

The first diagonal element of the OIM is given by

$$\mathcal{O}(\boldsymbol{n}; \boldsymbol{\theta}, \boldsymbol{N})_{1,1} = -\frac{\partial^2\ell(\boldsymbol{n}; \boldsymbol{\theta}, \boldsymbol{N})}{\partial a^2}.$$

To obtain the corresponding component of the FIM, the expected value with respect to $\boldsymbol{n}$ must be calculated. We note that the OIM component above does involve expectations with respect to each individual n for a variety of non-linear functions of n. If we denote a non-linear function of n by $g(n)$, its expectation is given by

$$\mathsf{E}[g(n)] = \sum_{i=1}^{N} g(i)p(n=i; N),$$

where $p(n=i; N)$ is the probability mass function of the beta-binomial distribution with N being the number of trials (the corresponding prey level that will be used). There is no analytical solution for this expectation so it must be evaluated numerically. Thus the computational cost of evaluating a single entry of the FIM is of the order $K \times \max(\boldsymbol{N})$.

In practice, we use the symbolic toolbox in Matlab to evaluate the necessary derivatives for the FIM as shown below. These expressions can be converted into Matlab code with some manual adjustments. Any terms involving non-linear functions of n need to replaced with code to compute the expected value as shown above. If there are some terms that appear several times in the derivatives for the FIM the code can be accelerated by computing such quantities once and re-using them.

```
%% Calculation of the partial derivatives for
the BBG model

% a,b,c are the parameters from Gompertz eqn
% alpha and beta are from the beta-binomial
function
% d is the overdispersion parameter of the beta-
binomial

syms N n a b c d alpha beta;

mu=(a/N)*(exp(-b*exp(-c*N))-exp(-b));

alpha=mu/d;
beta=(1 - mu)/d;

% define the loglikelihood equation
bbLL=(log(factorial(N)) - log(factorial(n)) -
log(factorial(N-n))...
+ log(gamma(n+alpha))+log(gamma(N-n+beta)) -
log(gamma(N+alpha+beta))...
+ log(gamma(alpha+beta)) - log(gamma(alpha)) -
log(gamma(beta)));

% first partial derivatives
bbLLa=diff(bbLL,a);
bbLLb=diff(bbLL,b);
bbLLc=diff(bbLL,c);
bbLLd=diff(bbLL,d);

% second partial derivatives
bbLLaa=diff(bbLLa,a);
bbLLbb=diff(bbLLb,b);
bbLLcc=diff(bbLLc,c);
bbLLdd=diff(bbLLd,d);

bbLLab=diff(bbLLa,b);
bbLLac=diff(bbLLa,c);
bbLLad=diff(bbLLa,d);
bbLLbc=diff(bbLLb,c);
bbLLbd=diff(bbLLb,d);

bbLLcd=diff(bbLLc,d);
```

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