Optimal Design of Experimental Epidemics

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Abstract

We consider the optimal design of experimental epidemics modelled as density dependent Markov processes. We focus on finding (i) the optimal times at which to collect data about the state of the system for a small number of discrete observations, (ii) the optimal numbers of susceptible and infective individuals to begin an experiment with, and (iii) the optimal number of replicate epidemics to use. We answer these questions by looking at three commonly used compartmental models in experimental epidemiology: the SI (Susceptible to Infected), SIS (Susceptible to Infected to Susceptible) and partially observed SIR (Susceptible to Infected to Recovered) epidemics. In particular, to demonstrate the wide range of density dependent models to which our methodology can be applied, we use a time-homogeneous SIS epidemic, a time-inhomogeneous SI epidemic with exponentially decreasing transmission rates and an partially observed SIR epidemic where the infectious period for an individual has a gamma distribution. Whilst compartmental models are

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widely applied in natural systems, we focus on the use of the models in the context of controlled experimental epidemics or *transmission experiments*, whose purpose is to inform the practitioner about disease transmission and recovery rates. We adopt the popular D -optimality criterion as providing an appropriate objective function for designing our experiments, since this leads to point estimates with maximum precision. As D -optimal designs for non-linear models are only locally optimal, we also consider the robustness of the designs relative to the misspecification of the model parameters.

Keywords: Markov chain; optimal design; Fisher information; sampling; SIS; SIR; SI; SI(k)R; epidemic.

1. Introduction

Transmission experiments are controlled experimental epidemics involving populations of diseased and healthy organisms, often contained in a microcosm or conducted in a laboratory. The objective is to observe, over time, the spread of disease amongst the organisms and to use this information to obtain point estimates of per capita transmission and recovery rates. In recent years, such experiments have been used to study the dynamics of foot-and-mouth disease (Streftaris and Gibson, 2004), avian influenza (van der Goot et al., 2005), damping off (Kleczkowski et al., 1997; Cook et al., 2008; Otten et al., 2003) and Belgian classical swine fever (Höhle et al., 2005). Some of the common epidemiological models used for studying the spread of disease among interacting organisms include the SI (susceptible to infected), SIS (susceptible to infected to susceptible) and SIR (susceptible to infected to recovered) epidemics, and variants thereof (see for example Stone et al.

15 (2008), McCormack and Allen (2007) and Kim and Radhakrishnan (2006)).
 16 They are examples of the compartmental epidemic models introduced ini-
 17 tially by Kermack and McKendrick (1927) as deterministic models and later
 18 popularized as stochastic processes by Bartlett (1949, 1956), Bailey (1950,
 19 1957) and Kendall (1956). Many belong to a broader class of birth-death
 20 processes or Markov population processes (Kingman, 1969) known as *density*
 21 *dependent Markov processes* (DDMPs), as identified and studied by Kurtz
 22 (1970), and to which the methodology, herein, applies.

23 Early work on inference for birth-death processes either considered scenar-
 24 ios where a process was observed continuously in time (Keiding, 1974, 1975)
 25 or observed at equally spaced times (Keiding, 1975; Kendall, 1949). These
 26 simplifications were necessary to obtain analytical expressions for maximum
 27 likelihood estimators. When dealing with discretely observed processes, there
 28 is often the complication that the transition probabilities are difficult to
 29 evaluate analytically and the likelihood cannot be written down in simple
 30 form. Such is the case when designing experiments for compartmental models
 31 such as the SI, SIS and SIR epidemics. Consequently, it becomes necessary
 32 to either evaluate probabilities numerically (for example using EXPOKIT
 33 (Sidje, 1998)), to rely on Monte Carlo methods (O'Neill and Roberts, 1999;
 34 Cauchemez and Ferguson, 2008) or to employ distributional approximations.

35 Given the widespread use of compartmental models, and the degree of
 36 attention given to parameter estimation, it is surprising that little atten-
 37 tion has been directed towards the design of efficient experiments. There is
 38 only a handful of contributions: Becker and Kersting (1983) examined the
 39 simple birth process, Cook et al. (2008) examined the simple death process

40 and a time-inhomogeneous SI epidemic, and Pagendam and Pollett (2009,
 41 2010b,a) examined the simple birth-death, the stochastic logistic model, and
 42 the simple death processes, respectively. In the models examined by Becker
 43 and Kersting (1983) and Pagendam and Pollett (2010a) there was a single
 44 parameter, and the model was sufficiently simple that optimal experimental
 45 designs could be obtained analytically. For multi-parameter models and some
 46 single parameter models (the SI epidemic for example), likelihoods are rarely
 47 in a form that allows calculation of the expected Fisher information matrix,
 48 which lies at the heart of most classical optimality criteria in experimental
 49 design.

50 The recent work of Cook et al. (2008) identified optimal observation times
 51 for an SI epidemic in a Bayesian framework. They relied on a method known
 52 as *moment closure* to approximate the likelihood function of their model. In
 53 essence, the transition kernel of their SI epidemic was approximated using
 54 a beta-binomial distribution as described by Krishnarajah et al. (2005), but
 55 choice of this particular distributional approximation was specific to their
 56 model. Many other distributions have been employed for moment closure:
 57 Whittle (1957) introduced the technique using the normal distribution; Keel-
 58 ing (2000) used the log-normal distribution; Nåsell (2003) used the Poisson,
 59 binomial and log-normal. (These methods have been compared recently by
 60 Clancy and Mendy (2011).) Here, we develop alternative methodology for
 61 optimal experimental design of DDMPs, as used in experimental epidemiol-
 62 ogy, which relies on Gaussian diffusion approximations. These offer a unified
 63 approach for rapidly obtaining designs for a wide range of single and multi-
 64 dimensional epidemiological models, provided that the system size (usually

the total population size) is reasonably large. We pose the design problem in the classical frequentist framework and illustrate some important findings using time-inhomogeneous SI, time-homogeneous SIS and partially observed SI(k)R (having a gamma distributed infectious period) epidemics as examples.

In estimating the parameters of epidemic models, our aims are threefold: (i) to find the optimal times to observe the epidemic, (ii) to find the optimal number of infected organisms to introduce to a susceptible population, and (iii) to determine whether there is any difference between running one large experiment or several smaller ones. This is in contrast to previous work that has focussed on optimal observation times alone. Our problem can be framed in the context of optimal experimental design and we employ the popular D -optimality criterion (see Atkinson et al. (2007)). The optimal designs obtained are *locally optimal* in the sense of Chernoff (1953), since the choice of observation times and initial conditions of the process will vary depending on the parameter vector θ . For the SI(k)R epidemic we may only use the D -optimal design for estimation of β and γ (the transmission and recovery rates) under the assumption that k (the number of infectious classes) is known. This is because k is discrete; the Fisher information is defined for continuous parameters. In the context of experimental epidemics, the choice of k is an issue of model selection, rather than a parameter we wish to estimate. Whilst model selection is beyond the scope of this paper, we note that T -optimal designs and their variants can be used for this purpose, and that the methods and theory presented here is also applicable in that context.

90 2. The SI and SIS epidemic

The SI and SIS epidemics are two closely related birth-death processes used for modelling epidemics where individuals make transitions from susceptible (disease free) to infected. In the case of the SIS epidemic, individuals can recover from the disease and transition back to the susceptible state so that reinfection may occur; for the SI epidemic recovery is impossible. Both models have state space $\mathcal{S} = \{0, \dots, N\}$, representing the number of infected individuals. We consider SI and SIS epidemics with the following general form for the transition rates:

$$q(i, i + l; t) = \begin{cases} \frac{\beta e^{-\lambda t}}{N} i(N - i) & (l = 1) \\ \mu i & (l = -1), \end{cases} \quad (1)$$

91 where N is the total population size, i is the number of infected individuals,
 92 β (> 0) is the disease transmission rate, μ (≥ 0) is the individual recovery
 93 rate and λ (> 0) is a parameter governing an exponential decline in the
 94 transmission rate with time. The latter parameter can be used, for example,
 95 to account for the decrease in infection risk as an organism ages, sometimes
 96 referred to as *quenching* (see Bailey et al. (2000) for example). The transition
 97 rates of the SI epidemic we will consider are a special case of those above
 98 with $\mu = 0$, so that the number of diseased organisms increases monotonically
 99 over time (a pure birth process). For both models, 0 is an absorbing
 100 state corresponding to the eradication of disease. Note, however, that the SI
 101 epidemic is absorbed only in the trivial situation where the epidemic begins
 102 with no infected organisms. The SI epidemic has a second absorbing state N
 103 corresponding to the infection of every individual in the population. Clearly,

104 once an experimental epidemic has reached an absorbing state, it provides
 105 no more information regarding the disease dynamics.

106 For the SIS epidemic, we shall restrict attention to the time-homogeneous
 107 case, where $\lambda = 0$. A useful reparameterization of this model is $\alpha = \beta - \mu$
 108 and $\rho = \mu/\beta$. As noted in previous work (Ross et al., 2006; Pagendam and
 109 Pollett, 2009), one advantage of using (α, ρ) is that there is much weaker de-
 110 pendence between the elements of the maximum likelihood estimate, $\hat{\theta}$, than
 111 for (β, μ) , greatly aiding visualization of the maximum likelihood estimator.
 112 A further rationale for using these parameters stems from their relationship
 113 with the phases of the SIS epidemic, as we now explain. Roughly speaking,
 114 the SIS epidemic has two phases (see Figure 1(b)): (i) an initial period of
 115 drift towards a stable equilibrium, and (ii) a period of fluctuation about this
 116 equilibrium. The rate at which the epidemic is attracted towards equilibrium
 117 is governed by α whilst the position of the equilibrium is determined by ρ .
 118 As we shall see, observing the process close to equilibrium provides more
 119 information about ρ than α , whilst the opposite is true in the drift phase.
 120 We emphasize, however, that these two phases do not exclusively provide in-
 121 formation about each of the parameters independently, since, for example, α
 122 also governs the decay rate of the correlation between successive observations
 123 in both phases.

124 **3. The partially observed SI(k)R epidemic**

125 The general SI(k)R epidemic (see Ross et al. (2009)) is a generalization of
 126 the standard SIR model, but where we suppose that each individual passes
 127 through k infectious stages (potentially with different parameters), where a

128 susceptible individual may contract a disease through interaction with an
 129 infected individual, but can subsequently recover, acquiring immunity from
 130 further infection. Clearly, the standard SIR model presented in Andersson
 131 and Britton (2000) is equivalent to the SI(1)R model. We shall limit our
 132 focus to a slightly simpler version of the more general SI(k)R model, where
 133 the parameters in each of the infectious stages are identical and therefore
 134 the total time an individual is infectious for has a Gamma(k, β) distribution.
 135 We make special note however, that this model is flexible enough to allow
 136 the infectious period to have any phase-type distribution (Neuts, 1975) and
 137 that the diffusion approximation methodology outlined here will still be ap-
 138 plicable. Let S_t denote the number of susceptible individuals, $I_{1,t}, \dots, I_{k,t}$ the
 139 numbers of infected individuals in k stages of infection and R_t the number
 140 of recovered (and immune) individuals in a closed population of size N . We
 141 impose the realistic constraint that we cannot distinguish between which of
 142 the k (somewhat artificial) stages of infection an individual is in; only the
 143 total number of infected individuals, $I_{\text{Total},t} = \sum_{j=1}^k I_{j,t}$ (the sum of individ-
 144 uals in each of the k classes), can be observed at any given time. In addition,
 145 infected individuals are more easily identified since they are symptomatic.
 146 However, it can be more difficult to discern between susceptible and recov-
 147 ered individuals and measure their numbers. We therefore assume that the
 148 initial numbers in $S_0, I_{1,0}, \dots, I_{k,0}$ and R_0 are known, but that for all subse-
 149 quent observations only $I_{\text{Total},t}$ can be measured. We refer to this scenario
 150 as the *partially observed* SI(k)R (henceforth poSI(k)R) epidemic.

The state space $\mathcal{S}$ of the SI(k)R epidemic $\mathbf{Y}_t = (S_t, I_{1,t}, \dots, I_{k,t}, R_t)$ is
 $(k + 2)$ -dimensional. However, in a closed population we need only account

for the number susceptible and the numbers in the infected classes since $R_t = N - S_t - \sum_{i=1}^k I_{i,t}$. For an SI(k)R epidemic the state space can be expressed as

$$\mathcal{S} = \{(s, i_1, \dots, i_k, r) \in Z_+^{k+2} : s + i_1 + \dots + i_k + r = N\},$$

151 having absorbing states at $\{\cdot, 0, \dots, 0, \cdot\}$ (those states corresponding to there
 152 being no infected individuals remaining). Here we have used $(s, i_1, \dots, i_k, r)$
 153 to represent a possible realisation of $\mathbf{Y}_t$. For our SI(k)R epidemic with
 154 Gamma(k, β) infectious period, there are only two parameters, β and γ ,
 155 which are the disease transmission and recovery rates respectively. The non-
 156 zero transition rates of the process are

$$\begin{aligned} q((s, i_1, \dots, i_k), (s-1, i_1+1, \dots, i_k)) &= \beta s \sum_{j=1}^k i_j \\ q((s, i_1, i_2, \dots, i_k), (s, i_1-1, i_2+1, \dots, i_k)) &= \gamma i_1 \\ q((s, \dots, i_l, i_{l+1}, \dots, i_k), (s, \dots, i_l-1, i_{l+1}+1, \dots, i_k)) &= \gamma i_l \\ q((s, \dots, i_k), (s, \dots, i_k-1)) &= \gamma i_k. \end{aligned}$$

157 4. Diffusion Approximations

158 We make use of Gaussian diffusion approximations of *density dependent*
 159 epidemic models, which allow us to approximate the likelihood when the
 160 number of organisms in our experiments N is relatively large. The theory is
 161 presented for multidimensional processes, but we will see that there is con-
 162 siderably simplification in the one-dimensional case. The approximation is
 163 based on the work of Kurtz (1970, 1971), McNeil and Schach (1973) and

164 Barbour (1972, 1974). A d -dimensional Markov process $\mathbf{Y}_t^{(N)}$ is density de-
 165 pendent, with index parameter N , if the transition rates can be written as

$$q(\mathbf{y}, \mathbf{y} + \mathbf{l}; t) = Nf\left(\frac{\mathbf{y}}{N}, \mathbf{l}; t\right) \quad (\mathbf{y}, \mathbf{l} \in \mathbb{Z}^d, \mathbf{l} \neq 0, t \geq 0). \quad (2)$$

166 So, they depend on the state $\mathbf{y}$ of the process only through the population
 167 density $\mathbf{y}/N$, but may depend on t (this is the setup of Barbour (1972)).
 168 Typically, in an experimental epidemic, the index parameter is simply the
 169 population ceiling.

170 In the time-inhomogeneous case, where the transition rates do not de-
 171 pend on t , Kurtz (1970) proved a *functional law of large numbers* for density
 172 dependent Markov processes, and this was extended to the present time-
 173 inhomogeneous case by Barbour (1974): as $N \rightarrow \infty$, the *density process*
 174 $\mathbf{X}_t^{(N)} := \mathbf{Y}_t^{(N)}/N$ converges to a unique deterministic trajectory $\mathbf{x}(t)$, with
 175 $\mathbf{x}(0) = \mathbf{x}_0$ and satisfying the system of d first-order ODEs $\partial \mathbf{x}(t)/\partial t =$
 176 $F(\mathbf{x}(t); t)$, where $F(\mathbf{x}; t) = \sum_{\mathbf{l}} \mathbf{l} f(\mathbf{x}, \mathbf{l}; t)$ ($\mathbf{x} \in E$). Convergence is sub-
 177 ject to certain technical conditions, which are satisfied for many biological
 178 models of interest, including all of the epidemic models considered here. See
 179 Appendix A for a detailed explanation.

180 Additionally, Kurtz (1971) and Barbour (1974) showed that the fluctu-
 181 ations of the density process about the deterministic trajectory, when ap-
 182 propriately scaled, converge over finite time intervals to a limiting Gaussian
 183 diffusion $\mathbf{Z}_t$ (see also Pollett (1990, 2001)). Let $\mathbf{Z}_t^{(N)} = \sqrt{N}(\mathbf{X}_t^{(N)} - \mathbf{x}(t))$
 184 be the *scaled density process*. Then, provided $\lim_{N \rightarrow \infty} \sqrt{N}(\mathbf{X}_0^{(N)} - \mathbf{x}_0) = \mathbf{z}$
 185 (exists), $\mathbf{Z}_t^{(N)}$ converges weakly in the space of all sample paths on finite time
 186 intervals to a Gaussian diffusion $\mathbf{Z}_t$ with initial value $\mathbf{z}$. There are simple

expressions for the expectation and cross-covariance of $\mathbf{Z}_t$: $\mathbb{E}(\mathbf{Z}_t) = \mathbf{M}_t \mathbf{z}$ and

$$\text{Cov}(\mathbf{Z}_t, \mathbf{Z}_{t+s}) = \mathbf{M}_t \int_0^t \mathbf{M}_u^{-1} \mathbf{G}(\mathbf{x}(u); u) (\mathbf{M}_u^{-1})^\top du \mathbf{M}_{t+s}^\top, \quad (3)$$

where $\mathbf{M}_t = \exp(\int_0^t \mathbf{H}(\mathbf{x}(u); u) du)$ ($\exp(\cdot)$ denotes the matrix exponential), $\mathbf{H}(\mathbf{x}; t)$ is the Jacobian matrix of $F(\mathbf{x}; t)$, with entries $h_{ij} = \partial F_j(\mathbf{x}; t) / \partial x_k$, and $\mathbf{G}(\mathbf{x}; t)$ is the matrix with entries $g_{ij}(\mathbf{x}; t) = \sum_{\mathbf{l}} l_i l_j f(\mathbf{x}, \mathbf{l}; t)$. When the initial condition is fixed as part of the design for an experimental epidemic we will have $\mathbf{z} = \mathbf{0}$.

For experimental epidemics these results are very useful for approximating the likelihood of a series of observations. Suppose we make n observations of the density process $\mathbf{X}_t^{(N)}$, denoting the random variables $\mathbf{X}^{\text{obs}} = (\mathbf{X}_1^{\text{obs}}, \dots, \mathbf{X}_n^{\text{obs}})$ and the corresponding observations $\mathbf{x}^{\text{obs}} = (\mathbf{x}_1^{\text{obs}}, \dots, \mathbf{x}_n^{\text{obs}})$, where $\mathbf{x}_i^{\text{obs}} = (x_{1,t_i}^{\text{obs}}, \dots, x_{d,t_i}^{\text{obs}})$ so that $\mathbf{x}^{\text{obs}}$ has length nd . Furthermore, let $\mathbf{x} = (\mathbf{x}_1, \dots, \mathbf{x}_n)$, where $\mathbf{x}_i = (x_1(t_i), \dots, x_d(t_i))$ is the vector value of the limiting deterministic trajectory at t_i . The pdf of $\mathbf{X}^{\text{obs}}$ can be approximated using a multivariate normal distribution: $\mathbf{X}^{\text{obs}} \sim \text{MVN}(\mathbf{x}, \frac{1}{N} \Sigma)$. Since $\mathbf{Y}_t^{(N)} = N \mathbf{X}_t^{(N)}$, we can approximate the likelihood for a series of observations $\mathbf{y}$ from the epidemic using the approximation $\mathbf{Y} \sim \text{MVN}(N \mathbf{x}, N \Sigma)$. Here Σ is the cross-covariance matrix having block structure

$$\Sigma = \begin{pmatrix} \Sigma_{1,1} & \Sigma_{1,2} & \dots & \Sigma_{1,n} \\ \Sigma_{2,1} & \Sigma_{2,2} & \dots & \Sigma_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ \Sigma_{n,1} & \Sigma_{n,2} & \dots & \Sigma_{n,n} \end{pmatrix},$$

where $\Sigma_{i,j} := \text{Cov}(\mathbf{Z}_{t_i}, \mathbf{Z}_{t_j})$ is the $d \times d$ cross-covariance matrix calculated according to (3).

195 In the case of the (one-dimensional) time-homogeneous ($\lambda = 0$) SIS epi-
 196 demic,

$$x(t) = \frac{x_0 x_{eq}}{x_0 + (x_{eq} - x_0)e^{-\alpha t}}, \quad (4)$$

197 where $x_{eq} = 1 - \rho$, is the deterministic trajectory tracked by $X_t^{(N)}$ (the
 198 proportion of infected individuals). Variances and covariances are calculated
 199 as:

$$\Sigma_{i,j} = \begin{cases} V(t_i) & (i = j) \\ V(t_i) \left(\frac{x_0 + (x_{eq} - x_0)e^{-\alpha t_j}}{x_0 + (x_{eq} - x_0)e^{-\alpha t_i}} \right)^2 e^{-\alpha(t_j - t_i)} & (i < j), \end{cases} \quad (5)$$

200 where

$$\begin{aligned} V(t) = & x_0 x_{eq} \left[(1 + \rho) \left(x_0^3 (e^{2\alpha t} - 1) + 2(x_{eq} - x_0)^3 (1 - e^{-\alpha t}) \right. \right. \\ & \left. \left. - 6x_0^2 (x_{eq} - x_0) (1 - e^{\alpha t}) + 6x_0 \alpha t (x_{eq} - x_0)^2 \right) \right. \\ & \left. - x_0 x_{eq} \left(x_0^2 (e^{2\alpha t} - 1) - 4x_0 (x_{eq} - x_0) (1 - e^{\alpha t}) + 2t\alpha (x_{eq} - x_0)^2 \right) \right] \\ & \times \left[2(1 - \rho) e^{2\alpha t} (x_0 + (x_{eq} - x_0)e^{-\alpha t})^4 \right]^{-1}. \end{aligned} \quad (6)$$

201 It is not always possible to obtain explicit analytical expressions for the en-
 202 tries of $\mathbf{x}$ and Σ as we have done above. This is true for the SI(k)R and
 203 many other multi-dimensional epidemic models, where numerical solution of
 204 the system of first order ODEs is required to obtain the limiting determinis-
 205 tic trajectory. In the case of the time-inhomogeneous SI and SIS epidemics
 206 defined by (1) with $\lambda > 0$, simple analytical expressions are available for
 207 the deterministic trajectory, but the expression for the covariances is far to
 208 long to be written out here. In any case, the cross-covariance of observation
 209 vectors can be obtained easily by numerically integrating (3). Whilst numer-
 210 ical solution of these equations is obviously not as computationally efficient
 211 as evaluating explicit analytical expressions, the methodology presented here

212 can be used to find optimal experimental designs in a matter of minutes using
 213 a package such as Matlab.

214 For the poSI(k)R epidemic, our inability to observe anything other than
 215 I_{Total} at each observation time requires us to make some modifications to
 216 Σ and $\mathbf{x}$. We first compute Σ and $\mathbf{x}$ as if all dimensions of the process
 217 were being observed at each observation. It is then necessary to delete all
 218 of the entries from Σ and $\mathbf{x}$ that correspond to the unobserved dimensions
 219 of the process. Finally, we sum the k elements of $\mathbf{x}$ that correspond to the
 220 deterministic trajectories of infectious classes and also over the k^2 elements
 221 of Σ that correspond to the variances/covariances between infectious classes.
 222 This reduces Σ to the $n \times n$ covariance matrix of the random variables
 223 $I_{\text{Total}, t_1}, \dots, I_{\text{Total}, t_n}$. Similarly, $\mathbf{x}$ is reduced to the vector of length n , whose
 224 entries are the population densities of infected individuals at times $t_1, \dots, t_n$
 225 from the deterministic trajectory.

A computationally efficient method for calculating the likelihood of the observed data from the quantities $\mathbf{x}$ and Σ is outlined in Appendix B of Ross et al. (2009). The results are useful since the Markov property allows the multivariate normal likelihood to be written as a product of n d -dimensional Gaussian probability density functions. These density functions are approximations of transition density functions, conditional on previous states. The method is particularly useful for computing the approximate likelihood when the number of observations n and/or the dimension of the epidemic model d is large. It also facilitates efficient computation of Fisher information matrices, since these can be written as the sum of n independent matrices, with each component corresponding to one of the d -dimensional transition den-

sities. For relatively small values of nd , it is much simpler to compute the log-likelihood of the observations $\mathbf{y}$ as

$$\begin{aligned} \ell(\mathbf{y}; \boldsymbol{\theta}) = & -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log(|N\boldsymbol{\Sigma}(\boldsymbol{\theta})|) \\ & - \frac{1}{2N} (\mathbf{y} - N\mathbf{x}(\boldsymbol{\theta}))\boldsymbol{\Sigma}(\boldsymbol{\theta})^{-1}(\mathbf{y} - N\mathbf{x}(\boldsymbol{\theta}))^\top, \end{aligned} \quad (7)$$

where the dependence of $\mathbf{x}$ and $\boldsymbol{\Sigma}$ on $\boldsymbol{\theta}$ has been made explicit. The Fisher information matrix $\mathcal{I}$ for our Gaussian process (see Patan and Bogacka (2007)) has entries

$$\begin{aligned} \mathcal{I}_{i,j} = & \underbrace{N \left(\frac{\partial \mathbf{x}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}_i} \right) \boldsymbol{\Sigma}(\boldsymbol{\theta})^{-1} \left(\frac{\partial \mathbf{x}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}_j} \right)^\top}_{\mathcal{I}_{i,j}^{(1)}} \\ & + \underbrace{\frac{1}{2} \text{tr} \left(\boldsymbol{\Sigma}(\boldsymbol{\theta})^{-1} \left(\frac{\partial \boldsymbol{\Sigma}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}_i} \right) \boldsymbol{\Sigma}(\boldsymbol{\theta})^{-1} \left(\frac{\partial \boldsymbol{\Sigma}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}_j} \right) \right)}_{\mathcal{I}_{i,j}^{(2)}}, \end{aligned} \quad (8)$$

226 which are increasingly dominated by $\mathcal{I}_{i,j}^{(1)}$ as $N \rightarrow \infty$.

227 5. Optimal Design of Experimental Epidemics

228 We assume that, in an experimental epidemic, the practitioner controls:
 229 (i) the times at which the epidemic is observed, (ii) the initial conditions of
 230 the epidemic (the numbers of susceptible and infected individuals at $t_0 =$
 231 0), and (iii) the number of replicate epidemics. Here a replicate epidemic
 232 consists of a closed susceptible laboratory population into which infected
 233 individuals are introduced. Our designs are of the form $(\mathbf{x}_0, r, \mathbf{t})$, where
 234 $\mathbf{x}_0 = (x_{0,1}, \dots, x_{0,d}) \in (0, 1]^d$ ($\sum_{i=1}^d x_{0,i} = 1$) is the initial condition, r is the
 235 number of replicate epidemics and $t_1 < \dots < t_n \leq t_{max}$ ($t_i \in \mathbf{t}$) are the

236 times at which the epidemic is observed. Here, $[0, t_{max}]$ represents the avail-
 237 able time over which the experiment is conducted. Experimental constraints
 238 might also dictate an upper limit on the number of replicate epidemics r that
 239 can be run. Since the determinant of the Fisher information matrix increases
 240 monotonically with N (for fixed $\mathbf{t}$ and $\mathbf{x}_0$), the total population size should
 241 be as large as experimental resources will permit. Let N_{max} denote the max-
 242 imum number of organisms available for the experiment. We shall consider
 243 only those designs where we arrange the N_{max} individuals into r replicate
 244 populations of equal size, each having N_{max}/r . Since each of the r replicate
 245 experiments is independent, the Fisher information matrix for such a design
 246 is simply $\mathcal{I}((x_0, r, \mathbf{t}); \boldsymbol{\theta}) = r\mathcal{I}((x_0, 1, \mathbf{t}); \boldsymbol{\theta})$.

247 We aim to find D -optimal experimental designs so that observations of
 248 the epidemic result in the most precise estimates of the parameters. Let g be
 249 an experimental design in the set of possible designs $\mathcal{G}$. Then a D -optimal
 250 design g_{opt} satisfies

$$g_{opt} = \operatorname{argmax}_{g \in \mathcal{G}} \det(\mathcal{I}(g; \boldsymbol{\theta})). \quad (9)$$

251 As mentioned previously, g_{opt} is locally optimal (Chernoff, 1953), since $\mathcal{I}$ is
 252 a nonlinear function of $\boldsymbol{\theta}$. Design construction therefore relies either on some
 253 prior information about the parameters (Pronzato and Walter, 1985, 1988)
 254 or an educated guess at their values. The robustness of designs with respect
 255 to the initial guess is considered towards the end of the paper. Typically,
 256 a D -optimal design g_{opt} is compared to another design g using D -efficiency
 257 (see Atkinson et al. (2007)):

$$D_e = \left(\frac{\det(\mathcal{I}(g, \boldsymbol{\theta}))}{\det(\mathcal{I}(g_{opt}, \boldsymbol{\theta}))} \right)^{\frac{1}{p}}, \quad (10)$$

258 where p is the dimension of $\boldsymbol{\theta}$.

259 In some situations, we may only be interested in estimating a subset of
 260 the parameters $\boldsymbol{\theta}_s \subset \boldsymbol{\theta}$ of a model, with the other parameters considered
 261 nuisance parameters. Such designs are referred to as D_s -optimal designs and
 262 are essentially the same as the D -optimal design, but where $\mathcal{I}$ is restricted
 263 to terms involving only partial derivatives with respect to the elements of $\boldsymbol{\theta}_s$.
 264 We use D_s -optimal designs (Atkinson et al., 2007) to estimate (β, μ) for the
 265 SIS epidemic defined in (1) where it is believed that the transmission rates
 266 are time-homogeneous ($\lambda = 0$).

267 We use a stochastic optimization method known as the Cross-Entropy
 268 (CE) method (Rubinstein and Kroese, 2004) for obtaining optimal designs.
 269 We generate random designs of the form $(\mathbf{X}; T_1, \dots, T_n)$ with $0 \leq T_1 <$
 270 $T_2 < \dots < T_n \leq t_{max}$ and initial condition $\mathbf{X} \in (0, 1]^d$, where $\sum_{i=1}^d X_i =$
 271 1. Each observation time T_i ($i = 1, \dots, n$) and initial condition X_i ($i =$
 272 $1, \dots, d - 1$), is drawn from a beta probability density function with its own
 273 set of parameters. At each iteration, we select schedules satisfying $\det(\mathcal{I}) \geq$
 274 γ (where γ is chosen as, say, the 90th percentile of the objective function
 275 evaluations $\det(\mathcal{I})_1, \dots, \det(\mathcal{I})_m$). The selected schedules are used to update
 276 the parameters for each of the beta densities and the process is repeated until
 277 convergence is achieved. A detailed description of the algorithm is provided
 278 in Appendix B.

279 For the SIS and SI epidemics, the partial derivatives needed for computing
 280 $\mathcal{I}$ can be obtained analytically, but the expressions are long, so for brevity we
 281 assume that these terms are calculated numerically where required. For the
 282 poSI(k)R epidemic, the partial derivatives must be calculated numerically.

283 6. Design Performance

284 We begin by comparing the performance of three designs for each of the
 285 time-inhomogeneous SI, time-homogeneous SIS and poSI(k)R epidemics via
 286 a Monte Carlo study. Tables 1 and 2 detail the parameters and designs for
 287 each of these epidemic models. Figure 1 depicts the D -optimal designs (initial
 288 conditions and observation times) for these three models, assuming $r = 1$.
 289 The three designs considered were: (i) the D -optimal design, (ii) the D -
 290 optimal, equidistant design (where the times between successive observations
 291 are constrained to be equal), and (iii) a simple equidistant design, where the
 292 the initial number of infected individuals was set to 1, the observation times
 293 were equally spaced and the last observation made at t_{max} . For all three
 294 models we chose $t_{max} = 10$.

295 Table 2 summarizes our findings from 10,000 simulations of each model
 296 with each design. It is clear that the D -optimal design can offer a significant
 297 improvement in the accuracy and precision of the maximum likelihood esti-
 298 mator compared to the other two designs for the three models considered. For
 299 all three models, the D -optimal equidistant design performs almost as well as
 300 the D -optimal design and may be simpler to implement in practice. Simple
 301 equidistant designs typically perform relatively poorly and, in the case of the
 302 SIS epidemic, performance is abysmal, with extreme bias and imprecision
 303 in the maximum likelihood estimator. Such results arise when observations
 304 miss the initial drift phase of the process of this model. In general, cov-
 305 erage probabilities for the simple equidistant designs demonstrate that the
 306 confidence regions computed under these designs are often unreliable.

307 Our optimal designs detailed in Table 2 (including optimal initial condi-

Table 1: Parameter sets used for main SI, SIS and poSI(k)R epidemic examples.

Model	θ	Composition of $\mathbf{x}_0$
SI	$(\beta, \lambda) = (1.0, 0.5)$	$x_0 = i_0$
SIS ($\lambda = 0$)	$(\beta, \mu) = (4.0, 1.0)$	$x_0 = i_0$
poSI(4)R	$(\beta, \gamma) = (4.0, 4.0)$	$\mathbf{x}_0 = (s_0, i_0)$

Table 2: D -optimal/ D_s -optimal and alternative designs ($n = 3, N = 1000$) for the SI, SIS and poSI(k)R epidemic models listed in Table 1.

Model	Design	$\mathbf{t}$	$\mathbf{x}_0$
SI	D -opt.	(1.94, 4.57, 10.00)	0.224
	D -opt. eq.	(3.33, 6.67, 10.00)	0.209
	Simp. eq.	(3.33, 6.67, 10.00)	0.001
SIS	D_s -opt.	(1.45, 5.99, 10.00)	0.042
	D_s -opt. eq.	(1.58, 3.16, 4.74)	0.034
	Simp. eq.	(3.33, 6.67, 10.00)	0.005
poSI(4)R	D -opt.	(1.11, 2.01, 3.50)	(0.948, 0.052, 0, 0, 0)
	D -opt. eq.	(1.03, 2.06, 3.09)	(0.938, 0.062, 0, 0, 0)
	Simp. eq.	(3.33, 6.67, 10.00)	(0.995, 0.005, 0, 0, 0)

Figure 1: D -optimal designs ($n = 3, N = 1000$) for the models listed in Table 1 and simulated (grey) trajectories (shown with limiting deterministic trajectory ± 2 standard deviations as black lines) for: (a) the SI epidemic ($n = 3$); (b) the SIS epidemic ($n = 3$); (c and d) the poSI(4)R epidemic ($n = 3$).

Table 3: Properties of the maximum likelihood estimator for models listed in Table 1 with corresponding designs listed in Table 2.

Model	Design	95% Conf.Reg. Cover. Prob.	Bias($\hat{\theta}$)	Std. Dev.($\hat{\theta}$)
SI	D -opt.	0.952	(1.85 E-3, 1.18 E-3)	(7.35 E-2, 2.94E-2)
	D -opt. eq.	0.952	(4.94 E-3, 1.98 E-3)	(7.66E-2, 3.01E-2)
	Simp. eq.	0.624	(0.7198, 1.71967)	(1.83, 2.72)
SIS	D_s -opt.	0.934	(1.00 E-2, 4.16 E-4)	(0.23, 0.0114)
	D_s -opt. eq.	0.949	(2.36 E-2, -2.07 E-5)	(0.232, 1.15E-2)
	Simp. eq.	0.953	(3.72, -6.34 E-4)	(4.86, 1.01E-2)
poSI(4)R	D -opt.	0.93	(1.85 E-2, 1.50 E-3)	(0.191, 8.67E-2)
	D -opt. eq.	0.921	(5.05E-4, 2.01 E-3)	(0.188, 8.43E-2)
	Simp. eq.	0.003	(5.60, -1.54)	(1.35, 0.356)

tions) were identified using our CE method (detailed in Appendix B), however, we also conducted exploratory analyses to identify how important the initial conditions were to the optimality of a design. To investigate this, the precision of the maximum likelihood estimator was studied by looking at D -optimal designs ($n = 3$, $r = 1$) for the SIS epidemic. Figure 2 shows the dramatic loss of precision that can occur when x_0 is varied over a number of values between 0.02 and 0.95 and compares the distributions of the maximum likelihood estimators. For each of the initial conditions, 1000 SIS epidemics were simulated and maximum likelihood estimates obtained under the corresponding D -optimal design. A two-dimensional kernel density estimation routine for Matlab (Botev et al., 2010) was then used to compare the maximum likelihood estimators under these designs. The parameter values chosen were $x_{eq} = 0.75$, $\alpha = 3.0$ and $\rho = 0.25$. We observe that the estimator behaves particularly poorly when $x_0 = x_{eq}$. This is perhaps not surprising, since no drift towards equilibrium is observed, providing little information about α . Figure 3 depicts the change in the D -efficiency as a function of x_0 for D -optimal designs under a number of different parameters. Typically, the worst designs are those where $x_0 = x_{eq}$, however, we also observe a loss of precision when x_0 is allowed to stray close to 0. The observed results are a consequence of very small values of x_0 generally resulting in larger variances for Σ , rather than as a result of there being a greater probability of the process being absorbed, although the latter point highlights an additional reason to avoid such designs.

Figure 4 shows the change in D -efficiency as s_0 (the initial proportion susceptible) is varied for the poSI(4)R epidemic. To demonstrate the accu-

Figure 2: Density estimates for the maximum likelihood estimator using 1000 simulated trajectories of the SIS epidemic (as per Table 1) and point estimates derived using D -optimal designs ($n=3$) for various values of x_0 .

Figure 3: D -optimal designs ($n = 3$) obtained for various values of x_0 with $N = 1000$ and different values of β and μ ($\lambda = 0$). D -efficiency is measured relative to the best of the optimal designs for each parameter set.

333 racy of our methods in identifying optimal designs, we also include estimates
 334 of the D -efficiency of the design based on Monte Carlo simulations. For
 335 each of the points plotted in Figure 4, we simulated 100 trajectories of the
 336 epidemic, obtained maximum likelihood estimates under the corresponding
 337 D -optimal designs (s_0 fixed) and calculated the observed Fisher information
 338 matrix $\mathcal{I}^{\text{obs}}$, having entries $\mathcal{I}_{i,j}^{\text{obs}} = -\partial^2 \ell(\mathbf{y}; \boldsymbol{\theta}) / \partial \theta_i \partial \theta_j$ evaluated at $\boldsymbol{\theta} = \hat{\boldsymbol{\theta}}$ ($\hat{\boldsymbol{\theta}}$
 339 being the maximum likelihood estimate). The average value of the 100 ob-
 340 served information matrices was then computed, denoted as $\bar{\mathcal{I}}^{\text{obs}}$ and plugged
 341 into (10) in place of $\mathcal{I}$. There is clearly very good agreement between the
 342 theoretical D -efficiency obtained under the diffusion approximation and the
 343 D -efficiency obtained through simulation, and it appears that our method is
 344 highly effective at identifying the optimal initial conditions.

345 We now turn attention to the issue of whether to run one large or several
 346 smaller experimental epidemics. Notice that the elements of $\mathcal{I}$ have two
 347 additive components, $\mathcal{I}_{i,j}^{(1)}$ being $O(N)$, and $\mathcal{I}_{i,j}^{(2)}$ being $O(1)$. Suppose there
 348 was a pool of 1000 individuals available for an experimental SI epidemic
 349 and 2 possible designs were under consideration: (i) a design that uses one
 350 large epidemic having $N = 1000$, and (ii) a design that uses 2 replicate
 351 epidemics, each having $N = 500$. Suppose also that x_0 and $\mathbf{t}$ are chosen so
 352 as to be optimal for the first experiment and we use the same design for both
 353 experiments. In the case of the SI epidemic, $\mathcal{I}$ is a scalar, so that for the first
 354 experiment we have $\mathcal{I}_a = 1000\mathcal{I}^{(1)} + \mathcal{I}^{(2)}$ and, since the Fisher information
 355 is additive for independent experiments, for the second experiment we have
 356 $\mathcal{I}_b = 1000\mathcal{I}^{(1)} + 2\mathcal{I}^{(2)}$. This indicates that $\mathcal{I}_b > \mathcal{I}_a$ under a design which was
 357 not even chosen to be optimal for the second experiment (so, in theory, it can

Figure 4: D -efficiency of D -optimal designs ($n = 3$) with fixed initial conditions for the poSI(4)R epidemic (as per Table 1).

358 potentially do better yet). However, the argument outlined above overlooks
 359 the very important point that calculation of $\mathcal{I}$ is based on an approximation,
 360 which improves as $N \rightarrow \infty$. Thus, comparing $\mathcal{I}$ for two experiments with
 361 different values of N is likely to result in errors. Figure 5 shows D -efficiencies
 362 of D -optimal designs using 1, 2, 4, 5 and 10 possible replicate epidemics from
 363 a pool of 5000 individuals for the SI, SIS and poSI(k)R epidemics. Each plot
 364 overlays the D -efficiency computed under the diffusion approximation with
 365 the D -efficiency computed by simulating 10,000 data sets for each replicate
 366 experiment for which D -efficiency was computed using $\bar{\mathcal{I}}_{\text{obs}}$ as before. The
 367 results highlight that the diffusion approximation should not be used for
 368 comparing the efficiency of experiments having different values of N . In fact,
 369 for the models considered here, the diffusion approximation gives precisely
 370 the *wrong* answer, since simulation suggests a small number of replicates is
 371 most efficient for all three models. In general, it appears that best practice is
 372 to use a very small number of replicate experiments, with the loss in efficiency
 373 associated with additional replicates being relatively minor.

374 **7. Robustness**

375 Finally, we consider the robustness of D -optimal designs to misspecifica-
 376 tion of the parameters for our three models. As mentioned previously, our
 377 D -optimal designs require us to have knowledge of the model parameters.
 378 Suppose that we guess the parameter θ to be θ_{guess} , so the percentage error
 379 in our guess equals $100 \times \frac{\theta_{\text{guess}} - \theta}{\theta}$. Figure 6 (a) shows the relative efficiency
 380 of D -optimal designs created with varying amounts of error in the design pa-
 381 rameters. For the SI epidemic, relative efficiency declines steeply if $\beta_{\text{guess}} - \beta$

Figure 5: D -efficiencies of experimental epidemics ($n = 2$), with 5000 individuals divided equally between r replicate experiments for: (a) the SI epidemic ($\beta = 1.0, \lambda = 0.5$); (b) the SIS epidemic ($\beta = 4.0, \mu = 1.0, \lambda = 0$); and (c) the poSI(1)R epidemic ($\beta = 4.0, \gamma = 1.0$). Solid lines connect the values calculated under the Gaussian diffusion approximation, whilst dashed lines connect the values calculated via simulation.

382 is negative compared to when it is positive. This occurs because trajec-
 383 tories are more likely to reach the absorbing state before all observations have
 384 been taken when β_{guess} is too small. Relative efficiency for the SIS epidemic
 385 (Figure 6 (b)) shows a similar response for the drift parameter α , because
 386 when α_{guess} is too small, observations are unlikely to be scheduled during the
 387 drift phase, missing vital information about α . Interestingly, designs for the
 388 SIS epidemic appear to be relatively insensitive to errors in ρ for the values
 389 considered here. For the poSI(1)R epidemic (Figure 6 (c)), we again observe
 390 some similar behaviour to the contours of the SIS epidemic, with relative ef-
 391 ficiency declining steeply when $\beta_{guess} - \beta$ is negative and insensitivity to error
 392 in γ . One interesting feature of Figure 6 (c) is that the relative efficiency
 393 increases in the bottom right corner, as the error in γ becomes large and

Figure 6: Relative efficiencies of optimal designs for: (a) the SI epidemic ($N = 1000$, any β) with error in β_{guess} ; (b) the SIS epidemic ($N = 1000$, $\alpha = 3.0$, $\rho = \frac{1}{4}$) with error in α_{guess} and ρ_{guess} (contour plot); and (c) the poSI(1)R epidemic ($N = 1000$, $\beta = 4.0$, $\gamma = 1.0$) with error in β_{guess} and γ_{guess} (contour plot).

positive and the error in β becomes large and negative. This occurs because when $\beta_{\text{guess}} - \beta$ is negative, there is a tendency for observations to occur later, but when $\gamma_{\text{guess}} - \gamma$ is positive, observations tend to be taken earlier, thus the effects of the combined errors on the design are reduced to some extent and we see an increase in the relative efficiency in the lower left region of the figure.

400 8. Conclusion

We have presented a general approach to optimal experimental design for epidemics and other density dependent Markov processes. Our methods rely on the use of Gaussian diffusion approximations which are valid when the system size (usually number of individuals) is relatively large (say $N > 100$).

405 The CE method outlined in Appendix B allows for efficient calculation of
 406 these designs. Whilst we have used D-optimality throughout this exposi-
 407 tion, our methods also work very well with other optimal design criteria,
 408 such as A-optimality and E-optimality. We have demonstrated the impor-
 409 tant effects that observation times, initial conditions and replications can
 410 have on the efficiency of such experiments through three example models:
 411 the time-inhomogeneous SI, time-homogeneous SIS and poSI(k)R epidemics.
 412 Whilst our focus has been on these examples, the class of models to which
 413 this methodology can be applied (DDMPs) is very rich indeed. These meth-
 414 ods and our analysis will be informative to practitioners in fields such as
 415 experimental epidemiology and biological control.

416 **Appendix A. Gaussian Diffusion Approximations**

417 Let $\mathbf{Y}_t^{(N)}$ ($t \geq 0$) be a d -dimensional continuous-time Markov process with
 418 state space $\mathcal{S}^{(N)} \subseteq \mathbb{Z}^d$ indexed by N . Let $Q(t) = (q(\mathbf{m}, \mathbf{n}; t), \mathbf{m}, \mathbf{n} \in \mathcal{S}^{(N)})$
 419 be a stable and conservative set of (possibly time-dependent) transition rates;
 420 $q(\mathbf{m}, \mathbf{n}; t)$ is the transition rate from state $\mathbf{m}$ to $\mathbf{n}$ ($\mathbf{n} \neq \mathbf{m}$) at time t and
 421 $q(\mathbf{m}, \mathbf{m}; t) := -q(\mathbf{m}; t)$, where $q(\mathbf{m}; t) = \sum_{\mathbf{n} \neq \mathbf{m}} q(\mathbf{m}, \mathbf{n}; t)$ ($< \infty$) is the
 422 total rate out of state $\mathbf{m}$ at time t .

Definition 1. Suppose there is an open set $E \subseteq \mathbb{R}^d$ and a function $f : E \times \mathbb{Z}^d \times [0, \infty) \rightarrow \mathbb{R}$ such that

$$q(\mathbf{m}, \mathbf{m} + \mathbf{l}; t) = Nf\left(\frac{\mathbf{m}}{N}, \mathbf{l}; t\right) \quad (\mathbf{m} \in \mathcal{S}^{(N)}, \mathbf{l} \in \mathbb{Z}^d, \mathbf{l} \neq 0, t \geq 0).$$

423 Then, the family $\{\mathbf{Y}_t^{(N)}\}$ of Markov processes is said to be density dependent.

The process $\mathbf{X}_t^{(N)}$, defined by $\mathbf{X}_t^{(N)} = \mathbf{Y}_t^{(N)}/N$ ($t \geq 0$), is called the *density process*. In the time-homogeneous case, where Q does not depend on t , Kurtz Kurtz (1970) proved a functional law, which, as noted by Barbour Barbour (1974), extends to the time-inhomogeneous case. This law stipulates that, for large values of N , the density process ‘tracks’ a deterministic trajectory $\mathbf{x}(t)$ satisfying $d\mathbf{x}/dt = F(\mathbf{x}; t)$, where $F : E \times [0, \infty) \rightarrow \mathbb{R}$ is given by

$$F(\mathbf{x}; t) = \sum_{\mathbf{l}} \mathbf{l} f(\mathbf{x}, \mathbf{l}; t) \quad (\mathbf{x} \in E).$$

424 More precisely, we have the following result (whilst more general statements
425 are available, the conditions given here are easy to check, and are satisfied
426 by many biological models of interest, including all of the epidemic models
427 considered in our paper).

Theorem 1. *Suppose that, for each $\mathbf{l} \neq 0$, $f(\mathbf{x}, \mathbf{l}; t)$ is continuous in t , uniformly in $\mathbf{x} \in E$, and that F satisfies the Lipschitz condition $|F(\mathbf{x}; t) - F(\mathbf{y}; t)| < M_E |\mathbf{x} - \mathbf{y}|$ ($\mathbf{x}, \mathbf{y} \in E$), for some constant M_E . Then, as $N \rightarrow \infty$, $\mathbf{X}_t^{(N)}$ converges uniformly in probability over finite time intervals $[0, t]$ to the unique deterministic trajectory satisfying*

$$\mathbf{x}(0) = \mathbf{x}_0,$$

$$\mathbf{x}(s) \in E \quad (0 \leq s \leq t) \quad \text{and}$$

$$\frac{d}{ds} \mathbf{x}(s) = F(\mathbf{x}(s); s).$$

That is to say, for fixed $t > 0$ and for all $\epsilon > 0$,

$$\lim_{N \rightarrow \infty} \mathbb{P} \left(\sup_{s \leq t} |\mathbf{X}_s^{(N)} - \mathbf{x}(s)| > \epsilon \right) = 0.$$

428 **Remark 1.** *Note that the continuity condition will hold if, as is commonly*
 429 *the case in applications, $f(\mathbf{x}, \mathbf{l}; t)$ is a multinomial function in the coordinate*
 430 *variables $x_1, \dots, x_d$. The Lipschitz condition will certainly then hold if E is a*
 431 *finite set.*

432 Kurtz Kurtz (1971) also established a functional central limit law stip-
 433 ulating that, for large N , the fluctuations of the scaled density process
 434 $\mathbf{Z}_t^{(N)} = \sqrt{N}(\mathbf{X}_t^{(N)} - \mathbf{x}(t))$ follow a Gaussian diffusion. Following Barbour Bar-
 435 bour (1972, 1974), we have the following result.

Theorem 2. *In addition to the conditions of Theorem 1, suppose that F*
has uniformly continuous first partial derivatives, and that the $d \times d$ matrix
 $G(\mathbf{x}; t)$ with entries

$$g_{ij}(\mathbf{x}; t) = \sum_{\mathbf{l}} l_i l_j f(\mathbf{x}, \mathbf{l}; t) \quad (\mathbf{x} \in E, t \geq 0)$$

is bounded and uniformly continuous on E . If

$$\lim_{N \rightarrow \infty} \sqrt{N} (\mathbf{X}_0^{(N)} - \mathbf{x}_0) = \mathbf{z},$$

then $\mathbf{Z}_s^{(N)}$ ($0 \leq s \leq t$) converges weakly in $D[0, t]$ (the space of right-continuous
functions with left limits on $[0, t]$) to a Gaussian diffusion $\mathbf{Z}_s$ ($0 \leq s \leq t$)
with initial value $\mathbf{Z}_0 = \mathbf{z}$ and characteristic function $\psi = \psi(t, \theta)$ satisfying

$$\frac{\partial \psi}{\partial t}(t, \theta) = -\frac{1}{2} \sum_{j,k} \theta_j \theta_k g_{jk}(\mathbf{x}(t); t) \psi(t, \theta) + \sum_{j,k} \theta_j h_{jk}(\mathbf{x}(t); t) \frac{\partial \psi}{\partial \theta_k}(t, \theta),$$

436 *where $h_{jk}(\mathbf{x}; t) = \partial F_j(\mathbf{x}; t) / \partial x_k$.*

437 **Remark 2.** *The additional conditions of Theorem 2 will also hold if $f(\mathbf{x}, \mathbf{l}; t)$*
 438 *is multinomial.*

Appendix A of Ross et al. (2009) provides simple expressions for the expected value and covariance of $\mathbf{Z}_t$, which can be extended in an obvious way to the present case. Let $\mathbf{M}_s = \exp(\int_0^s \mathbf{H}(\mathbf{x}(u); u) du)$, where $\mathbf{H}(\mathbf{x}; t)$, the Jacobian matrix of $F(\mathbf{x}; t)$, has entries $h_{jk}(\mathbf{x}; t)$. Then, $\mathbb{E}(\mathbf{Z}_t) = \mathbf{M}_t \mathbf{z}$ and

$$\text{Cov}(\mathbf{Z}_t, \mathbf{Z}_{t+s}) = \mathbf{M}_t \int_0^t \mathbf{M}_u^{-1} \mathbf{G}(\mathbf{x}(u); u) (\mathbf{M}_u^{-1})^\top du \mathbf{M}_{t+s}^\top \quad (s \geq 0).$$

439 Appendix B. A Cross-Entropy Method for the Optimal Design

440 We employ the Cross-Entropy (CE) method of stochastic optimisation Rubinstein and Kroese (2004) for identifying optimal initial conditions and ob-
 441 servation times. It operates in the present context by randomly generating
 442 designs of the form $(\mathbf{X}; T_1, \dots, T_n)$ with $0 \leq T_1 < T_2 < \dots < T_n \leq t_{max}$ and
 443 initial condition $\mathbf{X} \in (0, 1]^d$, where $\sum_{i=1}^d X_i = 1$, and d is the dimension of
 444 the epidemic. With each step of the routine, the top performing designs are
 445 used to update the parameters of the probability distributions (from which
 446 the random designs were generated). Ideally, this updating is done using
 447 their maximum likelihood estimates, however, since there is no closed form
 448 for the parameters of the beta distribution, we approximate using the method
 449 of moments estimators. With each iteration, the means of the probability
 450 densities converge towards the values corresponding to the optimal obser-
 451 vation times/optimal initial conditions and the variances decrease towards
 452 0.
 453

454 Our implementation of the CE method generates observation times on
 455 the interval $[0, t_{max}]$ and initial conditions on $(0, 1]^d$ using beta probability
 456 distributions, each with parameter vector $\boldsymbol{\nu}_i = (\alpha_i, \beta_i)$. The probability dis-
 457 tributions are initiated with parameter vectors $(1, 1)$, so that the densities

are uniform on the interval under consideration. Updating is done according to the algorithm described below, and is based upon recommendations in Rubinstein and Kroese (2004).

Appendix B.1. Cross-Entropy Algorithm

1. Define values for t_{max} , n , d , δ_{min} , y_0 , $\boldsymbol{\theta}$ and N .
2. Set the following parameter values controlling parameter updating: $\eta = 0.9$, $s_1 = 0.7$, $s_2 = 0.7$ and $s_3 = 5$. These parameters are used to ensure the optimisation routine takes a ‘smooth’ trajectory through the solution space and does not converge to a sub-optimal solution.
3. Set the maximum variance threshold, which is used to end the optimisation routine, to be $\epsilon = 10^{-5}$.
4. Set the timestep $k = 0$ and the initial parameter vectors $\boldsymbol{\theta}_i$ for each of $n + d - 1$ beta probability density functions $f_i(x_i; \boldsymbol{\nu}_i)$ for $i = 1, \dots, d - 1$ and $f_i(t_i; \boldsymbol{\nu}_i)$ for $i = d, \dots, n + d - 1$ as $(1, 1)$.
5. Create m designs $\mathbf{D}_{1,k}, \dots, \mathbf{D}_{m,k}$, such that the i th element of each design is generated from the beta probability density function $f_i(\cdot; \alpha_{i,k}, \beta_{i,k})$, where

$$\mathbf{D}_{j,k} = (X_{1,j,k}, \dots, X_{d-1,j,k}; T_{1,j,k}, \dots, T_{n,j,k}).$$

In addition, a rejection step is introduced to retain only those designs where the observation times satisfy $0 < T_1 < \dots < T_n \leq t_{max}$ and $\sum_{i=1}^{d-1} X_i \leq 1$. One can also impose $T_i - T_{i-1} \geq \delta_{min}$, $(1 \leq i \leq n; \delta_{min} \geq$

0) if desired. These observation times do not include the mandatory initial observation at $t = 0$. The beta probability density functions defined on the interval $[0, t_{max}]$ have the form:

$$f_i^{(t)}(t_i; \alpha_{i,k}^{(t)}, \beta_{i,k}^{(t)}) = \frac{\left(\frac{t_i}{t_{max}}\right)^{\alpha_{i,k}^{(t)}-1} \left(1 - \frac{t_i}{t_{max}}\right)^{\beta_{i,k}^{(t)}-1}}{B(\alpha_{i,k}^{(t)}, \beta_{i,k}^{(t)})},$$

whilst the beta density for the the initial conditions are:

$$f_i^{(x)}(x_i; \alpha_{i,k}^{(x)}, \beta_{i,k}^{(x)}) = \frac{x_i^{\alpha_{i,k}^{(x)}-1} (1 - x_i)^{\beta_{i,k}^{(x)}-1}}{B(\alpha_{i,k}^{(x)}, \beta_{i,k}^{(x)})},$$

477 where $B(\alpha, \beta)$ is the beta function $B(\alpha, \beta) = \Gamma(\alpha)\Gamma(\beta)/\Gamma(\alpha + \beta)$.

478 6. Calculate the performance (D-optimality) $p_{1,k}, \dots, p_{m,k}$ of each of the
479 m designs by calculating the determinant of the Fisher information
480 matrix, $\det(\mathcal{I}(\boldsymbol{\theta}, \mathbf{D}_{j,k}))$.

481 7. Calculate the η -quantile of $p_{1,k}, \dots, p_{m,k}$ and record this as q_k .

8. Let $D_{i,j,k}$ denote the i th design point (time or initial condition) of $\mathbf{D}_{j,k}$. Calculate the mean and variance of each design point at the k th time step as follows:

$$\bar{D}_{i,k} = \begin{cases} s_1 \left(\frac{\sum_{j=0}^m I_{\{p_{j,k} \geq q_k\}} D_{i,j,k}}{\sum_{j=0}^m I_{\{p_{j,k} \geq q_k\}}} \right) \\ \quad + (1 - s_1) \bar{D}_{i,k-1} \quad (k \geq 1), \\ \frac{\sum_{j=0}^m I_{\{p_{j,k} \geq q_k\}} D_{i,j,k}}{\sum_{j=0}^m I_{\{p_{j,k} \geq q_k\}}} \quad (k = 0), \end{cases}$$

$$\text{Var}(D_{i,k}) = \begin{cases} \left[u_k \left(\frac{\sum_{j=0}^m (I_{\{p_{j,k} \geq q_k\}} D_{i,j,k} - \text{Mean}(D_{i,k}))^2}{\sum_{j=0}^m I_{\{p_{j,k} \geq q_k\}}} \right)^{\frac{1}{2}} \right. \\ \left. + (1 - u_k)(\text{Var}(D_{i,k-1}))^{1/2} \right]^2 & (k \geq 1), \\ \frac{\sum_{j=0}^m (I_{\{p_{j,k} \geq q_k\}} D_{i,j,k} - \text{Mean}(D_{i,k}))^2}{\sum_{j=0}^m I_{\{p_{j,k} \geq q_k\}}} & (k = 0), \end{cases}$$

and

$$u_k = s_2 - s_2 \left(1 - \frac{1}{k} \right)^{s_3}.$$

- 482 9. Update the time step: $k = k + 1$.
10. Update the parameter vectors for each of the beta probability densities, in such a way that the density giving rise to the i th design point has parameters

$$\alpha_{i,k}^{(\cdot)} = \frac{\frac{r_{i,k}}{(1+r_{i,k})^2} - \text{Var}(D_{i,k})}{(\text{Var}(D_{i,k})(1+r_{i,k}))} \quad \text{and} \quad \beta_{i,k}^{(\cdot)} = \frac{\alpha_{i,k}^{(\cdot)} - \bar{D}_{i,k} \alpha_{i,k}^{(\cdot)}}{\bar{D}_{i,k}},$$

483 where $r_{i,k} = (1 - \bar{D}_{i,k})/\bar{D}_{i,k}$.

- 484 11. If $\max_i \text{Var}(D_{i,k}) \leq \epsilon$, then return the vector $(\bar{D}_{1,k}, \bar{D}_{2,k}, \dots, \bar{D}_{n+d-1,k})$
- 485 or $(\bar{D}_{1,k}, \dots, \bar{D}_{n,k})$ and terminate the routine, otherwise return to step
- 486 5.

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