

Experimental Design for Distributed Parameter Vector Systems

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Abstract

We formulate an optimal design problem for the selection of best states to observe and optimal sampling times and locations for parameter estimation or inverse problems involving complex nonlinear partial differential systems. An iterative algorithm for implementation of the resulting methodology is proposed.

Key words: Optimal design, inverse problems, optimal selection of observables and sampling points.

1 Introduction

We outline a design framework based on the Fisher Information Matrix (FIM) for a system of partial differential equations (PDEs) to determine when and where an experimenter should take samples and what variables to measure in collecting information on a physical or biological process that is modeled by a vector distributed system. The framework is intended for use in inverse problem methodologies in the context of dynamical system or mathematical model parameter estimation when a sufficient number of observations of one or more states (variables) are available. Experimental design using the Fisher Information Matrix (FIM), which is based on sensitivity matrices (traditional and generalized), is described in [2] for the case of scalar data. In [3], the authors develop an experimental design theory using the FIM to identify optimal sampling times for experiments on physical processes (modeled by an ODE system) in which scalar or vector data will be taken. In addition to when and where to take samples, the question of *what variables to measure* is also very important in designing effective experiments, especially when the *number of state variables is large*.

Building on the theory in [3], we formulate a previously unexplored optimal design problem to determine not only the optimal sampling variables out of a finite set of possible sampling variables but also the optimal sampling time and spatial distribution during a fixed experimental interval. We consider formulations for the SE-optimal design introduced in [2] along with the well-known methods of D-optimal and E-optimal design. The formulations we propose have been successfully used with several models [4] including an experimentally validated six-compartment HIV model and a thirty-eight dimensional enzyme kinetics model of the Calvin Cycle in spinach. Such models where there may be a wide range of variables to possibly observe are not only ideal on which to test our proposed methodology, but also are widely encountered in applications.

2 Mathematical and Statistical Models

The methodology we present can be readily applied to problems involving ordinary, partial and delay differential equations dynamics. We explore our experimental design questions using a **mathematical model** (here we illustrate with a partial differential equation that is first order in time and second order in space)

$$\frac{\partial \vec{u}}{\partial t} = \mathcal{F}(t, x, \vec{u}, \frac{\partial \vec{u}}{\partial x}, \frac{\partial^2 \vec{u}}{\partial x^2}, \vec{\theta}), \quad t \in [t_0, t_f], x \in [x_0, x_f] \quad (1)$$

with appropriate boundary and initial conditions, where $\vec{u}(t, x; \vec{\theta})$ is the m -vector of state variables of the system generated using a parameter vector $\vec{\theta} \in \mathbb{R}^p$. We define a corresponding **observation process**

$$\vec{f}(t, x; \vec{\theta}) = C\vec{u}(t, x; \vec{\theta}), \quad (2)$$

where C is an observation operator that maps $\mathbb{R}^m \rightarrow \mathbb{R}^N$, where $N < m$ is the number of variables observed at a single sampling time and location. Of course the full state observation involves $N = m$; however, this is most often not the case (due to the impossibility of or the expense in measuring all state variables such as in the plant metabolite example with 38 states studied in [4]). In other cases (such as the HIV example studied in [4]) we may be able to directly observe only combinations (e.g., total CD4+ cell counts including both uninfected and infected cells) of the states.

In order to discuss uncertainty in parameter estimates, we formulate a **statistical model** [5] of the form (this corresponds to an ordinary least squares optimal fit to data formulation)

$$\vec{Y}(t, x) = \vec{f}(t, x; \vec{\theta}_0) + \vec{\mathcal{E}}(t, x), \quad t \in [t_0, t_f], x \in [x_0, x_f], \quad (3)$$

where $\vec{\theta}_0$ is the hypothesized true values of the unknown parameters and $\vec{\mathcal{E}}$ is a vector random process that represents observation error for the measured variables. We make the standard assumptions that the errors are uncorrelated and independent with diagonal covariances $\text{Var}(\vec{\mathcal{E}}(t, x)) = V_0(t, x) = \text{diag}(\sigma_{0,1}(t, x)^2, \sigma_{0,2}(t, x)^2, \dots, \sigma_{0,N}(t, x)^2)$, $t \in [t_0, t_f]$, $x \in [x_0, x_f]$. Realizations of the statistical model (3) are written

$$\vec{y}(t, x) = \vec{f}(t, x; \vec{\theta}_0) + \vec{e}(t, x), \quad t \in [t_0, t_f], x \in [x_0, x_f].$$

When collecting experimental data, it is often difficult to take continuous measurements of the observed variables. Instead, we assume that we have kn observations at sampling points (t_i, x_j) , $i = 1, \dots, k$, $j = 1, \dots, n$, in periods $[t_0, t_f] \times [x_0, x_f]$. We then write the observation process (2) as

$$\vec{f}(t_i, x_j; \vec{\theta}) = C\vec{u}(t_i, x_j; \vec{\theta}), \quad i = 1, \dots, k, j = 1, \dots, n, \quad (4)$$

the discrete statistical model as

$$\vec{Y}_{ij} = \vec{f}(t_i, x_j; \vec{\theta}_0) + \vec{\mathcal{E}}(t_i, x_j), \quad i = 1, \dots, k, j = 1, \dots, n, \quad (5)$$

and a realization of the discrete statistical model as

$$\vec{y}_{ij} = \vec{f}(t_i, x_j; \vec{\theta}_0) + \vec{e}(t_i, x_j), \quad i = 1, \dots, k, j = 1, \dots, n.$$

Given a set of data \vec{y}_{ij} , we could attempt to estimate $\vec{\theta}_0$ in a process known as the **inverse problem**. We will use this mathematical and statistical framework to outline a methodology to identify sampling variables that provide the most information pertinent to estimating a given set of parameters as well as the most informative times and locations at which the samples should be taken.

3 Formulation of the Optimal Design Problem

We propose an optimal design problem formulation using a generalized weighted least squares criterion.

Let $\mathcal{P}(a, b)$ denote the set of all bounded distributions on the interval $[a, b]$. We consider the generalized weighted least squares cost functional for systems with vector output

$$J_{WLS}(\vec{y}, \vec{\theta}) = \int_{x_0}^{x_f} \int_{t_0}^{t_f} [\vec{y}(t, x) - \vec{f}(t, x; \vec{\theta})]^T V_0^{-1}(t, x) [\vec{y}(t, x) - \vec{f}(t, x; \vec{\theta})] dP_1(t) dP_2(x), \quad (6)$$

where $P_1, P_2 \in \mathcal{P}$ are general measures on the intervals $[t_0, t_f], [x_0, x_f]$, respectively. For a given continuous data set $\vec{y}(t, x)$, we search for a parameter $\hat{\theta}$ that minimizes $J_{WLS}(\vec{y}, \vec{\theta})$.

We next consider the case of observations collected at discrete points (t_i, x_j) . If we choose a set of kn time and space points $\tau = \{(t_i, x_j)\}, i = 1, \dots, k, j = 1, 2, \dots, n$, and take

$$P(t, x) = P_1(t)P_2(x) = P_\tau = \sum_{i,j=1}^{k,n} \delta_{(t_i, x_j)}, \quad (7)$$

where δ_a represents the Dirac delta distribution with atom at a , then the weighted least squares criterion (6) for a finite number of observations becomes

$$J_{WLS}^n(\vec{y}, \vec{\theta}) = \sum_{i,j=1}^{k,n} [\vec{y}(t_i, x_j) - \vec{f}(t_i, x_j; \vec{\theta})]^T V_0^{-1}(t_i, x_j) [\vec{y}(t_i, x_j) - \vec{f}(t_i, x_j; \vec{\theta})].$$

To select a useful distribution of sampling points and set of observation variables, we introduce the $N \times p$ sensitivity matrices $\left[\frac{\partial \vec{f}(t, x; \vec{\theta})}{\partial \vec{\theta}} \right]$ and the $m \times p$ sensitivity matrices $\left[\frac{\partial \vec{u}(t, x; \vec{\theta})}{\partial \vec{\theta}} \right]$ that are determined using the differential operator in row vector form $(\partial_{\theta_1}, \partial_{\theta_2}, \dots, \partial_{\theta_p})$ represented by $\nabla_{\vec{\theta}}$ and the observation operator defined in (2),

$$\nabla_{\vec{\theta}} \vec{f}(t, x; \vec{\theta}) = \frac{\partial \vec{f}(t, x; \vec{\theta})}{\partial \vec{\theta}} = C \frac{\partial \vec{u}(t, x; \vec{\theta})}{\partial \vec{\theta}} = C \nabla_{\vec{\theta}} \vec{u}(t, x; \vec{\theta}). \quad (8)$$

Using the sensitivity matrix $\nabla_{\vec{\theta}} \vec{f}(t, \vec{\theta}_0)$, we may formulate the GFIM. Consider the set $\mathcal{C} \subset \mathbb{R}^m$ of admissible observation maps and let $\mathcal{P}_0(\mathcal{C})$ represent the set of all bounded distributions $P_0(c)$ on \mathcal{C} . Then the GFIM may be written

$$\begin{aligned} \mathcal{F}(P_2, P_1, P_0, \vec{\theta}_0) &\equiv \int_{x_0}^{x_f} \int_{t_0}^{t_f} \int_{\mathcal{C}} \frac{1}{\sigma^2(t, x; c)} (\nabla_{\vec{\theta}} \vec{f}(t, x; \vec{\theta}_0))^T \nabla_{\vec{\theta}} \vec{f}(t, x; \vec{\theta}_0) dP_0(c) dP_1(t) dP_2(x) \quad (9) \\ &= \int_{x_0}^{x_f} \int_{t_0}^{t_f} \int_{\mathcal{C}} \frac{1}{\sigma^2(t, x; c)} \left(\nabla_{\vec{\theta}} c^T \vec{u}(t, x; \vec{\theta}_0) \right)^T \nabla_{\vec{\theta}} c^T \vec{u}(t, x; \vec{\theta}_0) dP_0(c) dP_1(t) dP_2(x). \quad (10) \end{aligned}$$

Taking N different sampling maps in \mathcal{C} represented by the m -dimensional vectors $c_l, l = 1, 2, \dots, N$, we construct the discrete distribution on \mathcal{C} given by $P_C = \sum_{l=1}^N \delta_{c_l}$, where δ_a again represents the Dirac delta distribution with atom at a . Using P_C in (10), we obtain the GFIM for multiple discrete observation methods taken continuously over $[t_0, t_f] \times [x_0, x_f]$,

$$\begin{aligned}
\mathcal{F}(P_2, P_1, P_C, \vec{\theta}_0) &= \int_{x_0}^{x_f} \int_{t_0}^{t_f} \sum_{l=1}^N \frac{1}{\sigma^2(t, x; c_l)} \left(\nabla_{\vec{\theta}} c_l^\top \vec{u}(t, x; \vec{\theta}_0) \right)^\top \nabla_{\vec{\theta}} c_l^\top \vec{u}(t, x; \vec{\theta}_0) dP_1(t) dP_2(x) \\
&= \int_{x_0}^{x_f} \int_{t_0}^{t_f} \nabla_{\vec{\theta}} \vec{u}(t, x; \vec{\theta}_0)^\top \left(C^\top V_0^{-1}(t, x) C \right) \nabla_{\vec{\theta}} \vec{u}(t, x; \vec{\theta}_0) dP_1(t) dP_2(x), \quad (11)
\end{aligned}$$

where $C = (c_1, c_2, \dots, c_N)^\top \in \mathbb{R}^{N \times m}$ is the observation operator in (2) and (4) and $V_0(t) \in \mathbb{R}^{N \times N}$ is the covariance matrix as described in (3). Applying the distribution P_τ as described in (7) to the GFIM (11) for discrete observation operators measured continuously yields the discrete $p \times p$ Fisher Information Matrix (FIM) for discrete observation operators measured at discrete times

$$F(\tau, C, \vec{\theta}_0) = F(P_\tau, P_C, \vec{\theta}_0) = \sum_{i,j=1}^{k,n} \nabla_{\vec{\theta}}^\top \vec{u}(t_i, x_j; \vec{\theta}_0) C^\top V_0^{-1}(t_i, x_j) C \nabla_{\vec{\theta}} \vec{u}(t_i, x_j; \vec{\theta}_0). \quad (12)$$

This describes the amount of information about the p parameters of interest that is captured by the observed quantities described by the sampling maps c_l , $l = 1, 2, \dots, N$, listed in C , when they are measured at the sampling points in τ .

The questions of determining the best (in some sense to be described below) C and τ are the paramount questions in the optimal design of an experiment. Recall that the set of sampling points τ has an associated distribution $P(\tau) = P_\tau \in \mathcal{P}([t_0, t_f] \times [x_0, x_f])$, where again $\mathcal{P}(a, b)$ is the set of all bounded distributions on $[a, b]$. Similarly, the set of sampling maps $\{c_l\}$ has an associated bounded distribution $P_C \in \mathcal{P}_0(\mathcal{C})$. Consider the space of bounded distributions $\tilde{\mathcal{P}} = \mathcal{P}([t_0, t_f] \times [x_0, x_f] \times \mathcal{C}) = \mathcal{P}_1(t_0, t_f) \times \mathcal{P}_2(x_0, x_f) \times \mathcal{P}_0(\mathcal{C})$ with elements $P = (P_\tau, P_C) \in \tilde{\mathcal{P}}$. Without loss of generality, we assume that $\mathcal{C} \subset \mathbb{R}^m$ is closed and bounded, and assume that there exists a functional $\mathcal{J} : \mathbb{R}^{p \times p} \rightarrow \mathbb{R}^+$ of the GFIM (10). Then the **optimal design problem** associated with \mathcal{J} consists of selecting a distribution $P^* \in \tilde{\mathcal{P}}$ such that

$$\mathcal{J} \left(\mathcal{F}(P^*, \vec{\theta}_0) \right) = \min_{P \in \tilde{\mathcal{P}}} \mathcal{J} \left(\mathcal{F}(P, \vec{\theta}_0) \right), \quad (13)$$

where \mathcal{J} depends continuously on the elements of $\mathcal{F}(P, \vec{\theta}_0)$.

Using the Prohorov metric on $\tilde{\mathcal{P}}$ we can develop a general theoretical framework for the existence of P^* and approximation in $\mathcal{P}([t_0, t_f] \times [x_0, x_f] \times \mathcal{C})$ (a general theoretical framework is developed in [1, 2]). The application of the Prohorov metric to optimal design problems formulated as (13) is explained more fully in [2]: briefly, define the Prohorov metric ρ on the space $\mathcal{P}([t_0, t_f] \times [x_0, x_f] \times \mathcal{C})$, and consider the metric space $(\mathcal{P}([t_0, t_f] \times [x_0, x_f] \times \mathcal{C}), \rho)$. Since $[t_0, t_f] \times [x_0, x_f] \times \mathcal{C}$ is compact, $(\mathcal{P}([t_0, t_f] \times [x_0, x_f] \times \mathcal{C}), \rho)$ is also compact. Additionally, by the properties of the Prohorov metric, $(\mathcal{P}([t_0, t_f] \times [x_0, x_f] \times \mathcal{C}), \rho)$ is complete and separable. Therefore an optimal distribution P^* exists and may be approximated by a finite discrete distribution which leads to efficient computational algorithms. Again, details are provided in [1, 2, 3].

The formulation of the cost functional (13) may take many forms. We illustrate with the use of traditional optimal design methods, SE-optimal, D-optimal, or E-optimal design criteria, to determine the form of \mathcal{J} . Each of these design criteria are functions of the inverse of the FIM (assumed hereafter to be invertible) defined in (12). Let N, n, k be fixed and given. The design question can be succinctly posed as: Given the possibility of observing $N < m$ states and sampling at points (t_i, x_j) , $i = 1, \dots, k, j = 1, \dots, n$, choose the best states and sample points to minimize the criterion in (13).

In SE-optimal design, \mathcal{J}_{SE} is a sum of the elements on the diagonal of $\left(F(\tau, C, \vec{\theta}_0)\right)^{-1}$ weighted by the respective parameter values [2, 3], written

$$\mathcal{J}_{SE}(F) = \sum_{i=1}^p \frac{\left(F(\tau, C, \vec{\theta}_0)\right)^{-1}_{i,i}}{\theta_{0,i}^2}.$$

Thus in SE-optimal design, the goal is to minimize directly the sum of squared errors of the parameters normalized by the true parameter values. As the diagonal elements of F^{-1} are all positive and all parameters are assumed non-zero in $\vec{\theta} \in \mathbb{R}^p$, $\mathcal{J}_{SE} : \mathbb{R}^{p \times p} \rightarrow \mathbb{R}^+$.

In D-optimal design, the cost functional is written

$$\mathcal{J}_D(F) = \det \left(F(\tau, C, \vec{\theta}_0)^{-1} \right) = \frac{1}{\det \left(F(\tau, C, \vec{\theta}_0) \right)}.$$

By minimizing \mathcal{J}_D , we minimize the volume of the confidence interval ellipsoid describing the uncertainty in our parameter estimates. Since F is symmetric and positive semi-definite, $\mathcal{J}_D(F) \geq 0$. Additionally, since F is assumed invertible, $\mathcal{J}_D(F) \neq 0$, therefore, $\mathcal{J}_D : \mathbb{R}^{p \times p} \rightarrow \mathbb{R}^+$.

In E-optimal design, the cost functional is \mathcal{J}_E is the largest eigenvalue of $\left(F(\tau, C, \vec{\theta}_0)\right)^{-1}$, or equivalently

$$\mathcal{J}_E(F) = \max \frac{1}{\text{eig} \left(F(\tau, C, \vec{\theta}_0) \right)}.$$

In this case we seek to reduce the length of the principal axis of the confidence interval ellipsoid. Since an eigenvalue λ solves $\det(F - \lambda I) = 0$, an eigenvalue of $\lambda = 0$ would mean $\det(F) = 0$, or that F is not invertible. Since F is positive definite, all eigenvalues are therefore positive. Thus $\mathcal{J}_E : \mathbb{R}^{p \times p} \rightarrow \mathbb{R}^+$.

In [3, 4], it is shown that the SE-, D-, and E-optimal design criteria select different sampling points and different state variables and subsequently yield different standard errors.

4 Algorithm and optimization constraints

An effective algorithm to implement the above optimization problems is proposed and illustrated in [4]. In finite state systems such as the large vector system considered in [4], there are not a continuum of measurement possibilities that may be used; rather, there are a finite number $N^* < \infty$ of possible observation maps c . We denote this set by $\mathcal{C}_{N^*} \subset \mathbb{R}^m$. Because \mathcal{C}_{N^*} is finite, all probability distributions for a fixed N of possible observation states made from the elements of \mathcal{C}_{N^*} have the form $P_0(\{c_l\}) = P_C = \sum_{l=1}^N \delta_{c_l}$. Moreover, the set $\mathcal{P}_0^N(\mathcal{C}_{N^*})$ of all distributions that use precisely N observation states is also finite. Therefore, for a fixed distribution of sampling points P_τ , we may compute using (12) the finite set of all possible FIM $F(P_\tau, P_C, \vec{\theta})$ that could be formulated from $c \in \mathcal{P}_0^N(\mathcal{C}_{N^*})$. Because this set is finite, it is well-ordered by the relation \leq and therefore has a minimal element. Hence for any distribution of time points P_τ , we may find at least one minimizing solution $\hat{P}_C \in \mathcal{P}_0^N(\mathcal{C}_{N^*})$. Moreover, for fixed k and n , \hat{P}_C may be determined by a search over all matrices $C = (c_1, c_2, \dots, c_N)^\top$ formed by N elements from \mathcal{C}_{N^*} .

Due to the computational demands of performing nonlinear optimization for kn sampling points

and N observation maps, we may solve the coupled set of equations

$$\hat{C} = \underset{\{C|P_C \in \mathcal{P}_0^N(\mathcal{C}_{N^*})\}}{\operatorname{argmin}} \mathcal{J} \left(F(\hat{\tau}, C, \vec{\theta}_0) \right) \quad (14)$$

$$\hat{\tau} = \underset{\{\tau|P_\tau \in \mathcal{P}([t_0, t_f] \times [x_0, x_f])\}}{\operatorname{argmin}} \mathcal{J} \left(F(\tau, \hat{C}, \vec{\theta}_0) \right), \quad (15)$$

where $C \in \mathbb{R}^{N \times m}$ represents a set of N sampling maps and $\tau = \{(t_i, x_j)\}_{i,j=1}^{k,n}$ is a set of kn sampling points. These equations can be solved iteratively as

$$\hat{C}_i = \underset{\{C|P_C \in \mathcal{P}_0^N(\mathcal{C}_{N^*})\}}{\operatorname{argmin}} \mathcal{J} \left(F(\hat{\tau}_{i-1}, C, \vec{\theta}_0) \right) \quad (16)$$

$$\hat{\tau}_i = \underset{\{\tau|P_\tau \in \mathcal{P}([t_0, t_f] \times [x_0, x_f])\}}{\operatorname{argmin}} \mathcal{J} \left(F(\tau, \hat{C}_i, \vec{\theta}_0) \right), \quad (17)$$

where \mathcal{J} is the D-, E-, or SE-optimal design criterion and $\hat{\tau}_0$ is taken as a uniformly spaced grid. Of course, for fixed k and n , we also combine these ideas with the sampling approximations $P^M([t_0, t_f] \times [x_0, x_f])$, $M = kn$, for $P([t_0, t_f] \times [x_0, x_f])$ as described in detail in [1]-[4].

Once the convergence requirements are met and \hat{C} and $\hat{\tau}$ are determined, we compute standard errors using the asymptotic theory as described in [5].

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