A Bayesian approach to parameter identification
with an application to Turing systems

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Abstract

We present a Bayesian methodology for infinite as well as finite dimensional parameter identification for partial differential equation models. The Bayesian framework provides a rigorous mathematical framework for incorporating prior knowledge on uncertainty in the observations and the parameters themselves, resulting in an approximation of the full probability distribution for the parameters, given the data. Although the numerical approximation of the full probability distribution is computationally expensive, parallelised algorithms can make many practically relevant problems computationally feasible. The probability distribution not only provides estimates for the values of the parameters, but also provides information about the inferability of parameters and the sensitivity of the model. This information is crucial when a mathematical model is used to study the outcome of real-world experiments.

Keeping in mind the applicability of our approach to tackle real-world practical problems with data from experiments, in this initial proof of concept work, we apply this theoretical and computational framework to parameter identification for a well studied semilinear reaction-diffusion system with activator-depleted reaction kinetics, posed on evolving and stationary domains.

Keywords: Bayesian inverse problems, parameter identification, inverse problems, Markov chain - Monte Carlo, reaction-diffusion, Turing spaces.
1 Introduction

1.1 Motivation and highlights

The Bayesian approach for infinite dimensional parameter identification problems, that we elucidate in the present work, is a powerful tool that allows mathematically, rigorous qualitative and quantitative inference to be made on the parameters in a mathematical model from the results of experimental studies of the system that is being modelled. Some aspects of the approach that we describe in detail of the remainder of this work are as follows;

- One seeks to find the conditional probability distribution of the parameters given the experimental data. For many problems in the life sciences, variation in parameters, across organisms for example, is commonplace. In such a setting, more widespread approaches that seek to identify a single parameter value, i.e., the most likely value given the data, may be next to worthless, whilst identifying the conditional probability distribution is significantly more informative. One example that we illustrate below is the computation of credible regions, the analogue of confidence intervals, for parameters. Such regions arise naturally from the approach and are typically tighter than those obtained using a method which seeks only a single value.

- Uncertainty associated with the measurements from experiments may be naturally incorporated in the framework. As experimental techniques and the associated confidence in them and understanding of them matures, such a framework becomes particularly attractive.

- Recent advances in the development of fast and efficient parallel algorithms can be employed in order to reduce the large computation times associated with the approach. We illustrate this by describing a robust and efficient parallel algorithm for the sampling of the aforementioned probability distribution in the sequel.

- It is possible to show the problem of parameter identification is well posed (in a mathematical sense) under very mild assumptions on the model and the experimental data. For example, in the present work we consider parameter identification for a pattern forming system of equations. Proving the problem is well posed requires little more effort than showing the pattern forming model itself is well posed.

The upshot is that we feel such a framework is ideally suited to tackling challenging parameter identification problems in biology, such as those in cell biology, where the natural variability in experimental measurements together with the prevalence of highly complex nonlinear mathematical models motivates an approach with the features described above.
1.2 Overview on parameter identification

In the study of a real world system, experiments provide measurements of quantities from the system, whilst theoretical work provides models predicting the behaviour of the real world system. Such models typically include independent variables—the parameters—inherent to the system under study.

Parameter identification is the problem of extracting information about the parameters of a model from the actual result of some measurement [52]. We consider mathematical models of the form of partial differential equations (PDEs) whose variables are elements of a Banach space. The data will be a noisy measurement of the solution of the system of PDEs, whilst the parameters will be the coefficients of the mathematical model, i.e. the coefficients of the system of PDEs, including maybe initial and boundary conditions which can be considered as parameters as well. The data may also be a functional of the solution, such as an average. Parameter identification problems are sometimes referred to as inverse problems, thus considering as a direct problem solving the system of PDEs given the parameters. Note that parameters may be functions in general. We remark that this approach applies directly to systems of ordinary differential equations as well, making the theory of interest to a wide range of fields.

There are two main approaches to solve parameter identification problems. On one hand, one can use techniques from optimal control to find the best possible value for the parameter. Here, the best possible value is defined in terms of the distance from the solution of the model to the given data. In a Banach space setting, when the data and the solution are elements of a Banach space, this corresponds to the problem of minimising the norm of the difference between the solution and the data. In general, this problem is ill-posed. A regularisation term must be added, enforcing the norm of the parameter to be minimised too, and effectively restricting the candidate parameters. Ill-posedness may come from different sources, like non-uniqueness or non-continuous dependence of the solution with respect to the data (see, for instance, [4, 7]).

A second approach to parameter identification is to use Bayesian techniques (see for instance [50, 27]). This approach consists of a set of techniques built around Bayes’ theorem, which roughly speaking allows one to compute the conditional probability of an event $A$ given the probability of an event $B$, in terms of the reverse conditional probability, i.e. the probability of $B$ given $A$. In the parameter identification framework, this will correspond to computing the probability of the parameters given the data, in terms of the probability of the data given the parameters. Note that the latter is given by the mathematical model: when the parameters are given, the mathematical model predicts the result of the experiment, i.e. the data.

In both cases, numerical algorithms are necessary to approximate the final result. In the optimal control framework, there is a range of minimisation techniques that may be used, for instance Gauss-Newton optimisation or the Levenberg-Marquardt algorithm (see [1] for a general description of these algorithms). These algorithms provide the best value for the parameters, in the sense of minimising the distance from the data to the solution of the mathe-
matical model. Similarly, an optimal value can be obtained from the Bayesian framework using maximum likelihood methods [38, 53, 5]. Additional methods can be used to estimate confidence intervals for the parameters. In the Bayesian framework, the problem will be to estimate a full probability distribution. In this case, usually a Markov Chain Monte Carlo algorithm is used to build a Markov chain with stationary distribution equal to the target distribution (see [41, 50, 55, 6, 10]). This usually requires a lot of evaluations of the observation functional—the mapping from parameters to observations, i.e. from parameters to the solution of the mathematical model—, solving the system of PDEs for each evaluation. Whilst this is computationally more expensive than a minimisation algorithm, the amount of information obtained—the full probability distribution—is larger compared to the single value that we get from the optimal control approach. Note that in both cases a parallel algorithm can be used to speed-up the computations.

In contrast with the value for the parameters given by the optimal control approach, the Bayesian framework provides a probability distribution. From the probability distribution one can extract information about the uncertainty of the parameters, thus avoiding situations where despite obtaining a value for the parameters, a more detailed study of the uncertainty shows that they are not well-determined [22]. In many practical situations, the exact value of the parameters is not useful in drawing conclusions. For instance, in [3] it is shown that correlations between parameters in a model for *Drosophila Melanogaster* gap gene impede the individual identification of the parameters, but it is still possible to obtain conclusions about the regulatory topology of the gene network. Furthermore, the information provided by the probability can be used in model selection problems [60], where several mathematical models are available and the goal is to find which one fits better to the experimental data.

There are other advantages inherent to the fact that a probability distribution for the parameters is available. For example, correlations between different parameters can be observed in the joint probability distribution. These correlations can be invisible when only a value for the parameters is computed, leading to an overestimation of the uncertainty [51]. Similarly, the correlations between parameters can suggest a non-dimensionalised form of the equations to eliminate non-relevant parameters from the problem.

A drawback of the Bayesian approach is its computational cost. To obtain a good approximation of the posterior probability distribution, we need to solve the system of partial differential equations many times. The use of parallelised algorithms makes many relevant problems feasible. The same problems were not suitable for this approach a few years ago due to the lack of computational power [49].

Parameter identification problems often arise in many areas of research such as biology, biomedicine, chemistry, material sciences, mathematics, statistics etc. Typically, a mathematical model needs to be fitted with experimental data. Only in a few cases is it possible to do a analytical parameter identification, see for instance [18]. Note also that parameters are not always directly measurable from experiments, or have a defined physical meaning. Hence, parameter iden-
tification through the proposed approach might help guide experimentalists in identifying regions of interest to which parameters belong.

The optimal control approach is widely used. In [2], it is applied to systems of ordinary differential equations modelling enzyme kinetics. In this case, confidence regions may be computed using the second derivatives of the cost functional that is being minimised. Since this only provides local information around the optimal point, the confidence regions computed with this method tend to be large. The optimal control approach has also been applied to geometric evolution problems for cell motility, and to Turing systems [19, 16, 9, 44, 61].

Bayesian techniques are common for parameter fitting in statistics. The main difference with the present work is the type of models. We use models given by partial differential equations instead of statistical models. In particular, our models are deterministic—with a uniquely determined solution for each admissible parameter. Statistical models, or stochastic models in general, incorporate randomness in the model. The Bayesian approach to parameter identification for models given by PDEs (see [50] and the references therein) is used in different fields, for example inverse problems in subsurface flow [25].

In the absence of a real experimental model, for illustrative purposes, we consider a well known system of partial differential equations of the form of reaction-diffusion type, also known as Turing systems [39, 40, 56]. The motivation is that parameter space identification for some reaction-diffusion system with classical reaction kinetics can be obtained analytically thereby offering us a benchmarking example for our theoretical and computational framework. Turing systems are a family of reaction-diffusion systems introduced by Turing in [56]. The main feature of these models is that small perturbations of homogeneous steady states may evolve to solutions with non-trivial patterns [39, 40]. An example of such a model is the Schnakenberg system (also known as the activator-depleted substrate model) [20, 45, 48]. This model has been widely studied, both analytically and numerically [19, 34]. Our first example is to identify a time-dependent growth rate function of the reaction-diffusion system on a one-dimensional growing domain. For this case, the rest of the model parameters are considered known and fixed. This example illustrates the infinite dimensional parameter identification example, rather than parameters. Our second example is that of parameter identification in a finite dimensional framework we consider the reaction-diffusion system posed on a stationary two-dimensional domain. For both examples, we use synthetic patterns – computer generated – based on previous works using a fixed set of parameters.

2 Methodology on parameter identification

The main ingredients of a parameter identification problem are the data (the measurement from the experiment), the parameters and the mathematical model. The data and the parameters are modelled as elements of suitable Banach spaces. To fix the notation, let \( U \) and \( Y \) be Banach spaces, let \( y \in Y \) be the data, and let \( p \in U \) be the parameter. Note that in general \( p \) is a vector.
of parameters. When one fixes a value for the parameter \( p \), one can solve the equations of the model to find the solution associated with this parameter. This process is known as the solution of the forward problem; in contrast, the problem of parameter identification is known as the inverse problem. The solution of the forward problem is formalised with a mapping \( G : U \to Y \), such that a parameter \( p \in U \) is mapped to the solution of the model with parameter \( p \). Since \( G \) maps parameters to the measurement space, \( G \) is called the observation operator. \( G \) is well-defined as long as for each possible parameter, there exists a unique solution to the mathematical model, otherwise \( G \) might not be defined in \( U \) or might be multivalued.

The measurements or observations generated by experiments typically have some error or uncertainty associated with them. Following the usual terminology, we refer to such errors as the noise of the measurement. We consider here additive noise, i.e. an error added to the true value of the measurement. Note that different sources of error can be taken into account and these can be included as several independent additive errors or as extra parameters in the mathematical model; different types of noise, e.g. multiplicative, can also be incorporated in this way [21, 42, 43, 12].

The noise is naturally modelled in terms of a probability distribution. Let \( Q_0 \) be a probability distribution. Let \( \eta \) be a realisation of \( Q_0 \). With this notation at hand, our measurement can be expressed as

\[
y = G(p) + \eta. \tag{1}
\]

The Bayesian approach to parameter identification assumes implicitly that a probability distribution models the state of knowledge about a quantity [52]. If the quantity is known with infinite precision then the probability distribution will be concentrated at one point—a Dirac delta distribution. The less we know, the more spread the distribution will be.

Equation (1) expresses the relation between the probability distribution of the data \( y \), the parameters \( p \) and the noise \( \eta \). In other words, (1) connects our knowledge about the different ingredients of the parameter identification problem. Note that the mathematical model, encoded in \( G \), is assumed to be known; our interest is to find information about the parameters of a given model, not to find the model itself, although dummy parameters could be used for model selection.

From the modelling point of view, equation (1) is well-defined as long as the data \( y \) lies in a Banach space. Some systems may require a more general framework, for instance if the data lies in a manifold or in a metric space, where the operation "+" may not be defined. The Banach space setting allows us to prove rigorous results on the parameter identification problem, and it is suitable for the numerical approximation of the solution [50, 17, 13]. In terms of applicability, in some situations the task of finding the noise distribution is not trivial [28, 24].

The parameter identification problem can be now stated as follows: find the probability distribution of the parameter \( p \) given the data \( y \). This probability
distribution is called the posterior, and is denoted by \(P(p|y)\), or \(P^y(p)\). All the information available about the parameter \(p\) is encoded in the posterior probability distribution. The goal now is to characterise this distribution.

From (1) we can compute directly the probability distribution of the data \(y\) given a parameter \(p\). Since we know the noise distribution \(Q_0\), given a parameter \(p\), the distribution of \(y\) is \(Q_0\) shifted by \(G(p)\). In terms of the probability density function (PDF) of \(Q_0\), denoted by \(\rho\), the PDF of the distribution of the data \(y\), given a parameter \(p\), is \(\rho(y - G(p))\). In the sequel it will be useful to use the so called log-likelihood of the parameter \(p\), given by [50, 17]

\[
\Phi(p; y) = -\log(\rho(y - G(p))). \tag{2}
\]

Bayes’ theorem characterises a conditional probability distribution \(P(p|y)\) in terms of the reverse conditional probability distribution \(P(y|p)\) and the marginal distribution \(P(p)\). The latter can be interpreted as the probability distribution of \(p\), i.e. the state of knowledge about the parameter, regardless of the data \(y\). Bayes’ theorem gives

\[
P(p|y) \propto P(y|p)P(p). \tag{3}
\]

The constant of proportionality can be computed explicitly but we do not need it, because the algorithm that we will use to numerically approximate the probability distribution only uses the ratio between probabilities; the constant of proportionality is itself cancelled.

The probability distribution \(P(p)\) is called the prior distribution, and encodes our prior knowledge about the parameter \(p\). This knowledge comes from any source that was available before the performance of the experiment that provides the data for the parameter identification. If there is not a previous knowledge about the parameter \(p\), the absence of knowledge can also be represented. These type of priors are sometimes called non-informative priors [29]. In a finite dimensional setting, a natural choice for a non-informative prior is the uniform distribution.

We can now apply Bayes’ theorem to (1). Let \(\mu^y\) be the probability density function of \(P(p|y)\). We have seen that the PDF of \(P(y|p)\) is given by \(\rho(y - G(p))\), where \(\rho\) is the PDF of the noise distribution \(Q_0\). Denote by \(\mu_0\) the PDF of the prior distribution. From Bayes’ theorem we obtain [50]

\[
\mu^y(p) \propto \rho(y - G(p))\mu_0(p).
\]

Bayes’ theorem can be generalised to an infinite dimensional setting. The formulation is more technical but analogous. With the general version of the theorem, the Bayesian approach to parameter identification can be applied to infinite dimensional problems. Let \(P_0\) be the prior distribution. The following result generalises the Bayes’ theorem to infinite dimensional settings [50, 17].

**Theorem 2.1 (Bayes’ theorem).** Assume that the log-likelihood \(\Phi : U \times Y \to \mathbb{R}\) is measurable with respect to the product measure \(P_0 \times Q_0\) and assume that

\[
Z := \int_U \exp(-\Phi(p; y)) P_0(dp) > 0.
\]
Then, the conditional distribution $\mathbb{P}(p|y)$, denoted by $\mathbb{P}^y(p)$, exists, and it is absolutely continuous with respect to the prior distribution $\mathbb{P}_0$. Furthermore,

$$\frac{d\mathbb{P}^y}{d\mathbb{P}_0} = \frac{1}{Z} \exp(-\Phi(p;y)).$$

Proof. See [17, theorem 3.4].

Using only properties of the forward problem, the following proposition (see [50]) guarantees that the parameter identification problem is well-posed: the posterior distribution exists, and it depends continuously on the data $y$. Denote by $B(0,r) \subset U$ the ball with centre at the origin and radius $r$, and by $\|\cdot\|_\Sigma$ the Euclidean norm with weight $\Sigma$.

**Proposition 2.1** (Well-posedness of the Bayesian inverse problem). Assume that $Q_0$ is a Gaussian distribution with covariance $\Sigma$, and that the log-likelihood is $\Phi(p;y) = \|y - G(p)\|_\Sigma^2$. Assume that the observation operator $G$ satisfies the following conditions.

i) For all $\varepsilon$, there exists $M \in \mathbb{R}$ such that for all $p \in U$,

$$\|G(p)\|_\Sigma \leq \exp(\varepsilon \|p\|_U^2 + M).$$

ii) For all $r > 0$, there exists a $K$ such that for all $p_1, p_2 \in B(0,r)$,

$$\|G(p_1) - G(p_2)\|_\Sigma \leq K\|p_1 - p_2\|_U.$$

Then, the distribution $\mathbb{P}^y(p)$ defined in Theorem 2.1 exists, and depends continuously on the data $y$.

Proof. See [50, theorem 4.2].

Note that the first condition is a bound on the growth of the solution with respect to the parameter $p$, whilst the second condition is the Lipschitz continuity of the observation operator. The first condition is not necessary to obtain well-posedness if the parameter space $U$ is finite dimensional.

We have characterised the posterior distribution – the probability distribution of the parameter $p$ given the data $y$ – in terms of the data, the model, the noise distribution and the prior distribution. Using this characterisation of the posterior, we shall use numerical tools to obtain useful information about the parameter. Note that in many cases it is crucial to know if the parameter is well-determined by the data [22], and often the precise value of it is not required to draw a conclusion [3]. For instance, we can compute credible regions, which are regions of the parameter space with a given probability. Credible regions are the analogue of confidence intervals in the Bayesian framework.

The direct or deterministic approach, connected to the optimal control methods (see for instance [16]), is to find the minimum of the log-likelihood function $\Phi$ given in (2). This approach is known as the maximum likelihood method.
(due to the minus sign in the definition of the log-likelihood, a minimum of the log-likelihood is a maximum of the likelihood). The log-likelihood can be interpreted as a distance between the data and the solution of the mathematical model, so a natural approach is to minimise this distance. For example, if the noise distribution $Q_0$ is Gaussian with mean 0 and covariance $\Sigma$, we have $\Phi(p; y) = \|y - G(p)\|_2^2$, i.e. the log-likelihood is the squared Euclidean distance with weight $\Sigma$.

The maximum likelihood method gives a value for the parameter, but does not provide any information about the uncertainty; the maximum likelihood is only a fraction of the information encoded in the posterior. Furthermore, a numerical algorithm could find a local maximum, so global optimisation algorithms may be necessary [2].

In order to use more information from the posterior, we have to approximate numerically the full posterior distribution. As long as we are able to obtain a good approximation, we can then extract any information encoded in the posterior from the approximation. To numerically approximate a probability distribution we shall generate a finite set of points distributed as samples from the target distribution.

A useful mathematical structure to approximate a probability distribution is a Markov chain. A Markov chain is a sequence such that the probability of the next value, termed the next state, depends only on the present value. Markov chain Monte Carlo methods (MCMC) are a family of methods that produce a Markov chain with a given distribution [41]. For the problem at hand, the target distribution is the posterior.

Metropolis–Hastings methods [37, 23] are a special case of the MCMC methods defined by a proposal kernel $k(x, y)$, the probability to propose a state $y$ if the present state is $x$, and an acceptance probability $a(x, y)$, the probability of accepting the proposed state $y$ if the present state is $x$. To generate a new state of the chain, one proposes a new state $y$ sampling from the proposal kernel $k(x, y)$, and then one accepts the proposal with probability $a(x, y)$. If the proposal $y$ is accepted, it becomes the next state. Otherwise, we stay in the present state, i.e. the next state is $x$. See [8] for a general introduction to MCMC methods. A simple choice for the proposal kernel is to sample from the prior distribution, i.e. $k(x, y) = \mu_0(y)$. More elaborate choices are possible (see for instance [13]). For symmetric proposal kernels, the acceptance probability is given by $a(x, y) = \min(\exp(\Phi(x) - \Phi(y)), 1)$. Algorithm 1 describes one step of the Metropolis–Hastings algorithm.

**Algorithm 1** One step of the standard Metropolis–Hastings algorithm. This will generate one new sample.

1. Draw a proposal $\bar{x}$ from the proposal kernel $k(x_k, \bar{x})$.
2. Evaluate $a(x_k, \bar{x}) = \min(\exp(\Phi(x_k) - \Phi(\bar{x})), 1)$.
3. Accept $\bar{x}$ with probability $a(x_k, \bar{x})$, i.e $x_{k+1} = \bar{x}$ with probability $a(x_k, \bar{x})$, and $x_{k+1} = x_k$ otherwise.
MCMC methods are robust but slow. The distribution of the Markov chain converges, under general conditions, to the target distribution, but long chains are necessary to obtain good approximations [41]. Also, the methods are inherently sequential. Furthermore, in the parameter identification framework, evaluation of the acceptance probability typically involves, at least, one evaluation of the log-likelihood, and in consequence, one evaluation of the observation operator $G$. This is an expensive operation in terms of computing time in cases where the model is a system of PDEs because it entails solving the system. Similarly, methods that require quantities like $\nabla \Phi$ may not be feasible.

To overcome these difficulties we shall use a parallel Metropolis–Hastings algorithm [11, 54]. The key idea is to generate an $N$-dimensional Markov chain, such that its distribution is $N$ copies of the target distribution. This can be done in a way that allows parallel evaluations of the log-likelihood.

The parallel Metropolis–Hastings algorithm goes as follows. Let $k(x, y)$ be a proposal kernel—the probability to propose a state $y$ if the present state is $x$. For ease of presentation assume that the proposal kernel is symmetric, i.e. $k(x, y) = k(y, x)$. Define $r(x, y) = \exp(\Phi(x) - \Phi(y))$. Let $x_i$ be the present state.

The algorithm is applied as follows. Given a present state $x_k$, we generate $N$ new proposals $\{\bar{x}_j\}_{j=1}^N$ from the proposal kernel $k(x_k, \bar{x}_j)$. Take $\bar{x}_0 = x_k$. Then, in parallel, we evaluate the log-likelihoods $\Phi(\bar{x}_j)$, $j = 1 \ldots N$. Note that this will be done by $N$ instances of the PDE solver running in parallel, but the solver itself need not to be parallel. With the values of $\Phi(\bar{x}_j)$ at hand, the acceptance probability of each proposal is computed by finding the stationary distribution of a Markov chain with $N + 1$ states, given by the transition matrix

$$A(i, j) = \begin{cases} \frac{1}{N} \min(1, r(\bar{x}_i, \bar{x}_j)) & \text{if } j \neq i, \\
1 - \sum_{j \neq i} A(i, j) & \text{if } j = i. \end{cases}$$

Finally, we sample $N$ times from the stationary distribution to produce $N$ new states (see Algorithm 2). Note this approach is nonintrusive and does not require modifications of the solver for the PDEs.

The method described above has been implemented in Python, using the module Scipy [26] and the module multiprocessing from the Python Standard Library. The evaluation of the log-likelihood can be implemented using a different language and then invoked from the Python code. In this paper, we use Python also for the evaluation of the log-likelihood; see Section 3 for details.

Our primary long term motivation is to work with experimental data, for this case one can use the proposed methodology as follows. Using the data, implement a routine to evaluate the log-likelihood. Since we are going to explore a range of possible parameters, the evaluation of the log-likelihood must be robust. Apply the parallel Metropolis–Hastings to generate several long Markov-Chains, for instance 10 chains of length $10^6$. Check the convergence of the chains, by checking the convergence of the means, or using other methods (see...
Algorithm 2 One step of the parallel Metropolis–Hastings algorithm. This will generate \( N \) new samples.

1. Draw \( N \) new points \( \{\bar{x}^j\}_{j=1}^N \) from the proposal kernel \( k(x_k, \bar{x}^j) \). Take \( \bar{x}^0 = x_k \).
2. Evaluate, in parallel, \( \Phi(\bar{x}^j) \), \( j = 1 \ldots N \).
3. Compute the acceptance probabilities of the proposals, given by the stationary distribution of a Markov chain with transition matrix

\[
A(i,j) = \begin{cases} 
\frac{1}{N} \min(1, r(\bar{x}^i, \bar{x}^j)) & \text{if } j \neq i, \\
1 - \sum_{j \neq i} A(i,j) & \text{if } j = i.
\end{cases}
\]

4. Sample \( N \) times from the stationary distribution to produce \( x_{k+1}, \ldots, x_{k+N} \).

for instance [46]). Discard a fraction at the beginning of each chain, where the effects of the choice of the initial state were still evident. Finally, recombine the chains in a large set, that approximates our target distribution. Note that using the parallel Metropolis-Hastings algorithm, we are able to generate longer chains than using the standard Metropolis-Hastings algorithm.

Following this approach we obtain a numerical approximation of the posterior distribution given by the application of Bayes' theorem to the parameter identification problem. Note that the method is non-intrusive: the solver for the model is independent of the parameter identification algorithms. Hence, it can be applied to a wide range of problems in particular those for which an existing fast and possibly complex solver for the forward problem is available. As a proof of concept of our approach, we will consider a well studied mathematical model of the form of reaction-diffusion systems to perform the parameter identification. We are motivated by the fact that a precise definition of the parameter space in which, for example, patterns can form for some specific reaction-kinetics (e.g. activator-depleted type) is known analytically and therefore, we have a clean example to validate the accuracy of our methodology. We present a concrete example in the next section.

2.1 HPC computations

For each of the examples shown in Section 3, we generate 10 Markov chains for a total of approximately \( 10^6 \) samples. The mean and the correlation of each chain are examined, and used to decide the burn-in—the fraction of the chain discarded due to the influence of the initial value. The burn-in fraction is determined by checking the convergence in mean for each chain. Finally, the chains are combined in a big set, that we use to generate the plots.

All the results shown are generated using the local HPC cluster provided and managed by the University of Sussex. This HPC cluster consists of 3000
computational units. The models of the computational units are AMD64, x86_64 or 64 bit architecture, made up of a mixture of Intel and AMD nodes varying from 8 cores up to 64 cores per node. Each unit is associated with 2GB memory space. Most of the simulations in this paper are executed using 8-48 units.

The wall-clock computation time for one chain ranged from 1 to 4 days, CPU time ranged from 10 to 35 days for one chain. It must be noted that there are two levels of parallelisation: first the algorithm is parallelised and uses the 8 available cores, and then many instances of the algorithm run at the same time to produce independent chains. We remark that we produce independent chains in order to test the convergence of the algorithm.

3 Applications and results

To illustrate the methodology proposed in this study, we consider infinite (as well as finite) dimensional parameter identification for a well-known mathematical model, a reaction-diffusion system on evolving and stationary domains. As mentioned earlier, we take the Schnakenberg kinetics [20, 45, 48] for illustrative purposes. We use our Bayesian parameter identification approach to find the growth function associated with the reaction-diffusion system as outlined next.

3.1 Reaction-diffusion system posed on uniform isotropic evolving domains

Let $\Omega_t \subset \mathbb{R}^m \ (m = 1, 2)$ be a simply connected bounded evolving domain for all time $t \in I = [0, t_F]$, $t_F > 0$ and $\partial \Omega_t$ be the evolving boundary enclosing $\Omega_t$. Also let $u = (u(x(t), t), v(x(t), t))^T$ be a vector of two chemical concentrations at position $x(t) \in \Omega_t \subset \mathbb{R}^m$. The growth of the domain $\Omega_t$ generates a flow of velocity $v$. For simplicity, let us assume a uniform isotropic growth of the domain defined by $x(t) = \rho(t)x(0)$ where, $x(0) \in \Omega_0$ is the initial domain and $\rho(t) \in C^1(0, 1)$ is the growth function (typically exponential, linear or logistic). We further assume that the flow velocity is identical to the domain mesh velocity $v := \frac{dx}{dt}$. The evolution equations for reaction-diffusion systems in the absence of cross-diffusion can be obtained from the application of the law of mass conservation in an elemental volume using Reynolds transport theorem. Since the domain evolution is known explicitly, a Lagrangian mapping from an evolving to a stationary reference initial domain yields the following non-dimensional reaction-diffusion system with time-dependent coefficients [14, 31,
\[
\begin{align*}
\left\{ \begin{array}{l}
\dot{u} + \frac{m\rho(t)}{\rho(t)} u &= \frac{1}{\rho^2(t)} \nabla^2 u + \gamma f(u, v), \\
\dot{v} + \frac{m\rho(t)}{\rho(t)} v &= \frac{d}{\rho^2(t)} \nabla^2 v + \gamma g(u, v),
\end{array} \right. \\
\mathbf{n} \cdot \nabla u = \mathbf{n} \cdot \nabla v = 0, \quad x \in \partial \Omega_0,
\end{align*}
\]
where \( \nabla^2 \) is the Laplace operator on domains and volumes, \( d \) is the ratio of the diffusion coefficients and \( \dot{\rho} := \frac{d\rho}{dt} \). Here, \( \mathbf{n} \) is the unit outward normal to \( \Omega_t \).

Initial conditions are prescribed through non-negative bounded functions \( u_0(x) \) and \( v_0(x) \). In the above, \( f(u, v) \) and \( g(u, v) \) represent nonlinear reactions and these are given by the activator-depleted kinetics \([15, 20, 45, 48]\)
\[
\begin{align*}
f(u, v) &= a - u + u^2 v, \\
g(u, v) &= b - u^2 v.
\end{align*}
\]

To proceed, let us fix the parameters \( a, b, d \) and \( \gamma \), and use the Bayesian approach to identify the domain growth rate function \( \rho(t) \), assuming \( \rho(0) = 1 \), \( \rho(t) > 0 \) for \( t > 0 \) and at the final fixed domain size \( \rho(T) \) is known.

Well posedness results for the system of equations (4), as well as stability results, can be found in \([57]\). Furthermore, the positivity of solutions is established. These results ensure that the conditions in Proposition 2.1 are satisfied, thus we can conclude well posedness of the parameter identification problem.

**Proposition 3.1** (Well-posedness of the parameter identification problem). Let \( G \) be the observation operator associated with the reaction-diffusion system (4) with reaction-kinetics (5). Assume that \( a, b, d, \gamma > 0 \), and \( \rho \in C^1(0, T), \rho > 0 \). Then, the conditions in Proposition 2.1 are satisfied, and thus the parameter identification problem is well-posed.

**Proof.** The result follows from the analysis in \([57]\), where well-posedness for the problem (4) is shown. In particular, the first condition in Proposition 2.1 is a consequence of the a priori estimates for the solution. \( \Box \)

Although this example is synthetic, it is biologically plausible. First, we generate the data by adding noise to a numerical solution of the system, but the parameter identification problem would be analogous in the case of experimental data (see for instance \([59]\) for an experiment that produces Turing patterns similar to the patterns that we use as data in Example 2).

### 3.1.1 Example 1: Infinite dimensional parameter identification

Without any loss of generality, we restrict our first example to the one-dimensional case \( (m = 1) \) where we fix model parameters with standard values in the literature as \([40]\)
\[
\begin{align*}
a &= 0.1, \quad b = 0.9, \quad d = 10, \quad \gamma = 1000.
\end{align*}
\]
We want to identify the growth function $\rho(t)$ given synthetic data generated from two different growth profiles defined by the exponential and logistic functions

$$
\rho_{\text{exp}}(t) = \exp(0.001t), \quad \text{and} \quad \rho_{\text{log}}(t) = \frac{\exp(0.01t)}{1 + \exp(0.006t)}.
$$

We fix the final time $T = 600$. Note that the size of the domain at time $T$ is the same in both cases.

Initial conditions are taken as small fixed random perturbations of the homogeneous steady state, $(u_*, v_*) = \left( a + b, \frac{b}{(a+b)^2} \right)$

$$
u_0(x) = 1 + 0.005 \sum_{k=1}^{9} \sin(k \pi x), \quad \text{and} \quad v_0(x) = 0.9 + 0.005 \sum_{k=1}^{9} \sin(k \pi x).
$$

We solve the system using the finite difference method both in space and time. The system of partial differential equations is solved on the mapped initial unit square domain using a finite difference scheme. Similar solutions can be obtained by employing finite element methods for example or any other appropriate numerical method. The algebraic linear systems are solved using a conjugate gradient method from the module SciPy [26].

The time-stepping scheme is based on a modified implicit-explicit (IMEX) time-stepping scheme where we treat the diffusion part and any linear terms implicitly, and use a single Picard iterate to linearise nonlinear terms [47, 32, 57]. The method was analysed in [30] for finite element discretisation. It is a first order, semi-implicit backward Euler scheme, given by

$$
\begin{align*}
\frac{u^{n+1} - u^n}{\tau} + \frac{\dot{\rho}^n}{\rho^n} u^{n+1} &= \frac{1}{\rho^2 n} \Delta_h u^{n+1} + \gamma (a - u^{n+1} + u^n u^{n+1} v^n), \\
\frac{v^{n+1} - v^n}{\tau} + \frac{\dot{\rho}^n}{\rho^n} v^{n+1} &= \frac{d}{\rho^2 n} \Delta_h v^{n+1} + \gamma (b - (v^n)^2 v^{n+1}),
\end{align*}
$$

where $\Delta_h$ is the standard 3-point (or 5-point) stencil finite difference approximation of the Laplacian operator in 1-D (or 2-D) respectively, with Neumann boundary conditions. The parameters of the solver are $h = 10^{-2}$ and $\tau = 10^{-4}$ for all the computations.

We remark that our aim here is to illustrate the applicability of the Bayesian approach and the Monte Carlo methods for parameter identification to problems emanating from experimental sciences. More sophisticated solvers can be used and will improve the computational time [58]. The synthetic data is generated by solving the reaction-diffusion system (4) with reaction-kinetics (5) up to the final time $T = 600$, and then construct the synthetic data by perturbing the solution with Gaussian noise with mean zero and standard deviation equal to 5% of the range of the solution and this data is illustrated in Figure 1.

In order to identify a time-dependent parameter $\rho(t)$, we approximate it on a finite dimensional space by using a polynomial of degree four, with only three degrees of freedom. The coefficients of order zero and four are fixed in order
to satisfy the conditions for $\rho(t)$ at times $t = 0$ and $t = T$, respectively. The prior for the coefficients of the polynomial approximation of $\rho(t)$ is selected by looking at the region of time-position space covered by 95% of the samples of the prior as shown in Figure 2 (large shaded region, yellow in color version).

The same prior is used for both the logistic and the exponential growth data sets. In Figure 2 we depict the regions where 95% of the samples from the posteriors lie, and also the region where 95% of the samples of the prior lie. Observe that we could also plot the credible regions for the coefficients of the finite dimensional approximation of $\rho$, but it is more difficult to visualise the result from it.

For the final time $T = 600$, we find that the region corresponding to the parameters identified from the exponential growth rate and the region corresponding to the logistic growth rate are completely separated: we can distinguish the type of growth from the solutions at a final time $T$.

### 3.1.2 Example 2: Finite dimensional parameter identification

Next we demonstrate the applicability of our approach to identifying credible regions for parameters which are constant and not space nor time-dependent and this is a prevalent problem in parameter identification. We will again use
the reaction-diffusion system (4) with reaction-kinetics (5) in the absence of domain growth, i.e. \( \rho(t) = 1 \) for all time. Our model system is therefore posed on stationary domains, for the purpose of demonstration, we assume a unit-square domain. We seek to identify \( a, b, d \) and \( \gamma \). For ease of exposition, we will seek parameters in a pair-wise fashion.

Our “experimental data” are measurements of the steady state of the system. We fix the initial conditions as a given perturbation of the spatially homogeneous steady state given by \( \begin{pmatrix} a + b, \frac{b}{(a+b)^2} \end{pmatrix} \). For the values of the parameters given in Table 1, the initial conditions are given by

\[
\begin{align*}
    u_0(x, y) &= 0.919145 + 0.0016 \cos(2\pi (x + y)) + 0.01 \sum_{j=1}^{8} \cos(2\pi j x), \\
    v_0(x, y) &= 0.937903 + 0.0016 \cos(2\pi (x + y)) + 0.01 \sum_{j=1}^{8} \cos(2\pi j x).
\end{align*}
\] (9)

We let the system evolve until the \( L_2 \) norm of the discrete time-derivative is smaller than a certain threshold. For the numerical experiments presented here,
### Table 1: Exact values of the parameters, used to generate the noisy data shown in Figure 3.

| Parameter | Value   |
|-----------|---------|
| $a$       | 0.126779|
| $b$       | 0.792366|
| $d$       | 10      |
| $\gamma$ | 1000    |

the threshold is $10^{-5}$. At that point, we assume that a spatially inhomogeneous steady state has been reached. We record the final $T$ time and save the solution. To confirm that the solution is indeed stationary, we keep solving the system until time $t = 2T$ and check that the difference between the solutions at time $T$ and $2T$ is below the threshold. To generate our synthetic measurement, we add Gaussian noise to the solution, as illustrated in Figure 3.

This synthetic experiment is a situation similar to what one will face in an actual experiment, although some assumptions, in particular the fixed known initial conditions, are not realistic. A detailed study of the dependence of the solution with respect to initial conditions will be necessary to drop this assumption. Alternatively, the initial conditions could be included as a parameter to identify.

**Case 1: Credible regions for $a$ and $b$ with little knowledge**

For our first example, we assume that the values of the parameters $\gamma$ and $d$ are known, and that we would like to find the values for the parameters $a$ and $b$. In a first approach, we assume very little knowledge about $a$ and $b$: only their order of magnitude is assumed to be known. This knowledge is modelled by a uniform prior distribution on the region given by $[0.1, 10]^2$. The data for this example has Gaussian noise with standard deviation 5% of the range of the solution. We can see in Figure 4 a 95% probability region for the posterior distribution. Observe how this region is concentrated around the exact value, in contrast to our original knowledge of a uniform distribution on the region $[0.1, 10]^2$. More precisely, the credible region is contained within the range $[0.126, 0.128] \times [0.789, 0.796]$. The length of the credible region in the $b$-direction is approximately 3.5 times larger than in the $a$-direction, although the size relative to the magnitude of the parameters is smaller in the $b$-direction.

For the Schnakenberg reaction kinetics [20, 45, 48], it is possible to compute the region that contains the parameters that can lead to non-homogeneous steady states, the Turing space (see next example for details). We can see that our original prior covered an area much much larger than the Turing space (almost 100 times larger), but the posterior is concentrated in a small region completely contained within it (see Figure 5).
Case 2: Credible regions for \(a\) and \(b\) using the Turing parameter space

Unlike the previous example, where we assume little knowledge of the prior, here we exploit the well-known theory for reaction-diffusion systems on stationary domains and use a much-more informed prior based on analytical theory of the reaction-diffusion system. On stationary domains, diffusion-driven instability theory requires reaction-diffusion systems to be of the form of long-range inhibition, short-range activation for patterning to occur (i.e. \(d > 1\)). More precisely, a necessary condition for Turing pattern formation is that the parameters belong to a well-defined parameter space [40] described by the inequalities (for the case of reaction-kinetics (5))

\[
\begin{align*}
    f_u + g_v &= \frac{b-a}{b+a} - (a+b)^2 < 0, \\
    f_u g_v - f_v g_u &= (a+b)^2 > 0, \\
    d f_u + g_v &= d \left( \frac{b-a}{b+a} \right) - (a+b)^2 > 0, \\
    (d f_u + g_v)^2 - 4d (f_u g_v - f_v g_u) &= d \left( \frac{b-a}{b+a} \right) - (a+b)^2 > 0,
\end{align*}
\]

where \(f_u, f_v, g_u\) and \(g_v\) denote the partial derivatives of \(f\) and \(g\) with respect to \(u\) and \(v\), evaluated at the spatially homogeneous steady state \((a+b, (b-a)/(a+b)^2))\).

In Figure 5 we plot the parameter space obtained with Schnakenberg kinetics.

In this second example, we use data with added Gaussian noise with standard deviation 10% of the solution range. For the prior, we now use a uniform distribution on the Turing space of the system. In Figure 6 we can now see that despite the increased noise, the improved prior reduced the size of the 95% probability region dramatically.

Case 3: Credible regions for \(d\) and \(\gamma\)

In a third example, we assume that \(a\) and \(b\) are known, and we would like to find \(\gamma\) and \(d\). To illustrate the use of different types of priors, here we assume a log-normal prior that ensures positivity of \(\gamma\) and \(d\), which in the case of \(d\) is necessary to ensure a well-posed problem. We use the data with 5% noise, and the prior distribution of a log-normal with mean \((5, 500)\) and standard distribution 0.95. A 95% probability region of the posterior is depicted in Figure 7. Note the use of a log-normal or similar prior is essential here to ensure positivity of the diffusion coefficient which is required for the well posedness of the forward problem. The prior distribution covers a range of one order of magnitude for each parameters, and the posterior distribution suggests relative errors of order \(10^{-3}\).
Case 4: Credible regions for $a$, $b$, $d$ and $\gamma$

Finally, we identify all four parameters $a$, $b$, $d$ and $\gamma$ from the set of data with 10% noise. We use the priors from Case 1 for $a$ and $b$, and from Case 3 for $d$ and $\gamma$. We do not apply any further restrictions.

In Figure 8 we depict the credible regions for the projection of the parameters to four different coordinate planes. The noise for this experiment is higher than in Case 1 and 3. Also note that compared to the previous experiments we assume here less knowledge a priori about the parameters. It must be noted that assuming that a parameter is known is equivalent in the Bayesian formulation to use a Dirac delta for the prior on the parameter; in comparison, the prior distributions for Case 4 are more spread, therefore they represent less knowledge. Since the level of noise was higher, and the prior knowledge lower, the credible regions that we obtain are larger.

4 Conclusion

We have presented a methodology for parameter identification based on Bayesian techniques. The Bayesian framework offers a mathematically rigorous approach that includes the prior knowledge about the parameters (including functions). Furthermore, well-posedness results for the problem are available.

Although exploring a whole probability distribution can be computationally expensive, very useful information about the uncertainty or correlation of the parameters can be inferred from it. The use of a parallel Metropolis-Hastings algorithm makes the computations feasible using HPC facilities.

To illustrate the applicability of this technique, we studied the parameter identification problem for reaction-diffusion systems using Turing patterns as data for both scenarios: infinite and finite dimensional parameter identification cases. We provided a rigorous proof for the well-posedness of the parameter identification problem in the Bayesian sense, and we performed several numerical simulations to find credible regions for the parameters.

The mathematical machinery behind the Bayesian framework can be more involved than in the optimal control approach. For the latter, the general idea is intuitive: find the parameter that minimises the distance between the data and the solution. On the other hand, the Bayesian approach requires to understand the knowledge about a parameter as a probability distribution, to formulate the problems in terms of conditional probabilities, and then to use Bayes' theorem to characterise the solution.

An advantage of the Bayesian approach is that it allows us to understand all the elements of the mathematical formulation of the parameter identification problem in terms of aspects of the real-world experiment. Whilst in the optimal control approach one chooses the type of distance, or the norm, and the regularisation, according to technical limitations of the mathematical methods (see for instance [9, 44, 61]). In the Bayesian approach these choices are given by the distribution of the experimental error and the prior knowledge about
the parameter. Therefore, following the Bayesian methodology we can incorporate in the parameter identification problem more detailed characteristics of the noise and the prior knowledge, leading to estimations of the parameters more consistent with the experimental framework. Note that in terms of the optimal control formulation of the parameter identification problem, a different noise means a different distance to measure the fit between the data and the model. In general, different distances will be minimised by different values of the parameters.

5  Outlook

In this work, we have treated the synthetic data parameter identification problem using only information that would be available if the data came from an actual experiment. We are now in the process of applying this techniques to problems in experimental sciences and beyond where experimental data is available. The information provided by the posterior distribution allows us to solve problems like model selection incorporating all the knowledge from the experiments.

6  Data accessibility

All the computational data output is included in the present manuscript.

7  Competing interests

We have no competing interests.

8  Authors contributions

ECF carried out the bulk of the analysis, algorithm development and implementation as well as drafting the manuscript as part of his PhD thesis. CV and AM conceived the study, coordinated, supervised the research study and contributed equally to the writing up of the manuscript. All authors gave final approval for publication.

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Figure 3: The $u$-component of the solution to the Schnakenberg system [20, 45, 48], with added Gaussian noise with mean zero and standard deviation 5% (b) and 10% (c) of the range of the solution. Solutions of the $v$-component are 180 out-of-phase with those of $u$ and as such their plots are omitted (Colour version online).
Figure 4: 95% credible region for the posterior distribution for the parameters $a$ and $b$, using a uniform prior on the region $[0.1, 10]^2$. Note that for ease of visualisation, scales for $a$ and $b$ are different (Colour version online).
Figure 5: Darker region (blue in the online version), the Turing space for the parameters $a$ and $b$ of the Schnakenberg reaction kinetics [20, 45, 48]. Lighter region (red in the online version), the region plotted in Figure 4, depicting where the credible region is contained (Colour version online).
Figure 6: 95% credible region for the posterior distribution for the parameters $a$ and $b$, using a uniform prior on the Turing space (Colour version online).
Figure 7: 95% credible region for the posterior distribution for the parameters $d$ and $\gamma$, a log-normal prior with mean (5,500) and standard deviation 0.95 (Colour version online).
Figure 8: 95% credible region for the posterior distribution for the parameters $a$, $b$, $d$ and $\gamma$. See Case 1 and 3 for a description of the priors. The data has a noise of 10% of the range of the solution. Each subplot corresponds to the projection of the credible region onto a coordinate plane for two of the parameters, given by the row and the column of the subplot. The exact value of the parameters is marked with a triangle. (Colour version online).
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