A METHODOLOGY FOR PARAMETER IDENTIFICATION IN TURING SYSTEMS

MARCUS R. GARVIE[†], PHILIP K. MAINI[‡¶], AND CATALIN TRENCHEA[§]

Abstract. We introduce a general methodology for parameter identification in reaction-diffusion systems that display pattern formation via the mechanism of diffusion-driven instability. A Modified Discrete Optimal Control Algorithm is illustrated with the Schnakenberg and Gierer-Meinhardt reaction-diffusion systems using PDE constrained optimization techniques. A quadratic cost functional that measures the discrepancy between morphogen concentrations and target concentrations is minimized with the reaction diffusion system as a constraint. The numerical optimal control procedure efficiently and accurately estimates key parameters in the systems concerned.

Key words. optimal control theory, parameter identification, reaction-diffusion equations, diffusion-driven instability, finite element method

AMS subject classifications. 49J20, 93B30, 35K57, 92C15

1. Introduction. One of the central challenges in developmental biology is to understand how spatial patterning arises in embryogenesis. Traditional mathematical biology has addressed this issue through a top-down approach, which assumes that either a gradient in signalling chemical (termed morphogen) is set-up to which cells respond by differentiating in a multi-threshold dependent manner (Wolpert, 1969), or that complex spatial patterns are set up in a self-organising manner which then only require a single threshold for differentiation (Murray, 2002, 2003). The most well-known such model is the Turing model in which spatial patterning emerges in a system of reacting and diffusing chemicals via the phenomenon of diffusion-driven instability (Turing, 1952). This idea was extended by Gierer and Meinhardt (1972) to the general patterning principle of short-range activation, long-range inhibition. Several top-down models have been proposed involving different biological hypotheses (for example, cell-chemotaxis (Keller and Segel, 1971), mechanochemical (Oster et al., 1983), and neural models (Ermentrout et al., 1986)) but they all obey this underlying patterning principle. As a result, all these models produce very similar patterns and therefore it makes sense to study the simplest such model, which is the Turing model.

The first step towards determining if an observed pattern is a consequence of activator-inhibitor self-organisation is to investigate if such a model system can produce the pattern. While this is by no means a proof that such a pattern in nature is generated by this type of model, it is a necessary starting point. To our knowledge, no systemic procedure exists to investigate this - while simple periodic patterns of stripes and spots can be investigated using linear stabily analysis, more complex patterns are not amenable to such analysis. The goal of this paper is to propose methods from control theory to address this problem.

The structure of our paper is outlined as follows. In Section 2 the governing reaction-diffusion systems ('state equations') are introduced and a Direct Problem

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defined where we seek morphogen concentrations associated with given key parameters. In Section 3 the Inverse Problem is defined where we seek to recover the key model parameters that led to given target morphogen concentrations. The mathematical theory of optimal control is then used to derive an optimality system, which allows us to characterize the optimal ('key') parameters of the systems in terms of adjoint variables (see Section 4). In Section 5 we discuss the numerical methods used to approximate the state and adjoint equations, construction of the target functions, and implementation of a Modified Discrete Optimal Control Algorithm. The results of some numerical experiments are presented in Section 6 and the results and implications discussed in Section 7.

2. Direct Problem. We study coupled pairs of reaction-diffusion equations, called the 'state equations', with the following general form

$$\begin{cases} \frac{\partial u}{\partial t} = D_u \nabla^2 u + f_1(u,v), \\ \frac{\partial v}{\partial t} = D_v \nabla^2 v + f_2(u,v), \end{cases} \tag{2.1}$$

where $u(\mathbf{x},t)$ and $v(\mathbf{x},t)$ are morphogen concentrations at (vector) position $\mathbf{x} = (x,y)^T \in \Omega$ and time $t \in (0,T)$. Here Ω is a bounded domain in $\mathbb{R}^2$. D_u and D_v are the positive diffusion coefficients of u and v respectively. The standard Laplacian operator in two space dimensions is given by $\nabla^2 = \partial^2/\partial x^2 + \partial^2/\partial y^2$. The functions f_1 and f_2 model the reaction kinetics of u and v. We assume there is no flux of the morphogen concentrations across the boundary of Ω and that the initial concentrations, $u_0(\mathbf{x})$, $v_0(\mathbf{x})$, are bounded and nonnegative. To illustrate our methodology we focus on the following nonlinear examples of f_1 and f_2:

(i) the Schnakenberg (1979) model (first proposed in Gierer and Meinhardt (1972)):

$$\begin{aligned} f_1(u,v) &:= \gamma(a - u + u^2 v), \\ f_2(u,v) &:= \gamma(b - u^2 v), \end{aligned} \tag{2.2}$$

where γ, a, and b are positive constants.

(ii) the Gierer and Meinhardt (1972) model:

$$\begin{aligned} f_1(u,v) &:= \frac{ru^2}{v} - \mu u + r, \\ f_2(u,v) &:= ru^2 - \alpha v, \end{aligned} \tag{2.3}$$

where r, μ, and α are positive constants.

The aim of this paper is to estimate key parameters associated with patterns arising via diffusion-induced instability. For concreteness we focus on parameters c_1 and c_2 where

$$\begin{aligned} &c_1 = a, \quad c_2 = b \quad \text{in the Schnakenberg model,} \\ &c_1 = \mu, \quad c_2 = \alpha \quad \text{in the Gierer-Meinhardt model.} \end{aligned} \tag{2.4}$$

It is natural to assume pointwise bounds on the parameters, and thus we restrict the parameters to the admissible set

$$\mathcal{U}_{ad} = \{(c_1,c_2) \in \mathbb{R}^2 \ : \ 0 < c_1 \leq C_1, \ 0 < c_2 \leq C_2\}, \tag{2.5}$$

where C_1 and C_2 are determined from knowledge of the Turing spaces of the systems concerned.

We now state the direct problem:

(**DP**) For given parameters (c_1, c_2) belonging to the admissible set $\mathcal{U}_{ad}$, find the morphogen concentrations $u(\mathbf{x}, t)$ and $v(\mathbf{x}, t)$ satisfying (2.1) with kinetics (i) or (ii) for all $(\mathbf{x}, t) \in \Omega \times (0, T)$.

In order to prove a technique for the identification of parameters in our method (see Garvie and Trenchea (2009)), it is necessary that the solutions of the reaction-diffusion system (2.1) exist, are unique, are nonnegative and depend continuously on the initial data. In the case of kinetics (i) as we were unable to find a proof in the literature we provide a proof in the Appendix. In the case of kinetics (ii), existence and uniqueness are proved in the monograph by Rothe (1984), and the nonnegativity of solutions follows from an analogous argument to the one given for kinetics (i).

3. Inverse Problem Statement and Parameter Identification. The basic description of the inverse problem is as follows. We start with given stationary 'target functions' $(\bar{u}, \bar{v})$ that represent some desired morphogen concentrations of the system (a 'pattern'). We then seek the key parameters such that the solution of the direct problem (DP) (u, v) matches the target functions $(\bar{u}, \bar{v})$ as closely as possible.

The target functions may be noisy due to measurement error, or may not be a solution of the direct problem (DP). Thus we employ a least squares technique so that (u, v) best approximates $(\bar{u}, \bar{v})$. The basic optimal control technique is to minimize a quadratic cost functional subject to the reaction-diffusion system as a constraint.

Denoting the Banach space of square integrable functions over $\Omega_T := \Omega \times (0, T)$ by $L^2(\Omega_T)$, for given $\bar{u}$ and $\bar{v}$ in $L^2(\Omega_T)$, the least-squares approach leads to the minimization problem:

$$\inf_{c_1, c_2 \in \mathcal{U}_{ad}} J(c_1, c_2) \tag{3.1}$$

where the cost functional J is defined by:

$$J(c_1, c_2) = \frac{1}{2} \int_\Omega \left(\gamma_1 |u(x, T) - \overline{u}(x)|^2 + \gamma_2 |v(x, T) - \overline{v}(x)|^2 \right) dx + \frac{\delta_1}{2} c_1^2 + \frac{\delta_2}{2} c_2^2, \tag{3.2}$$

subject to the reaction-diffusion system (2.1) as a constraint. The terms weighted by γ_i measure the discrepancy between the solution and targets at the final time T. The terms weighted by δ_i effectively bound the size of the key parameters c_1 and c_2, which is a requirement of (2.5) and also allow for possibly noisy data. By appropriately choosing the weights in the cost functional we can place more emphasis on the solutions matching the targets, or we can place more emphasis on limiting the size of the parameters.

We now state the inverse problem for parameter identification in the reaction-diffusion system (2.1) with kinetics (i) or (ii):

(**IP**) For given target functions $\bar{u}, \bar{v} \in L^2(\Omega_T)$, find optimal parameters $(c_1^*, c_2^*) \in \mathcal{U}_{ad}$ and optimal solutions (u^*, v^*) of (2.1) that satisfy the minimization problem (3.1).

The rigorous proof of the existence of a solution to the inverse problem (IP) for the reaction-diffusion system (2.1) with kinetics (2.3) is given in (Garvie and Trenchea,

2009) and first-order necessary conditions for optimality are used to derive an optimality system of partial differential equations whose solutions provide optimal states and controls. The corresponding results for the simpler system with the Schnakenberg kinetics (2.2) are proved in a similar fashion.

4. Optimality System. The mathematical theory of optimal control theory leads to the derivation of a linear reaction-diffusion system for 'adjoint' variables $(p(\mathbf{x},t), q(\mathbf{x},t))$ called the 'adjoint system'

$$\begin{cases} -\frac{\partial p}{\partial t} = D_u \nabla^2 p + g_1(p,q), \\ -\frac{\partial q}{\partial t} = D_v \nabla^2 q + g_2(p,q), \end{cases} \tag{4.1}$$

corresponding to the system for the Lagrange multipliers of the PDE constrained optimization problem. Corresponding to kinetics (i) we have

$$\begin{aligned} g_1(p,q) &:= 2\gamma uv(p-q) - \gamma p, \\ g_2(p,q) &:= \gamma u^2(p-q), \end{aligned} \tag{4.2}$$

and corresponding to kinetics (ii) we have

$$\begin{aligned} g_1(p,q) &:= \left(2r\frac{u}{v} - \mu\right) p + 2ruq, \\ g_2(p,q) &:= r\frac{u^2}{v^2} p - \alpha q. \end{aligned} \tag{4.3}$$

The adjoint equations are backward in time and thus terminal conditions are needed instead of initial conditions:

$$p(\cdot,T) = \gamma_1(u(\cdot,T) - \bar{u}(\cdot)), \quad q(\cdot,T) = \gamma_2(v(\cdot,T) - \bar{v}(\cdot)). \tag{4.4}$$

We also use the adjoint system to obtain an explicit characterization of the optimal controls in terms of the adjoint variables, which are called 'optimality conditions'

$$c_1^* = \max\left\{0, \min\left\{\frac{d_1}{\delta_u}\int_{\Omega_T} p\,dx\,dt,\ C_1\right\}\right\}, c_2^* = \max\left\{0, \min\left\{\frac{d_2}{\delta_v}\int_{\Omega_T} q\,dx\,dt,\ C_2\right\}\right\},$$

where with kinetics (i) $d_1 = d_2 = -\gamma$, and with kinetics (ii) $d_1 := u^*$, $d_2 := v^*$. The state equations (2.1), and the adjoint equations (4.1) together with the optimality conditions are called the 'optimality system'. For mathematical details concerning derivation of the optimality systems see (Lenhart and Workman, 2007; Garvie and Trenchea, 2009).

5. Numerical methods.

5.1. Approximation of the state and adjoint equations. We approximate the state equations and adjoint equations on the unit square using an unstructured grid generator. In all our simulations we partition the domain into 8192 approximately equilateral triangles with 4225 nodes and then apply the standard Galerkin finite element method (Ciarlet, 1978) with piecewise linear continuous basis functions. For a given generic reaction-diffusion equation of the form

$$\frac{\partial u}{\partial t} = D\nabla^2 u + f(u),$$

where D is the diffusion coefficient for a morphogen u, application of the finite element method leads to a large system of ordinary differential equations (an initial value problem (IVP)) in the form

$$\dot{\mathbf{U}} = D\nabla_h^2\mathbf{U} + \mathbf{F}(\mathbf{U}),$$

where ∇_h^2 is the discrete Laplacian depending on a (spatial) step-size h and $\mathbf{U}$ is the solution vector of approximate nodal values.

For the time discretization of the IVP it is well-known that several popular time-stepping schemes for reaction-diffusion equations modeling pattern formation yield qualitatively poor results (Ruuth, 1995). In order to approximate the reaction-diffusion system with kinetics (i) we employed the following 'first-order semi-implicit backward Euler difference scheme' (1-SBEM)

$$\begin{aligned}
\frac{u^{n+1}-u^n}{\Delta t} &= D_u\nabla^2 u^{n+1} + \gamma(a - u^{n+1} + u^n u^{n+1} v^n),\\
\frac{v^{n+1}-v^n}{\Delta t} &= D_v\nabla^2 v^{n+1} + \gamma(b - (u^n)^2 v^{n+1}),
\end{aligned} \tag{5.1}$$

where Δt is the uniform time-step of the time interval $[0, T]$ and n refers to the n-th time level at time $t_n := n\Delta t$. Note that the diffusion and linear components of the reaction kinetics are approximated implicitely, while the nonlinear components are treated semi-implicitely. This scheme was successfully used by Madzvamuse (2006) to accurately simulate Turing patterns of the Schnakenberg system.

To solve the reaction-diffusion system with kinetics (ii) we employed a second order, 3-level, implicit-explicit (IMEX) scheme (2-SBDF) recommended by Ruuth (1995) as a good choice for most reaction-diffusion problems for pattern formation, namely

$$\begin{aligned}
\frac{3u^{n+1}-4u^n+u^{n-1}}{2\Delta t} - D_u\nabla^2 u^{n+1} &= 2f_1(u^n, v^n) - f_1(u^{n-1}, v^{n-1}),\\
\frac{3v^{n+1}-4v^n+v^{n-1}}{2\Delta t} - D_v\nabla^2 v^{n+1} &= 2f_2(u^n, v^n) - f_2(u^{n-1}, v^{n-1}),
\end{aligned} \tag{5.2}$$

where f_1 and f_2 are given by the Gierer-Meinhardt kinetics (2.3). One of the advantages of this scheme is that we can use relatively large time-steps and still obtain a good approximation of highly oscillatory solutions. IMEX schemes use an implicit discretization of the diffusion term, and an explicit discretization of the reaction terms. As the scheme 2-SBDF involves three time levels we approximate the solutions at the first time level using a first order IMEX scheme (1-SBDF) with a small time-step (Ruuth, 1995).

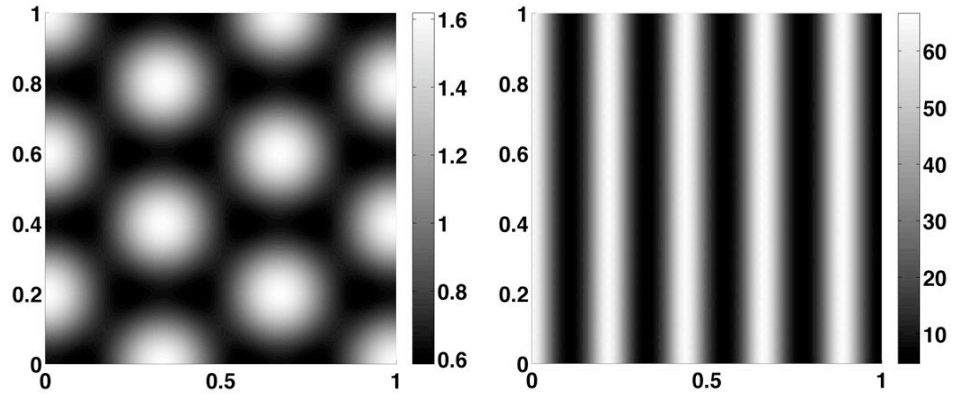
The numerical schemes used to approximate the linear adjoint equations were similar to the schemes used to approximate the state equations. Application of the finite element method for the spatial discretization coupled with the time-stepping schemes in all cases led to sparse linear systems of algebraic equations, which were solved in MATLAB (R2008a) using the GMRES iterative solver.

5.2. Construction of the Target Function. The target functions $(\bar{u}, \bar{v})$ used in this paper were generated from the reaction-diffusion systems themselves via the mechanism of diffusion-driven instability (the 'Turing mechanism'). Solutions were generated on the unit square with homogeneous Neumann boundary conditions. The standard approach in the literature for constructing Turing patterns is to prescribe

the initial data equal to small random perturbations about the corresponding stationary states of the spatially homogeneous systems, i.e., the reaction-diffusion systems without diffusion. The problem with this approach is that this is often done using an unspecified random number generator with an unspecified 'seed', and thus the numerical results are effectively not reproducible. To circumvent this problem we perturb the stationary states using known functions. For kinetics (i) we choose the initial conditions (see Ruuth (1995), or Madzvamuse (2006))

$$u(\mathbf{x},0) = 0.919145 + 0.0016\cos(2\pi(x+y)) + 0.01\sum_{j=1}^{8}\cos(2\pi jx),$$
$$v(\mathbf{x},0) = 0.937903 + 0.0016\cos(2\pi(x+y)) + 0.01\sum_{j=1}^{8}\cos(2\pi jx), \tag{5.3}$$

while the initial functions for kinetics (ii) were chosen equal to the same functions, but with 'cosine' function replaced with the 'sine' function.



(a) (b)

Fig. 5.1: (a) Target function $\bar{u}$ for the Schnakenberg kinetics: $T = 5$, $D_u = 1$, $D_v = 10$, $\gamma = 1000$, $a = 0.126779$, $b = 0.792366$, $\Delta t = 0.0001$ (1-SBEM). (b) Target function $\bar{u}$ for the Gierer-Meinhardt kinetics: $T = 238.853$, $D_v = 0.27$, $D_u = 9.45 \times 10^{-4}$, $r = 0.001$, $\alpha = 100$, $\mu = 2.5$, $\Delta t = 1 \times 10^{-8}$ (1-SBDF), $\Delta t = 0.001$ (2-SBDF). For details concerning the finite element methods and initial and boundary conditions see the main text above.

The state equations were solved until the transient solutions died out, which was determined by waiting until some large time $t = T$ when the l_2 norm of the change in state in one time-step was less than some small tolerance. We checked that the patterns were unchanged at $t = 2T$, thus confirming that the solutions were indeed stationary. Target functions for u are shown in Figures 5.1(a)-5.1(b) (the patterns for v are similar). See the caption for the parameter values.

5.3. Discrete optimal control procedure.

The Standard Algorithm. To approximate the inverse problem (IP) we apply a 'variable step gradient algorithm' (Garvie and Trenchea, 2009) yielding a sequence of approximations to the optimal solutions and optimal parameters (Ciarlet, 1989). We begin by making an initial guess for the parameters c_1^0, c_2^0 and the step length λ^0.

Initial conditions for the states were chosen to be the same as the initial conditions used to generate the target functions (see Section 5.2). Then for each iteration k of the gradient method we solve the nonlinear reaction-diffusion system for u^k, v^k $(k \geq 1)$, and store the cost $J(c_1^k, c_2^k)$. We also compute the adjoint variables p^k, q^k, determine $dJ(c_1^k, c_2^k)/d(c_1^k, c_2^k)$, the total derivative of J with respect to the vector (u^k, v^k), and take a step along this direction using the appropriate step length, provided the cost functional decreases. If the cost functional fails to decrease, then the step length is rejected and the step length decreased. If the step length is accepted, then the parameters (c_1^{k+1}, c_2^{k+1}) are updated using a standard gradient update

$$(c_1^{k+1}, c_2^{k+1}) = (c_1^k, c_2^k) - \lambda^k \frac{dJ(c_1^k, c_2^k)}{d(c_1^k, c_2^k)}, \quad k \geq 1.$$

The procedure is repeated until the relative change in the cost is smaller than some tolerance. This is computationally expensive as each iteration of the discrete optimal control algorithm requires the numerical solution of the state equation up to some final time T, the numerical solution of the adjoint equations backward in time from T, and gradient updates. The bulk of the computational costs are found in the backward-in-time solution of the adjoint system (4.1) and the forward-in-time solution of the state system (2.1).

A Modified Discrete Optimal Control Algorithm. We present a Modified Discrete Optimal Control Algorithm based on the Standard Algorithm above. The modified algorithm utilizes the fact that the target functions are stationary patterns. As the target functions are known data, we choose the initial data of the state equations equal to the target functions, take $T = 2\Delta t^*$, and seek parameters c_1 and c_2 that make the initial data stationary. All other aspects of the modified algorithm are the same as in the Standard Algorithm. If the parameters c_1 and c_2 are optimal then the cost after two time-steps $2\Delta t$ is zero and the algorithm stops. If the parameters c_1 and c_2 are suboptimal the initial data evolves over two time-steps $2\Delta t$. The discrepancy between the solutions and targets is then measured by the cost functional and the variable step gradient algorithm adjusts the parameters accordingly. A big advantage of the modified algorithm is that only two time-steps are needed to test if the initial data is stationary for the current parameters, which is a huge saving in computational cost compared to the Standard Algorithm.

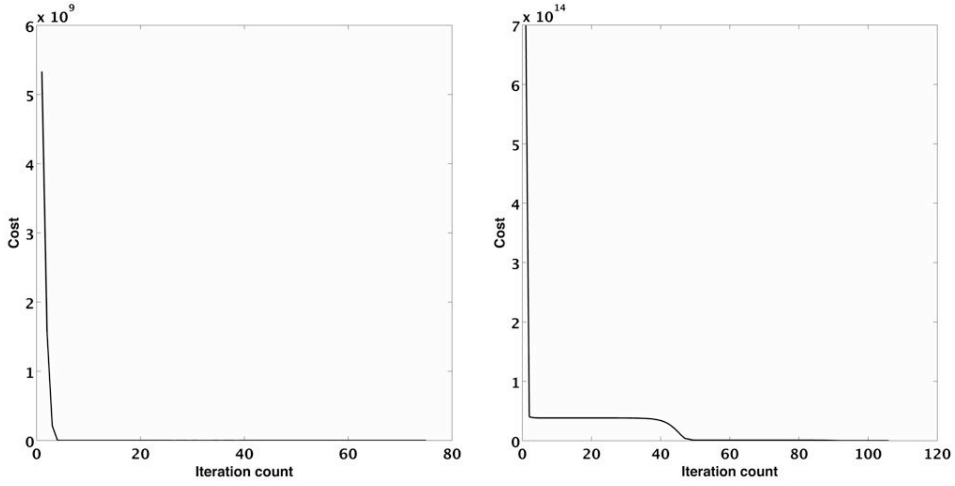
6. Numerical results. We were unable to obtain satisfactory results using the Standard Algorithm as the iterative procedure failed to converge and frequently stagnated, yielding parameter values far from the optimal ones (results not presented). However, the Modified Algorithm converged for almost all starting values ('initial guesses') of the key parameters c_1 and c_2, taking on the order of half a minute to accurately estimate the optimal parameters used to generate the target patterns (using a Mac Pro with a 2×3 GHz Dual-Core Intel Xeon processor). Table 6.1 shows the results of one experiment for each system. We obtained more significant figures of accuracy when estimating a and b than when estimating μ and α, which was generally the case. To verify convergence we also plotted the cost functional against iteration count for both reaction-diffusion systems. The plots show an initial rapid decrease in cost with a subsequent slow decrease after the first few iterations of the optimal control

*Two time-steps are the minimum number of time-steps that the discrete optimal control procedure needs to run.

algorithm (see Figures 6.1(a) - 6.1(b) and the caption for the remaining parameters used in the simulations).

Table 6.1: Model parameter estimates for the Modified Algorithm.

Parameter	Start value	Controlled value	Optimal value
a	5	0.126776	0.126779
b	0.3	0.792365	0.792366
μ	50	2.499473	2.5
α	30	99.994690	100

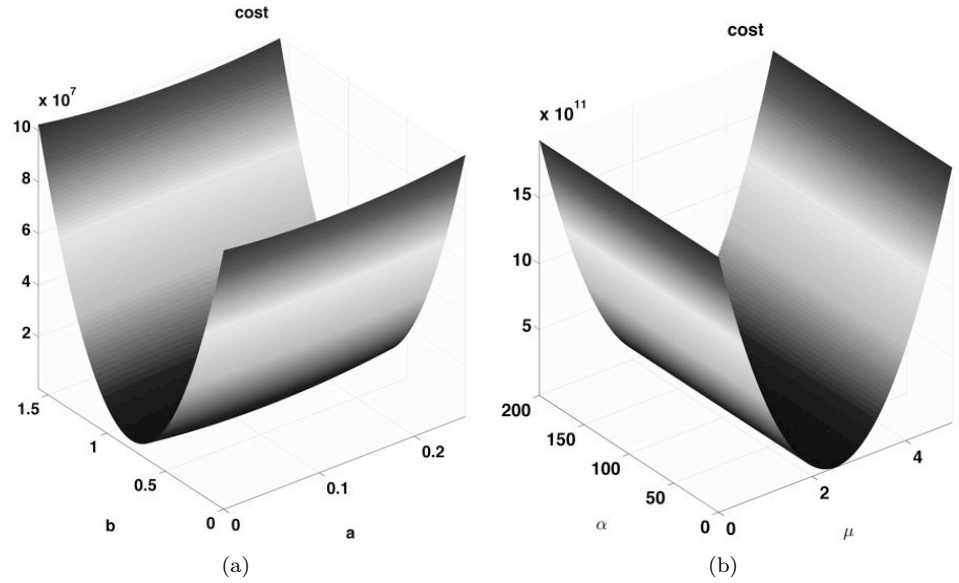


(a) (b)

Fig. 6.1: (a) Change in cost with iteration count. (a) Schnakenberg system: $D_u = 1$, $D_v = 10$, $\gamma = 1000$, $\Delta t = 0.0001$ (1-SBEM), $\gamma_1 = \gamma_2 = 1 \times 10^{10}$, $\delta_1 = \delta_2 = 1$. (b) Gierer-Meinhardt system: $D_v = 0.27$, $D_u = 9.45 \times 10^{-4}$, $r = 0.001$, $\Delta t = 1 \times 10^{-8}$ (1-SBDF), $\Delta t = 0.001$ (2-SBDF), $\gamma_1 = \gamma_2 = 1 \times 10^{15}$, $\delta_1 = \delta_2 = 0$.

7. Discussion. In this paper we presented a Modified Discrete Optimal Control Algorithm for the accurate and efficient estimation of parameters used to generate patterns via the mechanism of diffusion-driven instability. Unlike previous ad hoc studies of parameter estimation in Turing systems, the modified algorithm is based on the rigorous mathematical theory of optimal control theory and provides a systematic and reliable approach to parameter estimation. The methodology is illustrated with the Schnakenberg and Gierer-Meinhardt reaction-diffusion systems where two key parameters are estimated in each model.

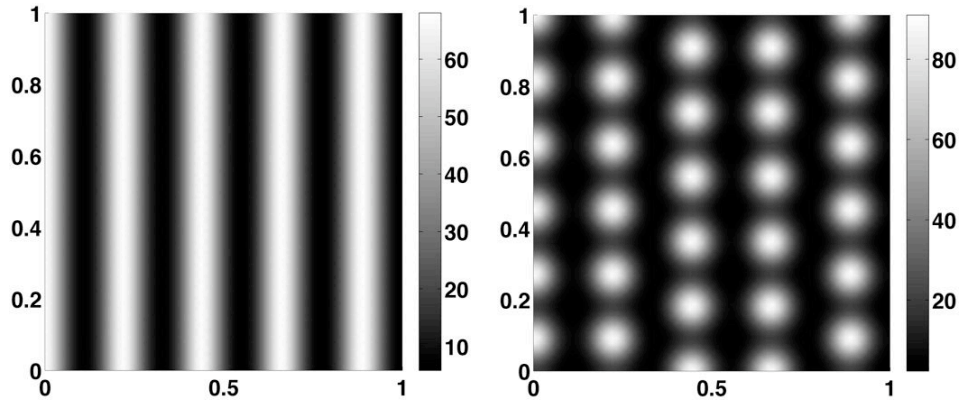
Sensitivity of pattern formation on model parameters. Once the optimal parameters of a system have been accurately found we can investigate how sensitive the patterns are to changes in the parameters. For fixed target patterns we plotted the surfaces corresponding to the cost as a function of the parameters in the Schnakenberg and Gierer-Meinhardt reaction-diffusion systems (see Figures 7.1(a) and 7.1(b)). We can see from Figure 7.1(a) that the target pattern is relatively insensitive to changes in a compared to changes in b. Similarly, we can see from Figure 7.1(b) that the target pattern is relatively insensitive to changes in α compared to changes in μ. The *insensitivity* of a pattern to changes in a model parameter tells us that there exists a family of similar patterns in a neighborhood of the optimal pair (c_1^*, c_2^*). For example,



(a) (b)

Fig. 7.1: (a) The cost functional as a function of the parameters c_1 and c_2 for (a) the Schnakenberg system, and (b) the Gierer-Meinhardt system. The surfaces were plotted using 200×200 points in the c_1-c_2 plane.

in Figure 7.1(b) if we fix μ at it's optimal value $\mu^* = 2.5$, then we expect the patterns associated with the points $(2.5, \alpha)$, $\alpha \in \mathbb{R}$, to be similar, provided we are close to the optimal pair $(2.5, 100)$. This is verified in Figures 7.2(a) and 7.2(b), which show the patterns associated with points close to the optimal parameter pair (μ^*, α^*), where we have perturbed either μ^* or α^*. As predicted, the pattern in Figure 7.2(a) is very similar to the target pattern in Figure 5.1(b), unlike the pattern in Figure 7.2(b) that is very different.



(a) (b)

Fig. 7.2: Morphogen concentrations u for the Gierer-Meinhardt system with $T = 238.853$, $D_v = 0.27$, $D_u = 9.45 \times 10^{-4}$, $r = 0.001$, $\Delta t = 1 \times 10^{-8}$ (1-SBDF), $\Delta t = 0.001$ (2-SBDF). (a) $\alpha = 90$, $\mu = 2.5$. (b) $\alpha = 100$, $\mu = 2.4$. For details concerning the finite element methods and initial and boundary conditions see the main text above.

An 'Image Driven Parameter Identification Methodology'. For the examples presented in this paper we used the reaction-diffusion systems themselves to generate the target patterns via the mechanism of diffusion-driven instability. Ideally we would like to identify the model parameters associated with target patterns $(\bar{u}, \bar{v})$ arising from some biological application. The Modified Algorithm does not require the target functions to be solutions of the reaction-diffusion system, however, if the patterns are far from solutions of the state equations then the discrete optimal control procedure may fail to converge. One of the difficulties in developing a general 'Image Driven Parameter Identification Methodology' for targets that arise in practical applications is that we may have no knowledge of the maximum and minimum values of those functions, for example, in the case of images taken from the web. In practical situations we would expect to be able to use knowledge of the biological situation to infer approximate bounds on the solutions. We also have flexibility in the choice of the weights δ_1 and δ_2 used in the cost functional (3.2) that allows us to take into account noisy data.

Potential biological applications. In developing mathematical models, ideally one determines parameter values from independent data sources. However, in many biological applications, this is very difficult to do. The methodology presented in this paper will allow us, in principle, to determine the parameter values necessary for such models to form a pattern in question or, indeed, determine if the pattern observed experimentally can be exhibited by a particular model. As such, the methodology presented here could have broad ranging application in mathematical modelling. In particular, it could determine to which parameters model behavior is most sensitive and therefore prioritize which parameters should be the focus of experimental investigation.

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8. Appendix.

8.1. Well-posedness of the Schnakenberg system. We provide a proof of the well-posedness of the Schnakenberg system using the theoretical setup of Morgan (1989).

THEOREM 8.1. *Let the initial concentrations* $(u_0(\mathbf{x}), v_0(\mathbf{x}))$ *be bounded and lie in* $[0,\infty)^2$ *for all* $\mathbf{x} \in \Omega$. *Then there exists a unique nonnegative classical solution of the Schnakenberg system* (2.1) *with kinetics* (2.2) *augmented with zero flux boundary conditions for all* $(\mathbf{x}, t)$ *in* $\Omega \times [0,\infty)$.

Proof. For notational convenience we swap u and v in the Schnakenberg system, which effectively swaps the first and second equations in the reaction kinetics (2.2), yielding the equivalent system

$$\begin{cases} \frac{\partial u}{\partial t} = D_u \nabla^2 u + \widehat{f}_1(u,v), \\ \frac{\partial v}{\partial t} = D_v \nabla^2 v + \widehat{f}_2(u,v), \end{cases}$$

where

$$\begin{aligned} \widehat{f}_1(u,v) &:= \gamma(b - v^2 u), \\ \widehat{f}_2(u,v) &:= \gamma(a - v + v^2 u). \end{aligned}$$

The local existence of solutions follows from well-known semigroup theory (see for example Pazy (1983), or Henry (1981)). In particular, from Proposition 1 in Hollis et al. (1987) it follows immediately that the Schnakenberg system has a unique noncontinuable classical solution (u, v) for $(\mathbf{x}, t) \in \Omega \times [0, T_{max})$. To prove the nonnegativity of solutions observe that the reaction kinetics satisfy

$$\widehat{f}_1(0,v),\ \widehat{f}_2(u,0) \geq 0 \quad \text{for all } u, v \geq 0,$$

and recall that the initial data lies in the positive quadrant of phase space by assumption. Thus by a maximum principle (Smoller (1983, Lemma 14.20)) the solution $(u(\mathbf{x},t), v(\mathbf{x},t))$ lies in $[0,\infty)^2$ for all $\mathbf{x} \in \Omega$ and for all time for which the solution exists. Thus $[0,\infty)^2$ is positively invariant for the system. We apply the theoretical framework of Morgan (1989) to prove global existence and uniqueness of classical solutions, which requires 'intermediate sum' conditions and polynomial growth conditions on the kinetics to hold.

We first define a so called Lyapunov-type function given by

$$H(u,v) := h_1(u) + h_2(v), \quad \text{where} \quad h_1(u) = u, \quad h_2(v) = v.$$

Then with $a_{11} = a_{22} = a_{21} = 1$, $K_2 = K_4 = K_6 = \gamma(a+b)$, $K_1 = r = 1$, $K_3 = \gamma/3$, $K_5 = 0$, and $q = 3$ the following conditions are easily verified for all $(u,v) \in [0,\infty)^2$, corresponding to conditions (H4)(i), (H5), and (H6) in Morgan (1989) respectively:

$$\begin{aligned} &a_{11} h_1'(u) \widehat{f}_1(u,v) \leq K_1 (H(u,v))^r + K_2, \\ &a_{21} h_1'(u) \widehat{f}_1(u,v) + a_{22} h_2'(v) \widehat{f}_2(u,v) \leq K_1 (H(u,v))^r + K_2, \\ &h_1'(u) \widehat{f}_1(u,v),\ h_2'(v) \widehat{f}_2(u,v) \leq K_3 (H(u,v))^q + K_4, \\ &\nabla H(u,v) \cdot \begin{pmatrix} \widehat{f}_1(u,v) \\ \widehat{f}_2(u,v) \end{pmatrix} \leq K_5 H(u,v) + K_6. \end{aligned}$$

Thus as $r = 1$ Theorems 3.2 and 2.2 in Morgan (1989) hold, which implies $T_{max} = \infty$, i.e. we have global existence of nonnegative, classical solutions. ∎

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