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ON THE OPTIMIZATION OF INITIAL CONDITIONS FOR A MODEL PARAMETER ESTIMATION

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Abstract: The design of an experiment, e.g., the setting of initial conditions, strongly influences the accuracy of the process of determining model parameters from data. The key concept relies on the analysis of the sensitivity of the measured output with respect to the model parameters. Based on this approach we optimize an experimental design factor, the initial condition for an inverse problem of a model parameter estimation. Our approach, although case independent, is illustrated at the FRAP (Fluorescence Recovery After Photobleaching) experimental technique. The core idea resides in the maximization of a sensitivity measure, which depends on the initial condition. Numerical experiments show that the discretized optimal initial condition attains only two values. The number of jumps between these values is inversely proportional to the value of a diffusion coefficient D (characterizing the biophysical and numerical process). The smaller value of D is, the larger number of jumps occurs.

Keywords: FRAP, sensitivity analysis, optimal experimental design, parameter estimation, finite differences

MSC: 65M32, 65N21, 49Q10, 49Q12, 65D25

1. Introduction

Image processing is one of the fastest growing areas in informatics and applied mathematics. However, it is not a rare case that a large amount of data, e.g., spatio-temporal FRAP (Fluorescence Recovery After Photobleaching) images, is routinely

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generated without a clear idea about further data processing. The FRAP technique is based on measuring the fluorescence intensity (proportional to non-bleached particles concentration) in a region of interest (being usually an Euclidian 2D domain) in response to a high-intensity laser pulse. The laser pulse (the so-called *bleach*) causes an irreversible loss in fluorescence of some particles residing originally in the bleached area, without any damage to intracellular structures. After the bleach, we observe the change in fluorescence intensity in a monitored region reflecting the diffusive transport of fluorescent particles from the area outside the bleach [9].

The aim of this paper is to establish the link between experimental conditions (protocol) and the accuracy of the results. The idea is presented in a simplified case study of FRAP data processing [8], [3]. It serves as a paradigmatic example of the inverse problem of the diffusion parameter estimation from spatio-temporal measurements of fluorescent particle concentration. A natural question is how the experimental settings influence the accuracy of resulting parameter estimates. There are many rather empirical recommendations related to the design of a photobleaching experiment, e.g., the bleach spot shape and size, the region of interest (its location and size), or the total time of measurement, see [9]. However, we should have a more rigorous tool for the choice of experimental design factors. This goal can be achieved through a reliable process model, i.e., the Fickian diffusion equation, and through performing the subsequent sensitivity analysis with respect to the model parameters. Thus, we can define an optimization problem as the maximization of the sensitivity measure described in Section 2. The special focus of this paper concerns the search for the optimal initial condition that in its discretized form represents the bleaching pattern [2], [5].

The paper is organized as follows. In Section 2, we define the sensitivity measure and formulate the optimization problem. Section 3 describes a numerical approach to reach the optimal initial condition. In Section 4, we provide a numerical example to show that the features of the optimal initial condition strongly depend on the diffusion coefficient. Finally, some conclusions are presented in Section 5.

2. Problem formulation

We consider the Fickian diffusion problem with a *constant* diffusion coefficient $D > 0$ and assume a spatially radially symmetric observation domain, i.e., the data are observed on a cylinder with the radius R and height T. In FRAP, the simplest governing equation for the spatio-temporal distribution of fluorescent particle concentration $u(r,t)$ is the diffusion equation as follows[1]

$$\frac{\partial u}{\partial t} = D\left(\frac{\partial^2 u}{\partial r^2} + \frac{1}{r}\frac{\partial u}{\partial r}\right), \tag{1}$$

[1]We consider the diffusion equation in polar coordinates since both the whole boundary value problem and the bleaching pattern used in the FRAP experiment have the rotational (axial) symmetry. In our preceding papers [8], [4], we employed the Cartesian coordinate system.

where $r \in (0, R],\ t \in [0, T]$, with the initial and Neumann boundary conditions

$$u(r, 0) = u_0(r), \quad \frac{\partial u}{\partial r}(R, t) = 0. \tag{2}$$

The main issue in FRAP and related estimation problems is to find the value of the diffusion coefficient D from spatio-temporal measurements of the concentration $u(r, t)$, see [7], [8].

Obviously, the measured data are discrete and each data entry quantifies the variable u at a particular spatio-temporal point (r, t) in a finite domain, i.e.,

$$u(r_i, t_j), \quad i = 0 \dots n, \quad j = 0 \dots m,$$

where i is the spatial index uniquely identifying the pixel position where the value of fluorescence intensity u is measured and j is the time index (the initial condition corresponds to $j = 0$). Usually, the data points are uniformly distributed both in time (the time interval Δt between two consecutive measurements is constant) and space, i.e., on an equidistant mesh with the step-size Δr, see [4].

Given the data as above, the diffusion coefficient D can be computed numerically by solving the inverse problem to (1)–(2). Because of unavoidable noise in the data, one obtains an estimated value $\overline{D}$ which reasonably well approximates the true D. It can be shown [1], [4], that for our case of single scalar parameter estimation and white noise as data error assumed, the expected relative error in D depends on the data noise and a factor, which we call the global semi-relative squared sensitivity S_{GRS}, as follows

$$\mathbb{E}\left(\left|\frac{\overline{D} - D}{D}\right|^2\right) \sim \frac{\sigma^2}{S_{GRS}}, \tag{3}$$

where $\mathbb{E}$ is the expected value and σ^2 denotes the variance of the additive Gaussian noise. The sensitivity measure S_{GRS}, that depends on the initial condition, is defined on a spatio-temporal mesh by

$$S_{GRS} = D^2 \sum_{i=0}^{n} \sum_{j=1}^{m} \left[\frac{\partial}{\partial D} u(r_i, t_j)\right]^2, \tag{4}$$

where $\frac{\partial}{\partial D} u(r_i, t_j)$ is the usual sensitivity of the model output at the spatio-temporal point (r_i, t_j) with respect to the parameter D. It is obvious from this estimate that if the noise level is fixed, the estimation of D can only be improved by switching to an experimental design with a higher sensitivity.

The sensitivity measure (4) involves several design parameters. If all the above parameters $R, T, \Delta r, \Delta t$ are fixed, there is only one way to maximize the sensitivity measure S_{GRS}: to consider the *initial condition* u_0 in (2) as the experimental design parameter. In the discretized problem, the aim is to find the initial condition $(u_0(r_0), \dots, u_0(r_n))^T \in \mathcal{R}^{n+1}$ such that S_{GRS} is maximized and hence the expected

error in D is minimized. In order to do so, we establish the bounds where the initial condition is considered: $\underline{u_0} \le u_0 \le \overline{u_0}$, where $\underline{u_0}, \overline{u_0} \in \mathcal{R},\ \underline{u_0} < \overline{u_0}$. The optimization problem can be formulated as follows

$$u_0^{opt} = \arg \max_{u_0 \in \mathcal{R}^{n+1}} S_{GRS}(u_0) \quad \text{subject to} \quad \underline{u_0} \le u_0 \le \overline{u_0}, \tag{5}$$

where, for brevity, u_0 is interpreted as a vector.

3. Optimization of the initial condition

Based on the parameters R, T, it is convenient to introduce the following scaling of the space and time coordinates and to define a scaled diffusion coefficient δ

$$\tilde{r} := \frac{r}{R}, \quad \tilde{t} := \frac{t}{T}, \quad \delta := \frac{DT}{R^2}. \tag{6}$$

The concentration u in the scaled coordinates $\tilde{r}, \tilde{t}$ then satisfies the equation

$$\frac{\partial u}{\partial \tilde{t}} = \delta \left(\frac{\partial^2 u}{\partial \tilde{r}^2} + \frac{1}{\tilde{r}} \frac{\partial u}{\partial \tilde{r}} \right), \tag{7}$$

where $\tilde{r} \in [0,1],\ \tilde{t} \in [0,1]$, with initial and Neumann boundary conditions

$$u(\tilde{r}, 0) = u_0(\tilde{r}), \quad \frac{\partial u}{\partial \tilde{r}}(1, \tilde{t}) = 0. \tag{8}$$

Let us fix $n+1$ as a number of spatial points and m as a number of time measurements. Consider a spatio-temporal grid $\{\tilde{r}_i, \tilde{t}_j\},\ i = 0 \dots n,\ j = 0 \dots m$, where $\tilde{r}_0 = 0,\ \tilde{r}_n = 1,\ \tilde{t}_0 = 0,\ \tilde{t}_m = 1$, with corresponding spatial and time steps $\Delta\tilde{r} = \frac{1}{n}$ and $\Delta\tilde{t} = \frac{1}{m}$, respectively. Consequently, $u(\tilde{r}_i, 0) = u_0(\tilde{r}_i),\ i = 0 \dots n$, represent the initial condition (evaluated at discrete points $\tilde{r}_i$) and $\frac{\partial u}{\partial \tilde{r}}(1, \tilde{t}_j) = 0,\ j = 1 \dots m$, represent the Neumann boundary condition.

We will use a finite difference Crank-Nicolson scheme to compute a numerical solution $u_{i,j} := u(\tilde{r}_i, \tilde{t}_j),\ i = 0 \dots n-1,\ j = 1 \dots m$, of the initial boundary value problem (7)–(8). After some algebraic manipulation [10] we arrive at a linear system

$$A u_{\cdot,j} = g \tag{9}$$

for $(u_{0,j}, \dots, u_{n-1,j})^T$ with a three-diagonal symmetric positive definite matrix

$$A = \begin{bmatrix} \frac{1}{4}\gamma^+ & -hs_0 & & & & \\ -hs_0 & \gamma^+ & -hs_1 & & & \\ & -hs_1 & 2\gamma^+ & -hs_2 & & \\ & & \ddots & \ddots & \ddots & \\ & & & -hs_{n-3} & (n-2)\gamma^+ & -hs_{n-2} \\ & & & & -hs_{n-2} & (n-1)\gamma^+ - hs_{n-1} \end{bmatrix}$$

and a right-hand side

$$\begin{aligned} g_0 &= \tfrac{1}{4}\gamma^- u_{0,j-1} + hs_0 u_{1,j-1}, \\ g_i &= hs_{i-1}u_{i-1,j-1} + i\,\gamma^- u_{i,j-1} + hs_i u_{i+1,j-1}, \quad i = 1,\dots,n-2, \\ g_{n-1} &= hs_{n-2}u_{n-2,j-1} + ((n-1)\gamma^- + hs_{n-1})u_{n-1,j-1}. \end{aligned}$$

The Neumann boundary condition implies that $u_{n,j} = u_{n-1,j}$. Here

$$h = \frac{\Delta\tilde{t}}{\Delta\tilde{r}}, \quad \gamma^+ = \frac{\Delta\tilde{r}}{\delta} + h, \quad \gamma^- = \frac{\Delta\tilde{r}}{\delta} - h, \quad s_k = \frac{2k+1}{4},\ k = 0,\dots,n-1.$$

The formula (4) for S_{GRS} involves the derivative of the solution $u(r,t)$ of (1)–(2) with respect to the diffusion parameter D. Taking the scaled variables (6) and using the derivative of a composite function, we find that

$$D\frac{\partial u}{\partial D} = D\frac{\partial u}{\partial \delta}\frac{\partial \delta}{\partial D} = \frac{DT}{R^2}\frac{\partial u}{\partial \delta} = \delta\frac{\partial u}{\partial \delta} = \delta\frac{\partial u}{\partial \tilde{t}}\frac{\partial \tilde{t}}{\partial \delta} = -\frac{Dt}{\delta R^2}\frac{\partial u}{\partial \tilde{t}} = -\tilde{t}\frac{\partial u}{\partial \tilde{t}}. \tag{10}$$

Thus the scaled sensitivity measure (4) has the form

$$S_{GRS} = \delta^2 \sum_{i=0}^{n}\sum_{j=1}^{m}\left[\frac{\partial}{\partial\delta}u(\tilde{r}_i,\tilde{t}_j)\right]^2 = \sum_{i=0}^{n}\sum_{j=1}^{m}\left[\tilde{t}_j\,\frac{\partial}{\partial\tilde{t}}u(\tilde{r}_i,\tilde{t}_j)\right]^2. \tag{11}$$

Replacing the derivative with a finite difference, and using the fact that $\tilde{t}_j = j\Delta\tilde{t}$, the sensitivity measure S_{GRS} can be approximated as follows

$$\begin{aligned} S_{GRS} &\approx \sum_{i=0}^{n}\sum_{j=1}^{m}\left[j\Delta\tilde{t}\,\frac{u(\tilde{r}_i,\tilde{t}_j) - u(\tilde{r}_i,\tilde{t}_{j-1})}{\Delta\tilde{t}}\right]^2 \\ &= \sum_{j=1}^{m} j^2 \sum_{i=0}^{n}\left[u_{i,j} - u_{i,j-1}\right]^2 =: S_{app}(u_0(\tilde{r})). \end{aligned} \tag{12}$$

The values $u_{i,j}$ are computed from $u_{i,j-1}$ using (9), thus no extra work is necessary. The problem (5) of finding the optimal initial condition u_0 maximizing the sensitivity measure S_{app} (the approximation of S_{GRS}) can be formulated algorithmically as follows.

Algorithm 1. *Data: a cylinder radius R, height T, number of spatial points $n+1$, time measurements m, and a diffusion coefficient D.*

1. *Perform the scaling of variables (6) to obtain the value δ.*
2. *Let an initial condition $u_0 \in \mathcal{R}^{n+1}$, $u_0 \in [\underline{u_0}, \overline{u_0}]$ be given.*
3. *Compute $u_{i,j}$, $i = 0\dots n$, by solving the linear system (9) for $j = 1\dots m$.*
4. *Compute the value S_{app} using (12).*
5. *Repeat steps 2-4 to find u_0 such that S_{app} is maximal.*

4. Numerical example

As an example to demonstrate the optimal configurations of the initial condition let us choose parameters

$$R = 1, \quad T = 1, \quad n = 30, \quad m = 200, \quad \underline{u_0} = 0, \quad \overline{u_0} = 1$$

and use Algorithm 1 to find such an initial condition $(u_0(r_0), \ldots, u_0(r_n))^T \in \mathcal{R}^{n+1}$ that maximizes S_{app} (12) for $1/\delta = 5, 10, \ldots, 225$ (notice the inverse values of δ).[2]

To solve the optimization problem (5), we used a global optimization method from the UFO system [6]. This method uses local optimization methods for finding local minima. Briefly speaking, we choose an initial $u_0^{(0)} = (1/2, \ldots, 1/2)^T$ and for $k = 0, 1, \ldots$, until the optimality conditions are satisfied, we update the next iterate $u_0^{(k+1)}$ from u_0^k based on the function value $S_{app}(u_0^{(k)})$ and its gradient.

Figure 1 shows the results. For each $1/\delta$ we obtained a solution on the boundary of the feasible region. Thus, $u_0^{opt}(r_i) \in \{1, 0\}$ is a binary-valued vector (there exist non-zero components of u_0^{opt}). As the components of u_0^{opt} attain only two values 1 and 0, the vertical lines indicate the non-zero components of u_0^{opt}. A small number of jumps between 1 and 0 in u_0^{opt} occurs for large values of δ. When δ decreases ($1/\delta$ increases), the number of jumps increases.

Figure 2 shows the time evolution of the solution $u_{i,j}$ computed using (9) with the optimal initial condition u_0^{opt} in case of $\delta = 1/20$, i.e., computed vectors $u(r_i, t_j)$ for $j = 10, 20, \ldots, 200$ with $u(r_i, t_0) = u_0^{opt}(r_i),\ i = 0, \ldots, n$. For increasing time index $j \to \infty$ the solution tends to a steady-state solution.

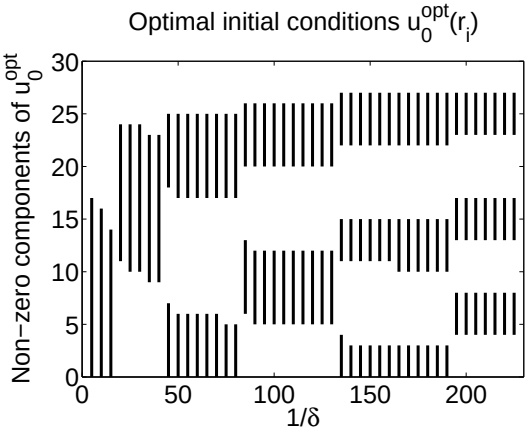

Figure 1: The result of optimization problem (5): vertical lines indicate the non-zero components of u_0^{opt}.

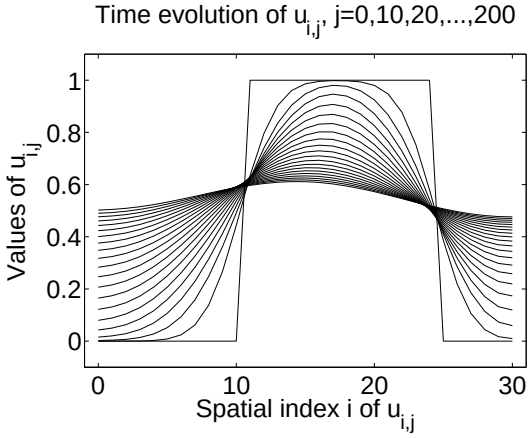

Figure 2: Optimal u_0^{opt} for $\delta = 0.05$ and the time evolution of the solution $u_{i,j}$ computed using (9).

[2]The corresponding original diffusion coefficient is $D = \delta$, see (6).

The following table shows the output from the UFO system for $\delta = 1/20$, where `F` denotes $-S_{app}$ and `X` denotes $(u_0^{opt}(r_0), \ldots, u_0^{opt}(r_n))^T$. The non-zero components of the solution have indices $i = 11, \ldots, 24$, i.e., two jumps between $\underline{u_0} = 0$ and $\overline{u_0} = 1$ occur (see Figure 1).

```
EXTREM   1 :
F = -0.2537705605D-01
X =  0.0000000000D+00  0.0000000000D+00  0.0000000000D+00  0.0000000000D+00
     0.0000000000D+00  0.0000000000D+00 -0.1734723476D-17  0.0000000000D+00
     0.0000000000D+00  0.0000000000D+00  0.0000000000D+00  0.1000000000D+01
     0.1000000000D+01  0.1000000000D+01  0.1000000000D+01  0.1000000000D+01
     0.1000000000D+01  0.1000000000D+01  0.1000000000D+01  0.1000000000D+01
     0.1000000000D+01  0.1000000000D+01  0.1000000000D+01  0.1000000000D+01
     0.1000000000D+01  0.0000000000D+00  0.0000000000D+00  0.0000000000D+00
     0.0000000000D+00  0.0000000000D+00  0.0000000000D+00
```

5. Conclusion

In this study, the problem of the optimal initial condition for further identification of a constant diffusion coefficient was formulated. We set a sensitivity measure S_{GRS} as the optimality criterion to be maximized in order to have the expected error minimal, see (4). Afterwards, we used the finite difference scheme to discretize both the scaled initial boundary value problem (7)–(8) and the sensitivity measure S_{app} eqrefsgrs. Our numerical results indicate that there exists specific optimal initial condition u_0^{opt} that maximizes the sensitivity measure S_{app} and therefore minimizes the error in the model parameter estimate (diffusion coefficient D), see (3). In discrete points $r_0, \ldots, r_n$, the components of the vector u_0^{opt} attain only two values ($\underline{u_0}$ and $\overline{u_0}$) and the number of jumps between these values depends on the diffusion coefficient D. The smaller value of D is (i.e., the slower the particle mobility due to the diffusion process is), the larger number of jumps occurs. These jumps in fact represent the discontinuities leading to more complex bleaching patterns, see [5] for more details.

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