On three equivalent methods for parameter estimation problem based on spatio-temporal FRAP data

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1 Introduction

The FRAP (Fluorescence Recovery After Photobleaching) method is based on measurement of the change of fluorescence intensity in a region of interest (being usually an Euclidian 2D domain) in response to an external stimulus, a short period of high-intensity laser pulse provided by the CLSM.[2] Stimulus, the so-called *bleach*, causes irreversible loss in fluorescence of autofluorescence molecules or fluorescently tagged compounds (e.g. green fluorescence proteins – GFP) in living cells in bleached area without any damage in intracellular structures. After the bleach, the observed recovery in fluorescence presumably reflects the diffusion of fluorescence compounds from the area outside the bleach. Based on spatio-temporal FRAP images, the process is reconstructed using either a closed form model or simulation based model. In the latter case, beside a single diffusion coefficient D, also the sequence $\{D_j\}$ can be estimated as well. Let us underline that FRAP images are usually very noisy, with small signal to noise ratio (SNR), i.e. in order to get reliable results for the sequence $\{D_j\}$, an adequate technique residing in *regularization* is mandatory [1, 5, 6].

2 Inverse Problem Formulation

Assuming the special geometry residing in one-dimensional simplification, getting the unbleached particle concentration y as a function of dimensionless quantities $x := \frac{r}{L}$ (r is a spatial coordinate in physical units, L is a characteristic length), $\tau := \frac{t}{T}$ (t is time, T is a constant with some characteristic value, e.g. the time interval between the initial and the last measurements), and $p := D\frac{T}{L^2}$ (re-scaled diffusion coefficient), we obtain the following dimensionless diffusion equation

$$\frac{\partial y}{\partial \tau} - p\frac{\partial^2 y}{\partial x^2} = 0 \tag{1}$$

with the initial condition and Dirichlet boundary conditions

$$y(x, \tau_0) = f(x), \quad x \in [0, 1], \tag{2}$$

$$y(0, \tau) = g_0(\tau), \quad y(1, \tau) = g_1(\tau), \quad \tau \geq \tau_0. \tag{3}$$

[2]Confocal laser scanning microscopy (CLSM) allows the selection of a thin cross-section of the sample by rejecting the information coming from the out-of-focus planes. However, the small energy level emitted by the fluorophore and the amplification performed by the photon detector introduces a measurement noise.

Spatio-temporal FRAP data

Based on FRAP experiments, we have a 2D dataset in form of a table with $(N+1)$ rows corresponding to the number of spatial points where the values are measured, and $(m+M+1)$ columns with m pre-bleach and $M+1$ post-bleach experimental values forming 1D profiles

$$y_{exp}(x_i, \tau_j), \quad i = 0 \dots N, \quad j = -m \dots M.$$

In fact, the process is determined by m columns of pre-bleach data containing the information about the steady state and optical distortion,[3] and $M+1$ columns of post-bleach data containing the information about the transport of unbleached particles (due to the diffusion) through the boundary.

Objective function

We construct an objective function $Y(p)$ representing the disparity between the experimental and simulated time-varying concentration profiles, and then within a suitable method we look for such a value $p \in \mathcal{R}^M$ minimizing Y.

The usual form of an objective function is the sum of squared differences between the experimentally measured and numerically simulated time-varying concentration profiles. Taking separately temporal (sub-index j) and spatial data points (sub-index i), we get:

$$Y(p) = \sum_{j=1}^{M} \sum_{i=0}^{N} \left[y_{exp}(x_i, \tau_j) - y_{sim}(x_i, \tau_j, p_j) \right]^2, \tag{4}$$

where $y_{sim}(x_i, \tau_j, p_j)$ are the simulated values resulting from the solution of problem (1)–(3), and $y_{exp}(x_i, \tau_0)$, $i = 0 \dots N$, represent the initial condition $f(x)$. The left and right Dirichlet boundary conditions $g_0(\tau)$ and $g_1(\tau)$ are represented by $y_{exp}(0, \tau_j)$ and $y_{exp}(1, \tau_j)$, $j = 1 \dots M$, respectively.

Ill-posedness

Our problem is ill-posed in the sense that the solution, i.e. the diffusion coefficients $p_1 \dots p_M$, do not depend continuously on the initial experimental data. This led us to the necessity of using some stabilizing procedure in form of the following regularized cost functions:

$$Y_j(p_j, p_{reg}, \alpha) = \sum_{i=0}^{N} \left[y_{exp}(x_i, \tau_j) - y_{sim}(x_i, \tau_j, p_j) \right]^2 + \alpha \left(p_j - p_{reg} \right)^2 \tag{5}$$

for $j = 1 \dots M$, where $\alpha \geq 0$ is a regularization parameter and $p_{reg} \in \mathcal{R}$ is an expected value. Taking $\alpha = 0$, function $Y(p, p_{reg}, \alpha) = \sum_{j=1}^{M} Y_j(p_j, p_{reg}, \alpha)$ turns to (4).

Values $p_j^*(\alpha)$, $j = 1 \dots M$, are approximate solutions of minimization problems [4]

$$p_j^*(\alpha) = \arg \min_{p_j, p_{reg}} Y_j(p_j, p_{reg}, \alpha). \tag{6}$$

[3] The noise identification can be performed using the pre-bleach data as well.

[4] Minimizing Y with respect to $p > 0$ represents a one-dimensional optimization problem. It was solved using variable metric method implemented in the UFO system [4].

It holds that $\lim_{\alpha \to 0} p_j^*(\alpha) = p_j^*(0)$. For $\alpha \to \infty$ we have that (i) $\|p^*(\alpha) - p_{reg}\|^2 \to 0$, i.e. the estimated parameter variance is diminishing or even $p_j^*(\alpha) \equiv p_{reg}$ $\forall j$, and (ii) function values $Y(p^*(\alpha), p_{reg}, \alpha)$ become larger (although there is a *supremum*). The problem of choosing in some sense optimal parameter α^* is discussed in the next section.

3 Tikhonov regularization vs. Least squares with a quadratic constraint regularization

A useful tool to see the relation between the residuum for different values of regularization parameter α, and the norm of a solution or relative standard deviation of the solution or some other measure of variability of the solution, is the so-called *L-curve*. Usually, this parametric plot, in our case with $Y(p^*(\alpha), p_{reg}, 0)$ (without the regularization term) in the abscissa, and $\|p^*(\alpha) - p_{reg}\|^2$ in the ordinate, is L-shaped (hence the name). In the upper left part we have small values of α (under-smoothing, the solution is corrupted by the noise in data) and the lower right part corresponds to the over-smoothing (the regularization term dominates for large α). Let see Figure 1 for the just introduced plot corresponding to our FRAP problem with the synthetic noisy data.

Tikhonov regularization

Tikhonov regularization [6] is based on adding a regularization term in (4) getting (5) and solving the problem

$$p^*(\alpha) = \arg \min_{p, p_{reg}} Y(p, p_{reg}, \alpha), \quad \text{st.} \quad p \geq 0. \tag{7}$$

The question is how to choose a "right" (in some sense optimal) parameter α^*. In [2], it is preferred the so-called L-curve criterion consisting in finding the point of maximal curvature on the L-curve. This point with corresponding solution $p^*(\alpha^*)$ is called *L-curve optimal*. However, in most cases this point is hard to determine.

Constraint based on determination of estimated parameter variance

To avoid the above mentioned situation of non-unambiguous choice of the parameter α^*, another approach, consisting in prescribing the value of $\|p^* - p_{reg}\|^2$ in advance, can be used. As the norm of a solution $p^*(\alpha)$ becomes more and more smaller for $\alpha \to \infty$, assume that we have prescribed the variance in the solution with some value ξ. If we denote $Y(p) = \sum_{j=1}^{M} Y_j(p_j, p_{reg}, 0)$, then according to Hansen [2], we can solve the following equivalent optimization problem with a quadratic constraint

$$p^*(\xi) = \arg \min_{p} Y(p), \quad \text{st.} \quad \|p - p_{\text{reg}}\|^2 \leq \xi, \quad p \geq 0. \tag{8}$$

Measurement noise based constraint

Suppose that we either know or can estimate the noise in input data. If we denote $y_{exp}^{\delta}(x_i, \tau_j)$ as real noisy data and $y_{exp}(x_i, \tau_j)$ as ideal data that would be measured without the noise, then

$$\sum_{j=1}^{M} \sum_{i=0}^{N} \left[y_{exp}^{\delta}(x_i, \tau_j) - y_{exp}(x_i, \tau_j) \right]^2 \leq \delta$$

where δ specifies the noise level (for the normally distributed non-correlated additive noise with the variance σ_0^2, we have $\delta \approx M\ N\ \sigma_0^2$). This leads to another possibility to determine (6). As Hansen [2] claims, the following optimization problem is again equivalent to the previous ones

$$p^*(\delta) = \arg\min_p \|p - p_{\text{reg}}\|^2, \quad \text{st.} \quad Y(p) \leq \delta, \quad p \geq 0. \tag{9}$$

By theory, L-curve is continuous and decreasing which means that both constraints in (8) and (9) are attained on the boundary. Thus each value δ (specifying the noise level) corresponds the value $L(\delta) = \xi$ on the L-curve so that

$$Y(p) = \delta \quad \Leftrightarrow \quad \|p - p_{\text{reg}}\|^2 = L(\delta).$$

Moreover, this point also corresponds to a certain Tikhonov regularization parameter α, i.e. $\alpha \equiv [\delta, L(\delta)]$. The respective α^* for a given noise δ^* is called *noise optimal.* Then the solution $p^*(\delta^*)$ corresponds to the solution found by applying the discrepancy principle [3].

The practical confirmation of the Hansen's conjecture about the equivalency of above three methods is shown in Figure 1.

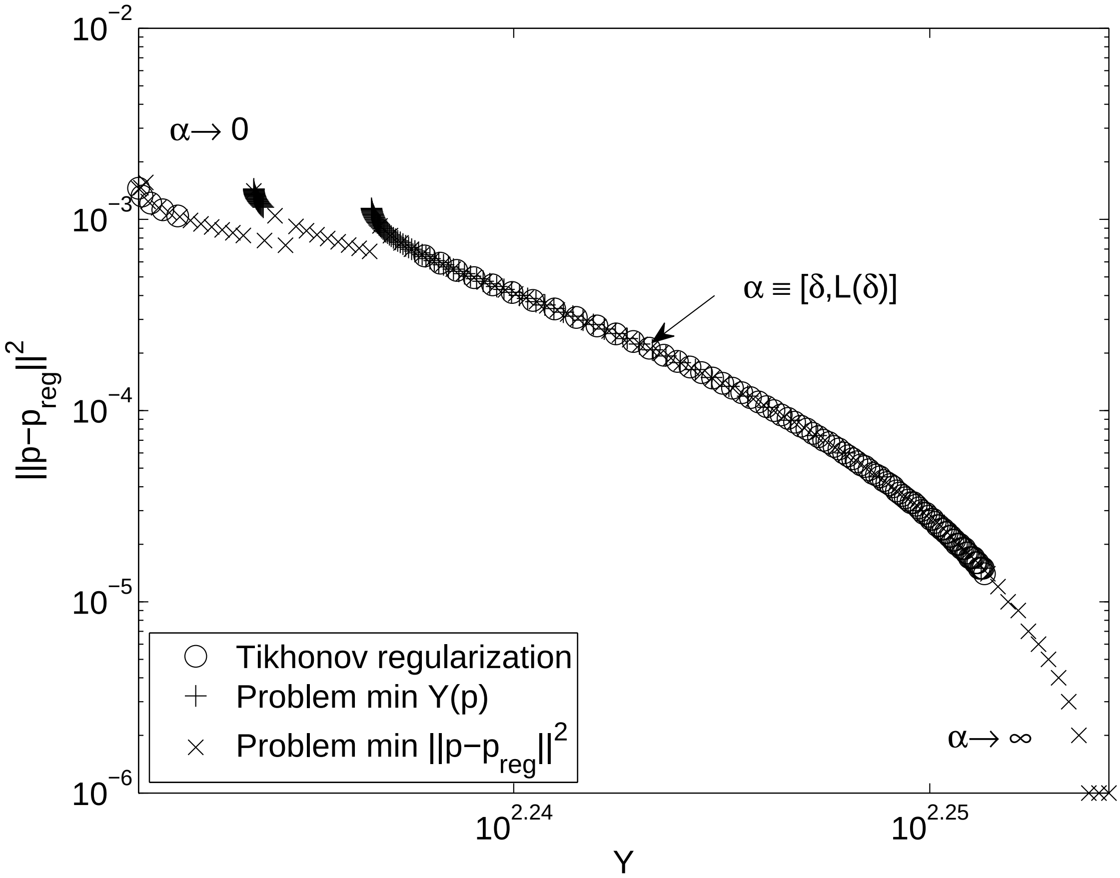

Figure 1: L-curves for three different regularization methods, i.e. the log-log-plot of the solution norm versus the residual norm, with α as the parameter.

4 Conclusions

We have presented three methods for the solution of the apparently simple parameter estimation problem. However, due to the noisy data from the spatio-temporal FRAP measurement, we have to look for a stabile numerical process. The most usual method is the Tikhonov regularization. Nevertheless, in our specific problem we had to deal with the complicated problem of determining the optimal regularization parameter α. Fortunately, there are two equivalent methods based on least squares with a quadratic constraint regularization enabling the application of the UFO system [4]. While the first method constrains the estimated parameter variance, the second is based on the measurement noise determination and constraining the residuum (proportional to the noise level). This latter approach naturally takes into account the noise level in the data and corresponds to the discrepancy principle as well. Furthermore, all three approaches were implemented into our software CA-FRAPwith satisfactory results on synthetic data.

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