Parameter estimation problem based on spatio-temporal data
Comparison of 2+1 FRAP methods

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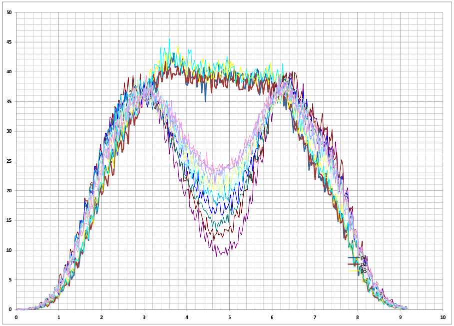
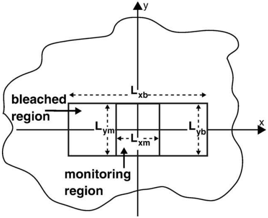
PANM 17, June 8-13 2014, Dolní Maxov

FRAP data: spatio-temporal image





Fluorescence intensity (in arbitrary units, averaged along the shorter axis) vs. Position (along the longer axis) [μm]. Experimental data from FRAP (**Fluorescence Recovery After Photobleaching**) experiment with red algae *Porphyridium cruentum* describing the phycobilisomes mobility (due to the DIFFUSION ONLY !?) on thylakoid membrane.

Outline

Outline

One-dimensional dimensionless (re-scaled) form of diffusion equation:

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

where y is the re-scaled fluorescent signal, $x := \frac{r}{L}$, L is a characteristic length, $\tau := \frac{t}{T}$, T is the time interval between two measurements, and $p := D\frac{T}{L^2}$ is the re-scaled diffusion coefficient.
The initial condition is

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

The time varying boundary conditions are of the Dirichlet type

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

Note: The Neumann type conditions can also be considered

$$-p\,\frac{\partial y}{\partial x}(0, \tau) = h_0(\tau), \quad p\,\frac{\partial y}{\partial x}(1, \tau) = h_1(\tau), \quad \tau \geq \tau_0. \tag{4}$$

Q.#1. What boundary condition to choose?

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
- $M+1$ columns of post-bleach data containing the information about the transport of unbleached particles (due to the diffusion) through the boundary

Comment: Future goal is to deal with 2D domain, thus the dataset would be the set of $(N_i \times N_k)_j$ matrices, j remains the time index.

Initial conditions: τ_0 corresponds to the first post-bleach measurement,

- $y_{exp}(x_i, \tau_0),\ i = 0 \ldots N$, represents the IC.

Boundary conditions: After re-scaling, we have $x_0 = 0,\ x_N = 1,$ and

- $y_{exp}(\mathbf{0}, \tau_j),\ j = 0 \ldots M$, represents the left Dirichlet BC,
- $y_{exp}(\mathbf{1}, \tau_j),\ j = 0 \ldots M$, represents the right Dirichlet BC.

Recall: Due to the measurement noise, both the respective $j-$*profiles* $y_{exp}(x_i, \tau_j),\ i = 0 \ldots N$, and the initial and boundary conditions cannot be simply approximated by a smooth function.

Note: The Neumann BC for each j^{th} time instant is determined using the Fick's first law. This is possible thanks to the numerically computed total flux $h(\tau_j)$ through the boundary. We suppose the symmetry, hence the total flux is equally divided into the left border $(x = 0)$ and the right border $(x = 1)$.

Outline

We construct an objective function $Y(p)$ representing the disparity between the experimental and simulated time-varying 1D (further 2D) concentration profiles, and then within a suitable method we look for such a scalar value p minimizing Y.
The isotropic, time and space independent diffusion is supposed, nevertheless, we further define a sequence of parameter estimation problems resulting in the sequence of solutions p_j, j beeing the time index.

The usual form of an objective function is the sum of squared differences between the experimentally measured and numerically simulated time-varying concentration profiles:

$$Y(p) = \sum_{j=0}^{M} \sum_{i=0}^{N} \left[y_{exp}(x_i, \tau_j) - y_{sim}(x_i, \tau_j, p) \right]^2 , \tag{5}$$

where $y_{sim}(x_i, \tau_j, p)$ are the simulated values resulting from the solution of the initial boundary value problem (IBVP) (1-2-3) or (1-2-4).

1D global or sequential optimization problem

Taking into account the biological reality residing in possible time dependence of diffusion coefficients, we further consider two cases for the minimization problem:

$$Y(p) = \sum_{j=1}^{M} Y_j(p) = \sum_{j=1}^{M} \sum_{i=0}^{N} \left[y_{exp}(x_i, \tau_j) - y_{sim}(x_i, \tau_j, p) \right]^2 \to \min_p \quad (6)$$

1. We take both sums for i and j in (6) together. In this case, the scalar p is a result of minimization problem for Y:

$$p^* = \arg\min_p Y(p) \quad (6a)$$

2. We consider each j^{th} time instant separately. In this case, the M solutions $p_1 \dots p_M$ correspond to each minimization problem for fixed j in sum (6) and we can observe a 'dynamics' of diffusion coefficient p_j evolution:

$$p_j^* = \arg\min_p Y_j(p), \quad j = 1 \dots M \quad (6b)$$

In order to compute a function value $Y_j(p)$ in (6) for a given value p, we need to know both

- the experimental values $y_{exp}(x_i, \tau_j),\ i = 0 \ldots N,\ j = 0 \ldots M$,
- the simulated values $y_{sim}(x_i, \tau_j, p),\ i = 0 \ldots N,\ j = 0 \ldots M$.

It means that in each iteration we need to solve the following IBVP similar to (1-2-3-4):

$$\frac{\partial y_{sim}}{\partial \tau} - p\,\frac{\partial^2 y_{sim}}{\partial x^2} = 0 \tag{7}$$

with the initial and Dirichlet boundary conditions defined by the experimental data:

$$y_{sim}(x, \tau_0, p) = y_{exp}(x, \tau_0), \quad x \in [0, 1] \tag{8}$$

$$y_{sim}(0, \tau, p) = y_{exp}(0, \tau), \quad y_{sim}(1, \tau, p) = y_{exp}(1, \tau), \quad \tau \geq \tau_0 \tag{9}$$

$$\boxed{\text{Q.\#2. How to improve DBC?}}$$

Problem (7-9) was solved numerically for uniformly distributed nodes:

- Space steplength: $\Delta h = 1/N$
- Time steplength: $\Delta\tau$ ideally of the same order as Δh

using the Crank-Nicholson scheme (order $\Delta\tau^2 + \Delta h^2$):

$$-\frac{\beta}{2} y_{i-1,j} + (1+\beta) y_{i,j} - \frac{\beta}{2} y_{i+1,j} = \frac{\beta}{2} y_{i-1,j-1} + (1-\beta) y_{i,j-1} + \frac{\beta}{2} y_{i+1,j-1}$$

Here $\beta = \frac{\Delta\tau}{\Delta h^2}\, p$ and $y_{i,j} \equiv y_{sim}(x_i, \tau_j, p)$ are the computed values in nodes that enter the function Y as values $y_{sim}(x_i, \tau_j, p)$.

In order to get from the $(j-1)^{th}$ time instant to the j^{th}, we need to perform $\kappa \in \mathbb{N}$ substeps, where κ is an integer depending on $\Delta\tau$.

$$\boxed{\text{Q.\#3. How to choose } \kappa\text{?}}$$

Outline

Minimizing Y with respect to $p > 0$ represents a one-dimensional optimization problem.

Basic optimization method is an iteration process starting from an initial point $p^{(0)}$ and generating a sequence of iterates $p^{(1)}, p^{(2)}, \ldots$ leading to a value p^* such that

$$p^{(l+1)} = p^{(l)} + \sigma^{(l)} d^{(l)},$$

where

- $d^{(l)}$ is a direction vector – is determined on the basis of values

$$p^{(j)},\ Y(p^{(j)}),\ Y'(p^{(j)}),\ Y''(p^{(j)}),\quad 0 \le j \le l,$$

- $\sigma^{(l)} > 0$ is a step-length – is determined on the basis of behavior of the function Y in the neighborhood of $p^{(l)}$.

$\boxed{\text{Q.\#4. How to choose } p^{(0)}\text{?}}$

The most suitable and effective method for solving problem (6) is the variable metric method (the type of the line-search methods).

The direction vector $d^{(l)}$ is constructed such that

$$d^{(l)} = -H^{(l)} Y'(p^{(l)})$$

where $H^{(l)}$ are symmetric positive definite matrices updated in each iteration in a recurrent way that approximate the inverse of Hessian matrices in points $p^{(l)}$.

The step-length $\sigma^{(l)}$ satisfies the weak Wolfe condition

$$Y(p^{(l+1)}) - Y(p^{(l)}) \leq \varepsilon_1 \sigma^{(l)} {d^{(l)}}^T Y'(p^{(l)}),$$

$$\varepsilon_2 {d^{(l)}}^T Y'(p^{(l)}) \leq {d^{(l)}}^T Y'(p^{(l+1)})$$

where $0 < \varepsilon_1 < \varepsilon_2 < 1$ are independent of l.

The UFO system:

http://www.cs.cas.cz/luksan/ufo.html

Outline

- C. W. Moullineax *et al.*, Nature (1997) [1],
- J. Ellenberg *et al.*, J. Cell Biol. (1997) [2],
- Numerical solution of IBVP (7-9) & Tikhonov regularization based method [3].

C.W. Moullineaux, M.J. Tobin, G.R. Jones
Mobility of photosynthetic complexes in thylakoid membranes.
Nature, 390:421-–424, 1997.

J. Ellenberg, E.D. Siggia, J.E. Moreira, C.L. Smith, J.F. Presley, H.J. Worman, J. Lippincott-Schwartz
Nuclear membrane dynamics and reassembly in living cells: targeting of an inner nuclear membrane protein in interphase and mitosis.
The Journal of Cell Biology, 138:1193-1206, 1997.

Š. Papáček, R. Kaňa, C. Matonoha
Estimation of diffusivity of phycobilisomes on thylakoid membrane based on spatio-temporal FRAP images.
Mathematical and Computer Modelling, 57: 1907-1912, 2013.

In [1] it is presented:

$$y(x,t) = \frac{y_{0,0}\, r_0}{\sqrt{{r_0}^2 + 8Dt}} \exp \frac{-2x^2}{{r_0}^2 + 8Dt},$$

as the closed form solution of 1D diffusion PDE. It is correct supposing:

1. infinite domain $x \in \mathcal{R}$,
2. Gaussian initial bleaching profile (halfwidth r_0 in rel. height e^{-2}),
3. the complete recovery (i.e. $y \to 0$ as $t \to \infty$).

Note: The calculation of diffusion coefficient D was performed in [1] as the weighted linear regression: a plot of $\left(\frac{y_{0,0}}{y_{0,t}}\right)^2$ against time gives a straight line with the tangent $\frac{8D}{{r_0}^2}$.
Error analysis based on statistics...

Notation: Let $F = G \circ S$ represent the parameter-to-output map, i.e. the concatenation of the PDE solution operator S onto the solution vector y of the underlying system (7-9), i.e. $S(p) = y_{i,j}$, and G is the observation operator.
Then (due to noisy data and model imperfections) the system $F(p) = z^\delta$ is replaced by a nonlinear least squares problem:

$$\| z^\delta - F(p) \|^2 \rightarrow \min_{p>0} .$$

How the measurement noise influences the result?
Experimentalists use the statistics...
Our (CM & SP) error analysis (for three FRAP methods) is based on the evaluation of

- the sensitivity matrix: $\chi = \frac{\partial z}{\partial p}$, i.e., on the Jacobian matrix of the output, being evaluated at p^* (estimated parameters vector), or
- Fisher information matrix (FIM): $FIM = \chi^T \chi$.

Let the statistical model for the observation process be the following:

$$z_j^\delta = z(\tau_j; p^*) + \varepsilon_j.$$

Assuming

$$E[\varepsilon_j] = 0, \quad \mathrm{var}(\varepsilon_j) = \sigma_0^2 < \infty, \quad \mathrm{cov}(\varepsilon_j, \varepsilon_k) = 0, \text{ for } j \neq k,$$

we have

$$E[z_j^\delta] = z(\tau_j; p^*), \quad \mathrm{var}(z_j^\delta) = \sigma_0^2.$$

The standard errors of estimated parameters p_k are then

$$SE_k(p^*) = \sigma_0 \sqrt{[\chi(p^*)^T \chi(p^*)]_{kk}^{-1}}, \quad 1 \leq k \leq q.$$

The propagation of uncertainty from the observation process (ε) to the estimated parameter vector is described by:

$$p \approx p^* + \left[\chi(p^*)^T \chi(p^*)\right]^{-1} \chi(p^*)^T \varepsilon.$$

The key is the evaluation of the semi-relative sensitivity:

- 1 (spatial) point Moullineax method:

$$
\begin{aligned}
z_M(t) &= \frac{y_{0,0} r_0}{\sqrt{{r_0}^2 + 8Dt}}, \\
FIM_M &= \sum_{j=1}^{m} \left[\frac{\partial z_M(t_j)}{\partial D} D \right]^2 = \sum_{j=1}^{m} \left[\frac{4 y_{0,0} r_0 D t_j}{({r_0}^2 + 8Dt_j)^{3/2}} \right]^2 .
\end{aligned}
$$

- Integrated Ellenberg method (n spatial points):

$$
\begin{aligned}
z_E(\tau) &= 1 - \frac{1}{\sqrt{1 + p\pi\tau}}, \quad \sigma_E = \frac{\sigma_0}{\sqrt{n}} \\
FIM_E &= \sum_{j=1}^{m} \left[\frac{\frac{1}{2}\pi p \tau_j}{(1 + \pi p \tau_j)^{3/2}} \right]^2, \quad SE_E(\hat{p}) = \frac{\sigma_E}{\sqrt{FIM_E}}.
\end{aligned}
$$

- Full data & numerical method based on [3]: TODO...

Outline

Problem (6b) 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 data. This lead us to the necessity of using some stabilizing procedure by adding a regularization term $\alpha R(p)$ to (5). Expecting the minimal variability of p_j, we have formulated the folowing regularized objective functions:

$$Y_j(p_j, p_{reg}, \alpha) = \sum_{i=0}^{N} \left[y_{exp}(x_i, \tau_j) - y_{sim}(x_i, \tau_j, p_j)\right]^2 + \alpha \left(p_j - p_{reg}\right)^2 \quad (10)$$

for $j = 1 \dots M$, where $\alpha \geq 0$ is a regularization parameter and p_{reg} is an expected value.

Note: p_{reg} is dynamically re-calculated with growing j ($p_{reg} := \o p_j^*(\alpha)$), thus it is performed some kind of smoothing between consecutive values of p_j.

Values p_j^* and $p_j^*(\alpha)$ are approximate solutions of two minimization problems:

$$p_j^* = \arg\min_{p_j, p_{reg}} Y_j(p_j, p_{reg}, 0), \quad p_j^*(\alpha) = \arg\min_{p_j, p_{reg}} Y_j(p_j, p_{reg}, \alpha)$$

Now:

- It holds
$$\lim_{\alpha\to 0} p_j^*(\alpha) = p_j^*$$
- For $\alpha \to \infty$:
  :-) the variance of solutions $p_j^*(\alpha)$ is diminishing, i.e. $p_j^*(\alpha) \equiv p_{reg}\ \forall j$
  :-(function values $\sum_j Y_j(p_j^*(\alpha), p_{reg}, \alpha)$ become larger (although there is a *supremum*).

We look for such a value α^* for which the $p_j^*(\alpha^*)$ variance (or $\mathcal{L}^2$-norm) is 'small enough'.

$$\boxed{\text{Q.\#5. How to get } \alpha^*?}$$

L-curve: USED FOR VISUALIZATION ONLY!

A plot of a norm of regularized solution versus the corresponding residual norm is called the L-curve. Further we plot one of

- the norm $\|p - p_{reg}\|^2$
- the (relative) standard deviation σ

$$\sigma = \sqrt{\frac{1}{M}\sum_{j=1}^{M}[p_j^*(\alpha) - \varnothing p_j^*(\alpha)]^2}$$

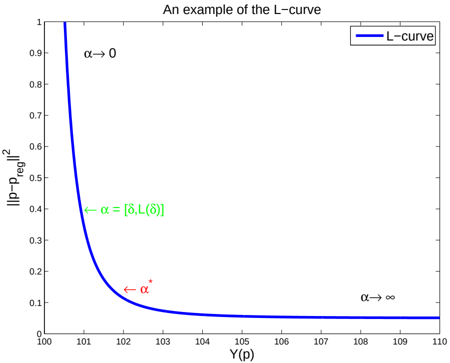
- the coefficient of variation $c_v = \frac{\sigma}{\varnothing p_j^*(\alpha)}$

versus

- the value of objective function Y (without the regularization term)

$$Y(p_1^*(\alpha)\dots p_M^*(\alpha)) = \sum_{j=1}^{M}\sum_{i=1}^{N}\left[y_{exp}(x_i,\tau_j) - y_{sim}(x_i,\tau_j,p_j^*(\alpha))\right]^2$$

L-curve in theory [1]



Note: The L-curve optimal parameter α^* corresponds (accordingly to [1]) to the point with maximal curvature. The more realistic approach is based on the discrepancy principle.

Per Christian Hansen
Rank-Deficient and Discrete Ill-Posed Problems: Numerical Aspects of Linear Inversion.
SIAM, 1997.

Let δ^* be a measure of the noise in input data. If we denote

- $y_{exp}^{\delta^*}(x_i, \tau_j)$ as really measured data with the noise
- $y_{exp}(x_i, \tau_j)$ as data that would be measured without the noise

then

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

There exists α^* such that

$$\alpha^* = [\delta^*, L(\delta^*)],$$

see the previous Figure, and this α^* is „noise" optimal.
Such a solution $p_1^*(\delta^*) \dots p_M^*(\delta^*)$ is based on the discrepancy principle.

$$\boxed{\text{Q.}\#6.\ \text{How to get } \delta^*?}$$

Hansen claims that Tikhonov's regularization is equivalent to the following two optimization problems with a nonlinear constraint (note that $Y(p) = \sum_{j=1}^{M} Y_j(p_j)$ with $p = (p_1, \ldots, p_M)^T \in \mathcal{R}^M$):

$$p^*(\delta) = \arg\min_p \|p - p_{\mathrm{reg}}\|^2, \quad \text{st.} \quad Y(p) \le \delta, \quad p_j \ge 0 \qquad (11)$$

and

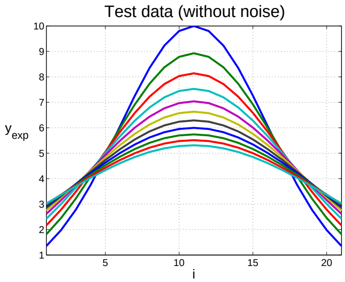
$$p^*(\delta) = \arg\min_p Y(p), \quad \text{st.} \quad \|p - p_{\mathrm{reg}}\|^2 \le L(\delta), \quad p_j \ge 0 \qquad (12)$$

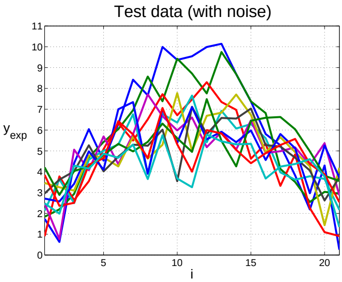
L-curve is continuous and decreasing which means that both constraints in (11) and (12) are attained on the boundary. Thus each value δ (specifying the noise) corresponds to the value $L(\delta)$ so that

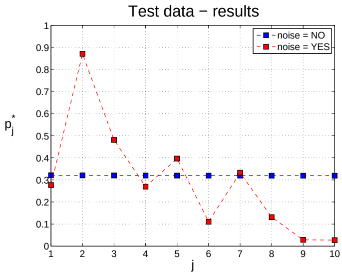
$$Y(p) = \delta \quad \Leftrightarrow \quad \|p - p_{\mathrm{reg}}\|^2 = L(\delta)$$

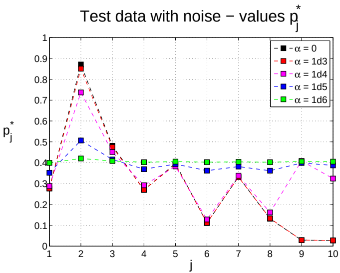
Outline

Test data without and with an additive Gaussian noise $\mathcal{N}(0,1)$









Test data - results for different $p^{(0)}$ and κ

Parameters: $\alpha = 1D5, \;\kappa = 20 \;(\Delta\tau = \Delta h)$

$p^{(0)}$	1D-6	0.1	1	10
$\o\{D_j\}$	0.3926	0.3926	39.455	399.86
$\|\|D - D_{reg}\|\|^2$	1.79D-02	1.79D-02	5.56D-05	2.63D-08
Y	177.33	177.33	1758.74	1830.26
NIT	43	43	1	1
time	1.30	1.37	0.51	0.47

Parameters: $\alpha = 1D5, \;p^{(0)} = 1D\text{-}6$

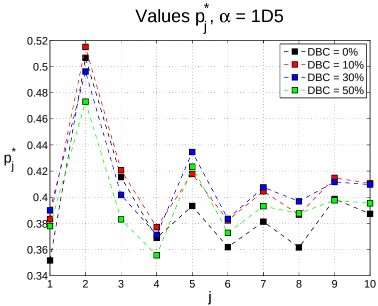
κ	3	5	10	20
$\o\{D_j\}$	0.3733	0.3918	0.3926	0.3926
$\|\|D - D_{reg}\|\|^2$	1.94D-02	1.76D-02	1.78D-02	1.79D-02
Y	177.72	177.40	177.34	177.33
NIT	33	43	43	43
time	0.28	0.44	0.76	1.30

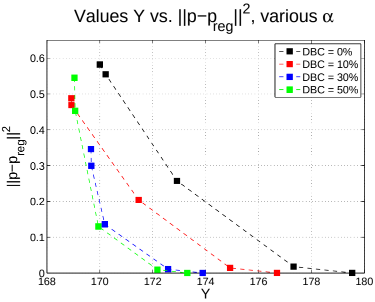
Test data - results for inexact Dirichlet boundary condition

Parameters: $\alpha = 1D5$, $p^{(0)} = 1D\text{-}6$, $\kappa = 100$

$DBC\%$	0	10	30	50
$\o\{D_j\}$	0.3927	0.4113	0.4103	0.3959
$\|\|D - D_{reg}\|\|^2$	1.79D-02	1.43D-02	1.09D-02	9.44D-03
Y	177.32	174.92	172.58	172.18
NIT	43	46	58	59
time	5.03	5.21	10.82	16.11

Test data with noise - results for inexact DBC:





Summary

Conclusions:

- Our method improves on other (closed form) models by accounting for the real conditions (without oversimplifications), e.g. for the experimentally measured post-bleaching fluorescence **profiles** (i.e. full data case) and for time-dependent boundary conditions.
- We deal with the ill-posed problem (and noisy data) by implementing a suitable *regularization technique* and a *robust optimization procedure*.
- We developed both the method for the computation of the mean value of diffusion coefficient (for the real FRAP measurements with the red algae *Porphyridium cruentum* is the range of result $10^{-14}\mathrm{m}^2\mathrm{s}^{-1}$ in agreement with reference values), and the method for numerical estimation of the standard error of the estimate.

Future prospects:

- 2D extension of our method (the membrane is 2D...) based on FD, CN scheme.
- The analysis of sensitivity based on Fischer information matrix enables the **optimal experimental design**, i.e. we aim in determining the optimal size of the bleach spot, time interval between measurements, etc.
- The deeper theoretical analysis of the uncertainty assessment for the FRAP measurements.