Parameter Evaluation for Bioconcentration Model Using Cellular Exclusion Method

S. G. Cruceanu [*]   D. Marinescu [*]

Contents

[*]Institute of Mathematical Statistics and Applied mathematics of Romanian Academy, Calea 13 Septembrie 13, Bucharest, Romania.

Abstract

We are considering a class of biological phenomena described by ordinary differential equations (ODEs). The problem we focus on consists of determining the best parameters fitting a given set of observable data. In this work we report on a new method for finding the set of parameters that minimizes the cost function associated to this problem. This method is based on the exclusion algorithm which is a powerful tool for finding all the solutions of a nonlinear system of equations over a compact domain. The authors will also emphasize how a carefully chosen dominant function can improve the efficiency and reduce the cost of such method. Applications to inverse problems when modeling in biology are also addressed.

1 A Bioconcentration Model with N Species

One considers a (biological) system populated by the species $S_1, S_2, \ldots, S_N$, and placed inside a certain environment contaminated with a substance (a metal, for example). The concentrations of the substance inside the organisms are $C_1, C_2, \ldots, C_N$, and the one inside the environment is c_w (see [1], [2], for example). One also supposes that the uptake and release fluxes are proportional to the concentrations.

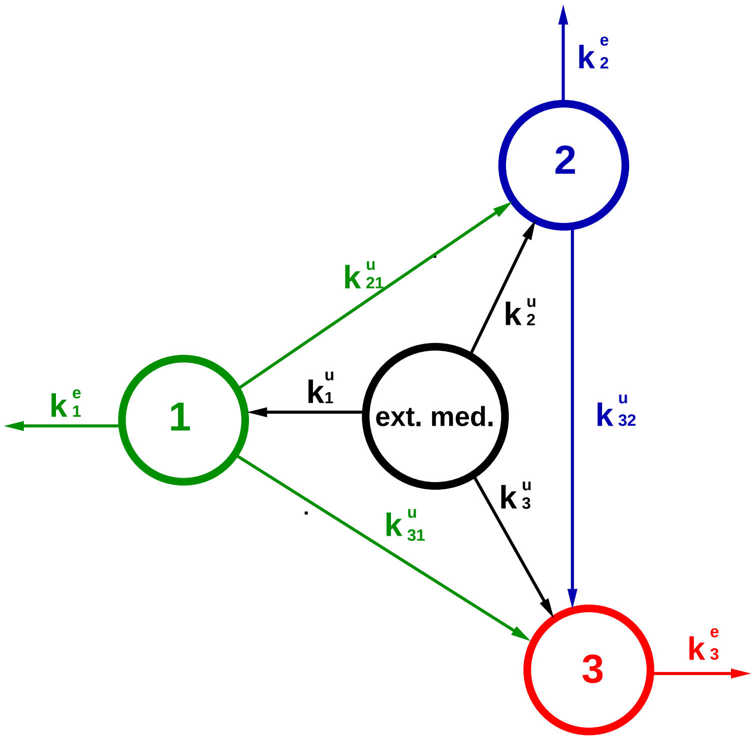


Figure 1: Bioconcentration Model with 3 Species

The contaminant circulates from the environment to the species following the rules bellow:

The uptake flux from environment for a species S_r ($r = 1, 2, \ldots, N$) is $k_r^u c_w$ and the release flux is $k_r^e C_r$. The uptake flux of the species S_r ($r = 2, 3, \ldots, N$) from a species S_p ($p = 1, 2, \ldots, r-1$) is $k_{rp}^u C_p$ (and it is null for $p \geq r$).

The model is described by the following linear system of differential equations

$$\begin{cases} \dfrac{dC_1}{dt} = k_1^u c_w - k_1^e C_1 \\ \dfrac{dC_2}{dt} = k_2^u c_w - k_2^e C_2 + k_{21}^u C_1 \\ \dfrac{dC_3}{dt} = k_3^u c_w - k_3^e C_3 + k_{31}^u C_1 + k_{32}^u C_2 \\ \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \\ \dfrac{dC_N}{dt} = k_N^u c_w - k_N^e C_N + \displaystyle\sum_{p=1}^{N-1} k_{Np}^u C_p \end{cases} \tag{1}$$

and for the particular case $N = 3$ species, it can be pictured as in Figure 1.
Giving the initial data $C_r(0) = C_{r,0}$, for $r = 1, 2, \ldots, N$, one can explicitly solve the system (1).

1.1 Analytic Solution for $N = 1$

For $N = 1$ one obtains

$$C_1(t) = \left(C_{1,0} - \frac{k_1^u}{k_1^e} c_w \right) e^{-k_1^e t} + \frac{k_1^u}{k_1^e} c_w. \tag{2}$$

Denote by

$$\begin{aligned} a_{11} &:= C_{1,0} - \frac{k_1^u}{k_1^e} c_w, \\ c_1 &:= \frac{k_1^u}{k_1^e} c_w. \end{aligned} \tag{3}$$

Rel.(2) becomes

$$C_1(t) = a_{11} e^{-k_1^e t} + c_1. \tag{4}$$

1.2 Analytic Solution for $N = 2$

Introducing (4) in the second equation of (1) one gets

$$\frac{dC_2}{dt} + k_2^e C_2 - (k_2^U L_w + k_{21}^u c_1) - k_{21}^u p_{11} e^{-k_1^e t} = 0. \tag{5}$$

Suppose that $\underline{k_1^e \neq k_2^e}$.

It can be shown the solution of (5) is of the form

$$C_2(t) = \left[C_{2,0} - \frac{k^u_{21} p_{11}}{k^e_2 - k^e_1} - \frac{k^u_2 c_w + k^u_{21} c_1}{k^e_2}\right] e^{-k^e_2 t} + \\ + \frac{k^u_{21} a_{11}}{k^e_2 - k^e_1} e^{-k^e_1 t} + \frac{k^u_2 c_w + k^u_{21} c_1}{k^e_2}. \tag{6}$$

Denote by

$$\begin{aligned} a_{22} &:= \left[C_{2,0} - \frac{k^u_{21} a_{11}}{k^e_2 - k^e_1} - \frac{k^u_2 c_w + k^u_{21} c_1}{k^e_2}\right], \\ a_{21} &:= \frac{k^u_{21} a_{11}}{k^e_2 - k^e_1}, \\ c_2 &:= \frac{k^u_2 c_w + k^u_{21} c_1}{k^e_2}. \end{aligned} \tag{7}$$

Rel.(6) becomes

$$C_2(t) = a_{22} e^{-k^e_2 t} + a_{21} e^{-k^e_1 t} + c_2. \tag{8}$$

1.3 The Solution for the General Case

By induction, one can show that the solution C_r of (1) is the form

$$C_r(t) = \sum_{m=1}^{r} a_{rm}\, e^{-k^e_m t} + c_r, \quad r = 1, \ldots, N. \tag{9}$$

Indeed, if

$$C_s(t) = \sum_{m=1}^{s} a_{sm}\, e^{-k^e_m t} + c_s, \tag{10}$$

for each $s = 1, \ldots, (r-1)$, then the ODE for C_r becomes

$$\frac{dC_r}{dt} = k^u_r c_w - k^e_r C_r + \sum_{s=1}^{r-1} k^u_{rs} \left[\sum_{m=1}^{s} a_{sm}\, e^{-k^e_m t} + c_s\right]. \tag{11}$$

Equivalently, this equation can be written as

$$\frac{dC_r}{dt} + k^e_r C_r - \left[k^u_r c_w + \sum_{s=1}^{r-1} k^u_{rs} c_s\right] - \sum_{m=1}^{r-1} \left[\sum_{s=m}^{r-1} k^u_{rs} a_{sm}\right] e^{-k^e_m t} = 0, \tag{12}$$

form for which the solution is

$$C_r(t) = \left[C_{r,0} + \sum_{m=1}^{r-1} \frac{\sum_{s=m}^{r-1} k^u_{rs} a_{sm}}{k^e_r - k^e_m} + \frac{k^u_r c_w + \sum_{s=1}^{r-1} k^u_{rs} c_s}{k^e_r}\right] e^{-k^e_r t} - \\ - \sum_{m=1}^{r-1} \frac{\sum_{s=m}^{r-1} k^u_{rs} a_{sm}}{k^e_r - k^e_m} e^{-k^e_m t} - \frac{k^u_r c_w + \sum_{s=1}^{r-1} k^u_{rs} c_s}{k^e_r}. \tag{13}$$

With

$$a_{rr} = C_{r,0} + \sum_{m=1}^{r-1} \frac{\sum_{s=m}^{r-1} k_{rs}^u a_{sm}}{k_r^e - k_m^e} + \frac{k_r^u c_w + \sum_{s=1}^{r-1} k_{rs}^u c_s}{k_r^e},$$

$$a_{rm} = -\frac{\sum_{s=m}^{r-1} k_{rs}^u a_{sm}}{k_r^e - k_m^e}, \quad m = 1, \dots, r-1, \tag{14}$$

$$c_r = -\frac{k_r^u c_w + \sum_{s=1}^{r-1} k_{rs}^u c_s}{k_r^e},$$

one now easily gets (9).

2 The Problem

Consider the general solution

$$C_r(t) = \sum_{m=1}^{r} a_{rm}\, e^{-k_m^e t} + c_r, \quad r = 1, \dots, N. \tag{15}$$

Suppose that we have experimentally measured the values of C_r for the moments of time $t_1, \dots, t_n$ and denoted them by $y_1, \dots, y_n$, respectively.
Suppose also that we know the values of the parameters k_m^e for all $m = 1, \dots, r-1$.
Our purpose is to determine the following set of parameters

$$\begin{cases} k_r^e \\ a_{rm}, \quad \forall\, m = 1, \dots, r \\ c_r \end{cases}$$

using the experimental measurements $y_1, \dots, y_n$ on C_r.[1]
In the following, consider n to be fixed. For simplification, we use the notations

$a_m := a_{rm}, \quad \forall\, m = 1, \dots, r,$
$b_m := -k_m^e, \quad \forall\, m = 1, \dots, r,$
$a := a_r,$
$b := b_r,$
$c := c_r.$

Note that we will alternatively use a and a_r as well as b or b_r. Also, denote

$$\overrightarrow{\boldsymbol{a}} := (a_1, \dots, a_r).$$

Define

$$h(t, \overrightarrow{\boldsymbol{a}}, b, c) := \sum_{m=1}^{r} a_m\, e^{t b_m} + c. \tag{16}$$

[1]The parameters $k_1^e, \dots, k_{r-1}^e$ can be determined using the procedure described bellow for experimental measurements on $C_1, \dots, C_{r-1}$, respectively

In order to determinate the parameters a_m, a, b, and c, we look for the minimum of the function $H : \mathbb{R}^{r+2} \to \mathbb{R}_+$ defined by

$$H(\overrightarrow{\boldsymbol{a}}, b, c) := \sum_{s=1}^{n} (h(t_s, \overrightarrow{\boldsymbol{a}}, b, c) - y_s)^2. \tag{17}$$

3 The Equations

First, we look for minimum points within the set of critical points of H defined by the solutions of the following equations:

$$\begin{cases} \dfrac{\partial H}{\partial a_m}(\overrightarrow{\boldsymbol{a}}, b, c) = 0, \qquad m = 1, \ldots, r \\[2ex] \dfrac{\partial H}{\partial b}(\overrightarrow{\boldsymbol{a}}, b, c) = 0 \\[2ex] \dfrac{\partial H}{\partial c}(\overrightarrow{\boldsymbol{a}}, b, c) = 0. \end{cases} \tag{18}$$

Let $E : \mathbb{R}^2 \to \mathbb{R}$ with $E(t, \beta) := e^{t\beta}$.
We introduce the notations

$$\begin{cases} f_m(t, y, \overrightarrow{\boldsymbol{a}}, b, c) := [h(t, \overrightarrow{\boldsymbol{a}}, b, c) - y]E(t, b_m), \qquad m = 1, \ldots, r \\[2ex] f_b(t, y, \overrightarrow{\boldsymbol{a}}, b, c) := [h(t, \overrightarrow{\boldsymbol{a}}, b, c) - y]taE(t, b) \\[2ex] f_c(t, y, \overrightarrow{\boldsymbol{a}}, b, c) := h(t, \overrightarrow{\boldsymbol{a}}, b, c) - y. \end{cases} \tag{19}$$

Rel.(18) becomes:

$$\begin{cases} \displaystyle\sum_{s=1}^{n} f_m(t_s, y_s, \overrightarrow{\boldsymbol{a}}, b, c) = 0, \qquad m = 1, \ldots, r \\[2ex] \displaystyle\sum_{s=1}^{n} f_b(t_s, y_s, \overrightarrow{\boldsymbol{a}}, b, c) = 0 \\[2ex] \displaystyle\sum_{s=1}^{n} f_c(t_s, y_s, \overrightarrow{\boldsymbol{a}}, b, c) = 0. \end{cases} \tag{20}$$

Let $F = F(\overrightarrow{\boldsymbol{a}}, b, c)$ be defined through its components by

$$\left[\begin{array}{l} F_m(\overrightarrow{\boldsymbol{a}}, b, c) := \displaystyle\sum_{s=1}^{n} f_m(t_s, y_s, \overrightarrow{\boldsymbol{a}}, b, c), \qquad m = 1, \ldots, r \\ F_b(\overrightarrow{\boldsymbol{a}}, b, c) := \displaystyle\sum_{s=1}^{n} f_b(t_s, y_s, \overrightarrow{\boldsymbol{a}}, b, c) \\ F_c(\overrightarrow{\boldsymbol{a}}, b, c) := \displaystyle\sum_{s=1}^{n} f_c(t_s, y_s, \overrightarrow{\boldsymbol{a}}, b, c). \end{array}\right. \tag{21}$$

Now (20) takes the form

$$F(\overrightarrow{\boldsymbol{a}}, b, c) = 0. \tag{22}$$

4 Cellular exclusion principle

Here, we briefly present the method used in this work for numerically solving nonlinear algebraic systems of equations, named *Cellular exclusion algorithm*. This method will be applied to (22). Essentially, the cellular exclusion principle is a very efficient tool used to locate the solutions of

$$F(\mathbf{x}) = 0, \tag{23}$$

where $F : \Omega \subset \mathbb{R}^n \to \mathbb{R}^n$ (see [3], [11], [12], for example).
Let $\boldsymbol{\alpha} := (\alpha_1, \ldots, \alpha_n) \in \mathbb{Z}_+^n$ and $\boldsymbol{x} := (x_1, \ldots, x_n) \in \mathbb{R}^n$. We call

$$\boldsymbol{\sigma} = [\boldsymbol{\mu} - \boldsymbol{\rho}, \boldsymbol{\mu} + \boldsymbol{\rho}] := \{\boldsymbol{x} \in \mathbb{R}^n \mid \boldsymbol{\mu} - \boldsymbol{\rho} \leq \boldsymbol{x} \leq \boldsymbol{\mu} + \boldsymbol{\rho}\}^2$$

a box-interval with center $\boldsymbol{\mu} \in \mathbb{R}^n$ and radius $\boldsymbol{\rho} \in \mathbb{R}_+^n$.
We need the following notations:

- $|\boldsymbol{\alpha}| := \sum_i \alpha_i$,
- $\boldsymbol{\alpha}! := \prod_i \alpha_i$,
- $\boldsymbol{x}^{\boldsymbol{\alpha}} := \prod_i x_i^{\alpha_i}$,
- $\partial^{\boldsymbol{\alpha}} := \prod_i \partial^{\alpha_i}$,
- $|\boldsymbol{x}| := (|x_1|, \ldots, |x_n|) \in \mathbb{R}^n$,
- for $\boldsymbol{\sigma} \subset \mathbb{R}^n$ a box-interval, let $|\boldsymbol{\sigma}| := \{\boldsymbol{y} \mid \boldsymbol{y} = |\boldsymbol{x}|,\ \boldsymbol{x} \in \boldsymbol{\sigma}\} \subset \mathbb{R}_+^n$.

Let $q \in \mathbb{N}^*$ and $\boldsymbol{\sigma}$ a box-interval in $\mathbb{R}^n$.

[2] In $\mathbb{R}^n$ we use the standard component-wise "$\leq$" as a partial ordering.

Definition 1 *Let $F : \boldsymbol{\sigma} \to \mathbb{R}^n$ be absolutely continuous. One says that $\Lambda_F : |\boldsymbol{\sigma}| \to \mathbb{R}_+$ dominates F of order q on $\boldsymbol{\sigma}$ (denoted by $F \prec_q \Lambda_F$) if the following properties hold.*
1. $\partial^{\boldsymbol{\alpha}} F$, $\partial^{\boldsymbol{\alpha}} \Lambda_F$ absolutely continuous for all $0 \le |\boldsymbol{\alpha}| < q$.
2. For all $\boldsymbol{x}, \boldsymbol{y} \in |\boldsymbol{\sigma}|$, if $\boldsymbol{x} \le \boldsymbol{y}$, then $\partial^{\boldsymbol{\alpha}} \Lambda_F(\boldsymbol{x}) \le \partial^{\boldsymbol{\alpha}} \Lambda_F(\boldsymbol{y})$, for all $0 \le |\boldsymbol{\alpha}| \le q$.
3. $|\partial^{\boldsymbol{\alpha}} F(\boldsymbol{x})| \le \partial^{\boldsymbol{\alpha}} \Lambda_F(|\boldsymbol{x}|)$, for all $\boldsymbol{x} \in \boldsymbol{\sigma}$ and $0 \le |\boldsymbol{\alpha}| \le q$.

Let $q \in \mathbb{N}^*$. Consider $\boldsymbol{\sigma} = [\boldsymbol{\mu} - \boldsymbol{\rho}, \boldsymbol{\mu} + \boldsymbol{\rho}] \subset \mathbb{R}^n$ a box-interval with center $\boldsymbol{\mu} \in \mathbb{R}^n$ and radius $\boldsymbol{\rho} \in \mathbb{R}^n_+$. The following statement represents the basic tool of the exclusion algorithm we have used in this work.

Theorem 1 *If $F \prec_q \Lambda_F$ on $\boldsymbol{\sigma}$ and if $F = 0$ has solution in $\boldsymbol{\sigma}$, then the following inequality holds:*

$$0 \le \Lambda_F(|\boldsymbol{\mu}| + \boldsymbol{\rho}) - \Lambda_F(|\boldsymbol{\mu}|) - |F(\boldsymbol{\mu})| - \sum_{0<|\boldsymbol{\alpha}|<q} [\, \partial^{\boldsymbol{\alpha}} \Lambda_F(|\boldsymbol{\mu}|) - |\partial^{\boldsymbol{\alpha}} F(\boldsymbol{\mu})| \,] \cdot \frac{\boldsymbol{\rho}^{\boldsymbol{\alpha}}}{\boldsymbol{\alpha}!}. \tag{24}$$

A good dominant function is the key for improving the numerical efficiency of this method. The following properties are useful in the construction of dominant functions.

Proposition 1 *Let $p, q \in \mathbb{N}^*$ be arbitrarily fixed.*
1. If $F \prec_q \Lambda_F$ then $F(\boldsymbol{m} + \cdot) \prec_q \Lambda_F(|\boldsymbol{m}| + \cdot)$.
2. If $F \prec_1 \Lambda_F$, then $|F| \prec_1 \Lambda_F$.
3. If $F \prec_q \Lambda_F$, then $a \cdot F \prec_q |a| \cdot \Lambda_F$, for any $a \in \mathbb{R}$.
4. If $F_i \prec_q \Lambda_{F_i}$ for $i = \overline{1,p}$, then $\sum_{i=1}^p F_i \prec_q \sum_{i=1}^p \Lambda_{F_i}$.
5. If $F_i \prec_q \Lambda_{F_i}$ for $i = \overline{1,p}$, then $\prod_{i=1}^p F_i \prec_q \prod_{i=1}^p \Lambda_{F_i}$.
6. Let $F = f(f_1, \dots, f_p)$ and $\Lambda_F = \Lambda_f(\Lambda_{f_1}, \dots, \Lambda_{f_p})$. If $f \prec_q \Lambda_f$ and $f_i \prec_q \Lambda_{f_i}$ for $i = \overline{1,p}$, then $F \prec_q \Lambda_F$.

(For more information concerning the cellular exclusion algorithm the reader is refereed to [4], [7], [8], [9], [10], [13].)

5 The Derivatives of f_m, f_b, f_c

We introduce the convention $\frac{\partial^n}{\partial a_p^n} := \partial_p^n$, for all $p = 1, \dots, r$, and any $n \in \mathbb{N}^*$.
It is convenient to introduce the following notation

$$\tilde{h}(t, \overrightarrow{\boldsymbol{a}}, c) := \sum_{m=1}^{r-1} a_m\, E(t, b_m) + c.$$

Obviously,

$$h(t, \overrightarrow{\boldsymbol{a}}, b, c) = \tilde{h}(t, \overrightarrow{\boldsymbol{a}}, c) + aE(t, b).$$

Then we can write

$$f_r(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = (\tilde{h}(t, \overrightarrow{\boldsymbol{a}}, c) - y)E(t, b) + aE(2t, b).$$

As $f_b(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = f_r(t, y, \overrightarrow{\boldsymbol{a}}, b, c)ta$, one has

$$f_b(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = (\tilde{h}(t, \overrightarrow{\boldsymbol{a}}, c) - y)atE(t, b) + a^2 tE(2t, b).$$

The derivatives of $f_1, \ldots, f_r$, f_b, f_c are obtained by direct computations:

- the derivatives of f_m for $m = 1, \ldots, r$:

$$\left[\begin{array}{l} \partial_p^n f_m(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = \partial_p^n h(t, \overrightarrow{\boldsymbol{a}}, b, c)E(t, b_m) = E(t, b_p + b_m)\delta_{1,n} \\ \\ \partial_b^n f_m(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = t^n aE(t, b_m + b), \quad m = 1, \ldots, r-1 \\ \\ \partial_b^n f_a(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = (\tilde{h}(t, \overrightarrow{\boldsymbol{a}}, c) - y)t^n E(t, b) + a(2t)^n E(2t, b) \\ \\ \partial_c^n f_m(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = E(t, b_m)\delta_{1,n} \end{array}\right. \tag{25}$$

- the derivatives of f_b:

$$\left[\begin{array}{l} \partial_p f_b(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = ta \sum_{m=1}^{r-1} E(t, b_m + b)\delta_{p,m} + \\ \qquad\qquad + t\left[(\tilde{h}(t, \overrightarrow{\boldsymbol{a}}, c) - y)E(t, b) + 2aE(2t, b)\right]\delta_{p,r} \\ \\ \partial_\rho \partial_p f_b(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = t \sum_{m=1}^{r-1} E(t, b_m + b)\delta_{\rho,m}\delta_{p,r} + \\ \qquad\qquad + t\left[\sum_{m=1}^{r-1} E(t, b_m + b)\delta_{p,m} + 2E(2t, b)\delta_{p,r}\right]\delta_{\rho,r} \\ \\ \partial^{\boldsymbol{\alpha}} f_b(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = 0 \quad |\boldsymbol{\alpha}| \geq 3, 4, \ldots \quad (\partial^{\boldsymbol{\alpha}} := \partial_1^\alpha \ldots \partial_r^\alpha) \end{array}\right. \tag{26}$$

$$\left[\begin{array}{l} \partial_b^n f_b(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = (\tilde{h}(t, \overrightarrow{\boldsymbol{a}}, c) - y)t^{n+1} aE(t, b) + 2^n t^{n+1} a^2 E(2t, b) \\ \\ \partial_c^n f_b(t, y, \overrightarrow{\boldsymbol{a}}, b, c) = taE(t, b)\delta_{1,n} \end{array}\right. \tag{27}$$

$p = 1, 2, \ldots$.

Let $\partial^{\tilde{\boldsymbol{\alpha}}} := \partial^{\alpha_1} \ldots \partial^{\alpha_{r-1}}$. Using the above formulas for $t > 0$, we obtain the following derivation rules (for the non-null derivatives):
For $m = 1, \ldots, r-1$.

$\partial^{\tilde{\boldsymbol{\alpha}}} \partial_a^i \partial_b^j \partial_c^k f_m$	$\lvert\tilde{\boldsymbol{\alpha}}\rvert$	i	j	k	Comment
$\partial_p f_m = E(t, b_p + b_m)$	1	0	0	0	$p = 1, \ldots, r-1$
$\partial_a \partial_b^n f_m = t^n E(t, b_m + b)$	0	1	$n \geq 0$	0	
$\partial_b^n f_m = t^n aE(t, b_m + b)$	0	0	$n \geq 1$	0	
$\partial_c f_m = E(t, b_m)$	0	0	0	1	

(28)

(29)

$\partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_b^j\partial_c^k f_a$	$\lvert\tilde{\boldsymbol{\alpha}}\rvert$	i	j	k	Comment
$\partial_p\partial_b^n f_a = t^n E(t, b_p + b)$	1	0	$n \geq 0$	0	$p = 1, \ldots, r-1$
$\partial_a\partial_b^n f_a = (2t)^n E(2t, b)$	0	1	$n \geq 0$	0	
$\partial_b^n f_a = (\tilde{h} - y)t^n E(t, b) + a(2t)^n E(2t, b)$	0	0	$n \geq 1$	0	
$\partial_b^n\partial_c f_a = t^n E(t, b)$	0	0	$n \geq 0$	1	

(30)

$\partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_b^j\partial_c^k f_b$	$\lvert\tilde{\boldsymbol{\alpha}}\rvert$	i	j	k	Comment
$\partial_p\partial_b^n f_b = t^{n+1} a E(t, b_p + b)$	1	0	$n \geq 0$	0	$p = 1, \ldots, r-1$
$\partial_p\partial_a\partial_b^n f_b = t^{n+1} E(t, b_p + b)$	1	1	$n \geq 0$	0	$p = 1, \ldots, r-1$
$\partial_a\partial_b^n f_b = t^{n+1}(\tilde{h} - y)E(t, b) + (2t)^{n+1} a E(2t, b)$	0	1	$n \geq 0$	0	
$\partial_b^n f_b = t^{n+1} a(\tilde{h} - y)E(t, b) + 2^n t^{n+1} a^2 E(2t, b)$	0	0	$n \geq 1$	0	
$\partial_a^2\partial_b^n f_b = (2t)^{n+1} E(2t, b)$	0	2	$n \geq 0$	0	
$\partial_b^n\partial_c f_b = t^{n+1} a E(t, b)$	0	0	$n \geq 0$	1	
$\partial_a\partial_b^n\partial_c f_b = t^{n+1} E(t, b)$	0	1	$n \geq 0$	1	

(31)

$\partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_b^j\partial_c^k f_c$	$\lvert\tilde{\boldsymbol{\alpha}}\rvert$	i	j	k	Comment
$\partial_p f_c = E(t, b_p)$	1	0	0	0	$p = 1, \ldots, r-1$
$\partial_b^n f_c = t^n a E(t, b)$	0	0	$n \geq 1$	0	
$\partial_a\partial_b^n f_c = t^n E(t, b)$	0	1	$n \geq 0$	0	
$\partial_c f_c = 1$	0	0	0	1	

Using the derivatives of f_m, f_b and f_c, the derivatives of F_m, F_b and F_c can be written:

$$\left[\begin{array}{l} \partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_b^j\partial_c^k F_m(\overrightarrow{\boldsymbol{a}}, b, c) := \displaystyle\sum_{s=1}^{n} \partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_b^j\partial_c^k f_m(t_s, y_s, \overrightarrow{\boldsymbol{a}}, b, c) \quad m = 1, \ldots, r \\ \partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_b^j\partial_c^k F_b(\overrightarrow{\boldsymbol{a}}, b, c) := \displaystyle\sum_{s=1}^{n} \partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_b^j\partial_c^k f_b(t_s, y_s, \overrightarrow{\boldsymbol{a}}, b, c) \\ \partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_b^j\partial_c^k F_c(\overrightarrow{\boldsymbol{a}}, b, c) := \displaystyle\sum_{s=1}^{n} \partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_b^j\partial_c^k f_c(t_s, y_s, \overrightarrow{\boldsymbol{a}}, b, c). \end{array}\right. \tag{32}$$

6 Dominant Functions

6.1 The Dominant Function Λ_E

Usually, for the exponential function $E(t,x)$ of variable x, it is used the following dominant function of order q “around b”.

$$\Gamma_E(t,b,x,\rho,q) := \sum_{k=0}^{q-1} \frac{(xt)^k}{k!} + \frac{(xt)^q}{q!} E(t,b+\rho),$$

for $x \in [b-\rho, b+\rho]$ (see [4], for example).
For $E(t,b+x)$ as function of x, we proposed in [5] a more efficient dominant function of order q, namely $\Lambda_E(t,b,x,\rho,q)$, introduced by

$$\Lambda_E(t,b,x,\rho,q) := E(t,b) \left[\sum_{k=0}^{q-1} \frac{(xt)^k}{k!} + \frac{(xt)^q}{q!} E(t,\rho) \right], \tag{33}$$

for $x \in [-\rho, \rho]$ and some fixed $\rho > 0$. This means that

$$\left| \left. \frac{d^j E(t,z)}{dz^j} \right|_{z=b+x} \right| \leq \frac{d^j \Lambda_E(t,b,|x|,\rho,q)}{dx^k}, \tag{34}$$

for all $j = 0, 1, \ldots, q$.

6.2 The Dominant Functions Λ_{f_m}, Λ_{f_b}, Λ_{f_c}

For $t > 0$, we associate the dominant functions of order q w.r.t. the variables $a_1, \ldots, a_r, b, c$ to the functions $f_1, \ldots, f_m, f_b, f_c$.

1. For $m = 1, \ldots, r-1$ we have

$$\begin{cases} f_m(t,y,\overrightarrow{\boldsymbol{a}},b,c) := [\tilde{h}(t,\overrightarrow{\boldsymbol{a}},b,c) - y]E(t,b_m) + aE(t,b_m)E(t,b) \\ \Lambda_{f_m}(t,y,\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q) := \\ \qquad := [\tilde{h}(t,\overrightarrow{\boldsymbol{a}},c) + |y|]E(t,b_m) + aE(t,b_m)\Lambda_E(t,b,x_b,\rho_b,q) \end{cases} \tag{35}$$

2.

$$\begin{cases} f_a(t,y,\overrightarrow{\boldsymbol{a}},b,c) := [\tilde{h}(t,\overrightarrow{\boldsymbol{a}},c) - y]E(t,b) + aE(2t,b) \\ \Lambda_{f_a}(t,y,\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q) := \\ \qquad := [\tilde{h}(t,\overrightarrow{\boldsymbol{a}},c) + |y|]\Lambda_E(t,b,x_b,\rho_b,q) + a\Lambda_E(2t,b,x_b,\rho_b,q) \end{cases} \tag{36}$$

3.

$$\begin{cases} f_b(t,y,\overrightarrow{\boldsymbol{a}},b,c) := [\tilde{h}(t,\overrightarrow{\boldsymbol{a}},b,c)-y]taE(t,b)+ta^2E(2t,b) \\ \Lambda_{f_b}(t,y,\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q) := \\ \qquad := [\tilde{h}(t,\overrightarrow{\boldsymbol{a}},c)+|y|]ta\Lambda_E(t,b,x_b,\rho_b,q)+ta^2\Lambda_E(2t,b,x_b,\rho_b,q) \end{cases} \tag{37}$$

4.

$$\begin{cases} f_c(t,y,\overrightarrow{\boldsymbol{a}},b,c) := [\tilde{h}(t,\overrightarrow{\boldsymbol{a}},b,c)-y]+aE(t,b) \\ \Lambda_{f_c}(t,y,\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q) := \\ \qquad := [\tilde{h}(t,\overrightarrow{\boldsymbol{a}},c)+|y|]+a\Lambda_E(t,b,x_b,\rho_b,q) \end{cases} \tag{38}$$

(In (35-38) $x_b \in [-\rho_b, \rho_b]$.)
Correspondingly, $\Lambda_F = \Lambda_F(t,y,\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q)$ are defined on components by

$$\left[\begin{array}{l} \Lambda_{F_m}(\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q) := \displaystyle\sum_{s=1}^{n} \Lambda_{f_m}(t_s,y_s,\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q) \\ \qquad\qquad\qquad\qquad\qquad\qquad m=1,\ldots,r \\ \Lambda_{F_b}(\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q) := \displaystyle\sum_{s=1}^{n} \Lambda_{f_b}(t_s,y_s,\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q) \\ \Lambda_{F_c}(\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q) := \displaystyle\sum_{s=1}^{n} \Lambda_{f_c}(t_s,y_s,\overrightarrow{\boldsymbol{a}},b,c,x_b,\rho_b,q). \end{array} \right. \tag{39}$$

6.3 The Derivatives of Λ_{f_m}, Λ_{f_b}, Λ_{f_c}

One has to compute the derivatives of the dominant functions Λ_f

$$\frac{\partial^{\boldsymbol{\alpha}}\Lambda_f}{\partial \boldsymbol{x}^{\boldsymbol{\alpha}}}(t,y,x_1,\ldots,x_r,b,x_{r+2},x_{r+1},\rho_b,q)$$

only in the points of the form $\boldsymbol{x} = (|a_1|,\ldots,|a_{r-1}|,|a|,0,|c|)$. Here, f stands for f_m, f_b, f_c.
The following tables present these derivatives.
Let $q' = q-1$. For $m = 1,\ldots,r-1$ one has.

$\partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_x^j\partial_c^k\Lambda_{f_m}$	$\lvert\tilde{\boldsymbol{\alpha}}\rvert$	i	j	k	Comment
$\partial_p\Lambda_{f_m} = E(t,b_p+b_m)$	1	0	0	0	$p=1,\ldots,r-1$
$\partial_a\partial_x^n\Lambda_{f_m} = t^nE(t,b_m+b)$	0	1	$n=\overline{0,q'}$	0	
$\partial_x^n\Lambda_{f_m} = t^naE(t,b_m+b)$	0	0	$n=\overline{1,q'}$	0	
$\partial_c\Lambda_{f_m} = E(t,b_m)$	0	0	0	1	

(40)

$\partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_x^j\partial_c^k\Lambda_{f_a}$	$\lvert\tilde{\boldsymbol{\alpha}}\rvert$	i	j	k	Comment
$\partial_p\partial_x^n\Lambda_{f_a} = t^nE(t, b_p + b)$	1	0	$n = \overline{0, q'}$	0	$p = 1, \dots, r-1$
$\partial_a\partial_x^n\Lambda_{f_a} = (2t)^nE(2t, b)$	0	1	$n = \overline{0, q'}$	0	
$\partial_x^n\Lambda_{f_a} = (\tilde{h} + \lvert y\rvert)t^nE(t, b) + a(2t)^nE(2t, b)$	0	0	$n = \overline{1, q'}$	0	
$\partial_x^n\partial_c\Lambda_{f_a} = t^nE(t, b)$	0	0	$n = \overline{0, q'}$	1	

(41)

$\partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_x^j\partial_c^k\Lambda_{f_b}$	$\lvert\tilde{\boldsymbol{\alpha}}\rvert$	i	j	k	Comment
$\partial_p\partial_x^n\Lambda_{f_b} = t^{n+1}aE(t, b_p + b)$	1	0	$n = \overline{0, q'}$	0	$p = 1, \dots, r-1$
$\partial_p\partial_a\partial_x^n\Lambda_{f_b} = t^{n+1}E(t, b_p + b)$	1	1	$n = \overline{0, q'}$	0	$p = 1, \dots, r-1$
$\partial_a\partial_x^n\Lambda_{f_b} = t^{n+1}(\tilde{h} + \lvert y\rvert)E(t, b) + (2t)^{n+1}aE(2t, b)$	0	1	$n = \overline{0, q'}$	0	
$\partial_x^n\Lambda_{f_b} = t^{n+1}a(\tilde{h} + \lvert y\rvert)E(t, b) + 2^nt^{n+1}a^2E(2t, b)$	0	0	$n = \overline{1, q'}$	0	
$\partial_a^2\partial_x^n\Lambda_{f_b} = (2t)^{n+1}E(2t, b)$	0	2	$n = \overline{0, q'}$	0	
$\partial_x^n\partial_c\Lambda_{f_b} = t^{n+1}aE(t, b)$	0	0	$n = \overline{0, q'}$	1	
$\partial_a\partial_x^n\partial_c\Lambda_{f_b} = t^{n+1}E(t, b)$	0	1	$n = \overline{0, q'}$	1	

(42)

$\partial^{\tilde{\boldsymbol{\alpha}}}\partial_a^i\partial_x^j\partial_c^k\Lambda_{f_c}$	$\lvert\tilde{\boldsymbol{\alpha}}\rvert$	i	j	k	Comment
$\partial_p\Lambda_{f_c} = E(t, b_p)$	1	0	0	0	$p = 1, \dots, r-1$
$\partial_x^n\Lambda_{f_c} = t^naE(t, b)$	0	0	$n = \overline{1, q'}$	0	
$\partial_a\partial_x^n\Lambda_{f_c} = t^nE(t, b)$	0	1	$n = \overline{0, q'}$	0	
$\partial_c\Lambda_{f_c} = 1$	0	0	0	1	

(43)

7 The Exclusion Criterion

In order to explicitly write the exclusion criterion given by Theorem 1, we introduce some notations.

$$\begin{aligned}
&\Theta_a^j(\overrightarrow{\boldsymbol{a}}, b, c, q) := \\
&:= \sum_{s=1}^{n}[(\tilde{h}(t_s, \lvert\overrightarrow{\boldsymbol{a}}\rvert, \lvert c\rvert) + \lvert y_s\rvert)t_s^jE(t_s, b) + \lvert a\rvert(2t_s)^jE(2t_s, b)] - \\
&- \left\lvert\sum_{s=1}^{n}[(\tilde{h}(t_s, \overrightarrow{\boldsymbol{a}}, c) - y_s)t_s^jE(t_s, b) + a(2t_s)^jE(2t_s, b)]\right\rvert,
\end{aligned} \tag{44}$$

for all $j > 0$.

$$\begin{aligned}&\Theta_b^{0,j}(\overrightarrow{\boldsymbol{a}},b,c,q):=\\&:=\sum_{s=1}^{n}[(\tilde{h}(t_s,|\overrightarrow{\boldsymbol{a}}|,|c|)+|y_s|)t_s^{j+1}|a|E(t_s,b)+(2t_s)^j t_s a^2 E(2t_s,b)]-\\&-\left|\sum_{s=1}^{n}[(\tilde{h}(t_s,\overrightarrow{\boldsymbol{a}},c)-y_s)t_s^{j+1}aE(t_s,b)+(2t_s)^j t_s a^2E(2t_s,b)]\right|,\end{aligned} \tag{45}$$

for all $j > 0$.

$$\begin{aligned}&\Theta_b^{1,j}(\overrightarrow{\boldsymbol{a}},b,c,q):=\\&:=\sum_{s=1}^{n}[(\tilde{h}(t_s,|\overrightarrow{\boldsymbol{a}}|,|c|)+|y_s|)t_s^{j+1}E(t_s,b)+(2t_s)^{j+1}|a|E(2t_s,b)]-\\&-\left|\sum_{s=1}^{n}[(\tilde{h}(t_s,\overrightarrow{\boldsymbol{a}},c)-y_s)t_s^{j+1}E(t_s,b)+(2t_s)^{j+1}aE(2t_s,b)]\right|,\end{aligned} \tag{46}$$

for all $j > 0$.
Define $\Delta\Lambda_E(t,b,\rho,q) := \Lambda_E(t,b,\rho,\rho,q) - \Lambda_E(t,b,0,\rho,q)$. From (33) we obviously have

$$\Delta\Lambda_E(t,b,\rho,q) := E(t,b)\left[\sum_{k=1}^{q-1}\frac{(\rho t)^k}{k!}+\frac{(\rho t)^q}{q!}E(t,\rho)\right]. \tag{47}$$

Let $\overrightarrow{\boldsymbol{\rho}} := (\rho_1,\ldots,\rho_r) \in \mathbb{R}^r$, and

$$\Delta\Lambda_\Phi(\overrightarrow{\boldsymbol{a}},b,c,\overrightarrow{\boldsymbol{\rho}},\rho_b,\rho_c,q) := \Lambda_\Phi(|\overrightarrow{\boldsymbol{a}}|+\overrightarrow{\boldsymbol{\rho}},b,|c|+\rho_c,\rho_b,\rho_b,q)-\Lambda_\Phi(|\overrightarrow{\boldsymbol{a}}|,b,|c|,0,\rho_b,q),$$

where Λ_Φ is any of the dominant functions $\Lambda_{F_1},\ldots,\Lambda_{F_r},\Lambda_{F_b},\Lambda_{F_c}$.
From (21), (35) and (39), for $m = 1,\ldots,r-1$, we obtain

$$\begin{aligned}&\Delta\Lambda_{F_m}(\overrightarrow{\boldsymbol{a}},b,c,\overrightarrow{\boldsymbol{\rho}},\rho_b,\rho_c,q)=\\&=\sum_{s=1}^{n}E(t_s,b_m)\left[\tilde{h}(t_s,\overrightarrow{\boldsymbol{\rho}},\rho_c)+|a|\Delta\Lambda_E(t_s,b,\rho_b,q)+\rho_a\Lambda_E(t_s,b,\rho_b,\rho_b,q)\right].\end{aligned} \tag{48}$$

From (21), (36) and (39), we obtain

$$\begin{aligned}\Delta\Lambda_{F_a}(\overrightarrow{\boldsymbol{a}},b,c,\overrightarrow{\boldsymbol{\rho}},\rho_b,\rho_c,q)&=\sum_{s=1}^{n}\left\{\left[\tilde{h}(t_s,|\overrightarrow{\boldsymbol{a}}|,|c|)+|y_s|\right]\Delta\Lambda_E(t_s,b,\rho_b,q)+\right.\\&\left.+\tilde{h}(t_s,\boldsymbol{\rho},\rho_c)\Lambda_E(t_s,b,\rho_b,q)+\rho_a\Lambda_E(2t_s,b,\rho_b,\rho_b,q)+|a|\Delta\Lambda_E(2t_s,b,\rho_b,q)\right\}.\end{aligned} \tag{49}$$

From (21), (37) and (39), we obtain

$$\Delta\Lambda_{F_b}(\overrightarrow{\boldsymbol{a}}, b, c, \overrightarrow{\boldsymbol{\rho}}, \rho_b, \rho_c, q) = \sum_{s=1}^{n} t_s \left\{ \left[\tilde{h}(t_s, |\overrightarrow{\boldsymbol{a}}|, |c|) + |y_s| \right] |a| \Delta\Lambda_E(t_s, b, \rho_b, q) + \right.$$
$$+ \left[\tilde{h}(t_s, \overrightarrow{\boldsymbol{\rho}}, \rho_c)(|a| + \rho_a) + (\tilde{h}(t_s, |\overrightarrow{\boldsymbol{a}}|, |c|) + |y_s|)\rho_a \right] \Lambda_E(t_s, b, \rho_b, \rho_b, q) + \tag{50}$$
$$\left. +(2|a|\rho_a + \rho_a^2)\Lambda_E(2t_s, b, \rho_b, \rho_b, q) + a^2 \Delta\Lambda_E(2t_s, b, \rho_b, q) \right\}.$$

From (21), (35) and (39), we obtain

$$\Delta\Lambda_{F_c}(\overrightarrow{\boldsymbol{a}}, b, c, \overrightarrow{\boldsymbol{\rho}}, \rho_b, \rho_c, q) =$$
$$= \sum_{s=1}^{n} \left[\tilde{h}(t_s, \overrightarrow{\boldsymbol{\rho}}, \rho_c) + |a| \Delta\Lambda_E(t_s, b, \rho_b, q) + \rho_a \Lambda_E(t_s, b, \rho_b, \rho_b, q) \right]. \tag{51}$$

Using Rels. (19), (21), (44), (45), (46), (49), (50), and (51), we can write the exclusion inequalities:

$$\left[\begin{array}{l} 0 \le \Delta\Lambda_{F_m}(\overrightarrow{\boldsymbol{a}}, b, c, \overrightarrow{\boldsymbol{\rho}}, \rho_b, \rho_c, q) - |F_m(\overrightarrow{\boldsymbol{a}}, b, c)| \\ \qquad\qquad\qquad\qquad\qquad\qquad m = 1, \dots, r-1 \\ 0 \le \Delta\Lambda_{F_a}(\overrightarrow{\boldsymbol{a}}, b, c, \overrightarrow{\boldsymbol{\rho}}, \rho_b, \rho_c, q) - |F_a(\overrightarrow{\boldsymbol{a}}, b, c)| - \sum_{j=1}^{q-1} \Theta_a^j(\overrightarrow{\boldsymbol{a}}, b, c, q) \dfrac{\rho_b^j}{j!} \\ 0 \le \Delta\Lambda_{F_b}(\overrightarrow{\boldsymbol{a}}, b, c, \overrightarrow{\boldsymbol{\rho}}, \rho_b, \rho_c, q) - |F_b(\overrightarrow{\boldsymbol{a}}, b, c)| - \sum_{j=1}^{q-1} \Theta_b^{0,j}(\overrightarrow{\boldsymbol{a}}, b, c, q) \dfrac{\rho_b^j}{j!} - \\ \qquad\qquad\qquad - \sum_{j=0}^{q-2} \Theta_b^{1,j}(\overrightarrow{\boldsymbol{a}}, b, c, q) \dfrac{\rho_a \rho_b^j}{j!} \\ 0 \le \Delta\Lambda_{F_c}(\overrightarrow{\boldsymbol{a}}, b, c, \overrightarrow{\boldsymbol{\rho}}, \rho_b, \rho_c, q) - |F_c(\overrightarrow{\boldsymbol{a}}, b, c)| \end{array} \right. \tag{52}$$

Remark: *These inequalities represent the base relations used in the exclusion cellular algorithm for solving (20).*

Some theoretical and numerical results obtained in this framework have been communicated in [5], [6]; more numerical results are considered in the following section.

8 Numerical Results

We have considered the case of three parameters for which we have generated couple of non-perturbed and perturbed data sets. Having the goal of estimating the values of these parameters and using the exclusion algorithm adapted to the bioconcentration problem we have obtained the results presented in what it follows.

8.1 Non-perturbed Data

Using the exact solution of the model, we have generated a set of 200 non-perturbed data $\{y_s\}_{s=1}^{200}$ corresponding to $\{t_s\}_{s=1}^{200} \subset [0, 10]$ and starting from $(a, b, c) = (1, -1, 1)$. For estimating the values of the parameters corresponding to this data set we have used the method previously described starting from the initial box interval $\boldsymbol{\sigma}$, defined by $\boldsymbol{\mu_\sigma} = (2, -2, 2.5)$, and $\boldsymbol{\rho_\sigma} = (1.5, 1.5, 2)$. The results are of very good precision. For example, at the iteration level $l = 30$, where the radius of any of the remaining 74 box-interval is $\boldsymbol{\rho} = (1.397, 1.397, 1.863) \cdot 10^{-9}$ the estimated values are

$a_{aprox} \in [0.99999996, 0.99999998]$
$b_{aprox} \in [-1, -0, 999999995]$
$c_{aprox} = 1.$

The number $\#I$ of retained intervals at each iteration level l is presented in the following table.

l	0	1	2	3	...	7	...	15	...	20	...	28	29	30
$\#I$	1	5	13	46	...	111	...	78	...	79	...	67	68	74

For the next case, we have generated different sets of n non-perturbed data, but using $(a, b, c) = (5 \cdot 10^6, -10, 1)$ (remark the big order difference for the values of these parameters). Starting with the box-interval

$$\boldsymbol{\sigma} : \quad \boldsymbol{\mu_\sigma} = (4099750, -7, 2.5), \quad \boldsymbol{\rho_\sigma} = (10^6, 4, 2 \cdot 10^3),$$

we have obtained the results summarized in the next two tables.

	l / n	0	1	2	3		15		28	29	30
$t \in [0, 2]$	20	1	8	36	84		29141		29111	29111	29116
$t \in [0, 2]$	2000	1	6	24	44		523		586	454	521
$t \in [0, 2]$	200	1	6	28	24		198		200	186	255
$t \in [0, 5]$	200	1	6	25	32		147		102	109	133

Level $l = 30$: $\quad \boldsymbol{\rho} = (9.313 \cdot 10^{-4}, 3.725 \cdot 10^{-9}, 1.863 \cdot 10^{-6})$;

	n	a_{aprox}	b_{aprox}	c_{aprox}
$t \in [0, 2]$	20	[4999998.4,5000001.5]	[-10.000002,-9.9999981]	[0.99832617,1.0016901]
$t \in [0, 2]$	2000	[5000000,5000000]	[-10,-10]	[0.99959649,1.0002372]
$t \in [0, 2]$	200	[5000000.1,5000000.1]	[-10,-10]	[1.0008929,1.0013101]
$t \in [0, 5]$	200	[5000000,5000000]	[-10,-10]	[1.0004645,1.0006172]

One of the remarks the reader should make is that the results are good, but the numerical effort of getting them is considerably higher when the number of data is small. Also, it has been observed that the accuracy as well as the efficiency are improved when the range time interval is larger. It is also important to emphasize that the "exact data" $\{y_s\}_s$ were truncated to the 6^{th} decimal, fact that will affect the numerical values of the estimated parameters.

8.2 Perturbed Data

In this section, we have simulated different sets of n data affected by measurement errors: each exact datum was perturbed with a random error between $[-p\%, p\%]$ of itself.
First, starting from $(a, b, c) = (1, -1, 1)$, we have considered the two cases corresponding to $p = 10$ and $p = 2.5$, respectively.

Case **p=10**: Starting with the interval

$$\boldsymbol{\sigma}: \quad \boldsymbol{\mu_\sigma} = (2, -2, 2.5), \quad \boldsymbol{\rho_\sigma} = (1.5, 1.5, 2),$$

we have obtained the following results:

	l / n	0	1	2	3		15		28	29	30
$t \in [0, 10]$	2000	1	5	16	52		102		203	111	105
$t \in [0, 10]$	200	1	5	16	49		118		115	118	115
$t \in [0, 10]$	20	1	5	16	80		1221		1227	1229	1226
$t \in [0, 2]$	20	1	4	16	54		12560		12416	12410	12412

Level $l = 30$: $\quad \boldsymbol{\rho} = (1.397, 1.397, 1.863) \cdot 10^{-9}$;

a_{aprox}	b_{aprox}	c_{aprox}	σ	σ_a
[1.0072475,1.0072475]	[-0.97994829,-0.97994822]	[0.99533893,0.99533894]	0.064947	0.064823
[0.91090072,0.91090075]	[-0.94568878,-0.94568869]	[1.0026692,1.0026693]	0.066365	0.064343
[1.2705622,1.2705629]	[-1.3324567,-1.3324561]	[1.0254773,1.0254773]	0.068847	0.066008
[1.0593118,1.0593134]	[-0.78527480,-0.78527198]	[0.91569570,0.91569762]	0.092270	0.089797

Case **p=2.5**: Using the same starting interval as in the previous case, we have obtained:

	l / n	0	1	2	3		15		28	29	30
$t \in [0, 10]$	200	1	5	16	48		105		107	109	107
$t \in [0, 2]$	20	1	4	16	55		7156		7113	7113	7108

Level $l = 30$: $\quad \boldsymbol{\rho} = (1.397, 1.397, 1.863) \cdot 10^{-9}$;

a_{aprox}	b_{aprox}	c_{aprox}	σ	σ_a
[0.97785788,0.97785792]	[-0.98772550,-0.98772541]	[1.0007406,1.0007406]	0.016591	0.016089
[1.0102417,1.0102417]	[-0.94526203,-0.94526004]	[0.98304536,0.98304631]	0.023068	0.022447

One can observe that the remarks written in the end of the previous section hold also here. Moreover, as expected, the accuracy of the determined parameters increases with the precision of the measurements. In the tables where we are presenting the estimated values a_{aprox}, b_{aprox}, c_{aprox} of the parameters a, b, c, respectively, the last two columns contain the standard deviations σ and σ_a corresponding to (a, b, c) and $(a_{aprox}, b_{aprox}, c_{aprox})$, respectively. Remark that $\sigma > \sigma_a$ here, as well as in next perturbed data sets. This is natural since the method mathematically locates the minimum of (17) for data affected by "error measurements" and not for exact data.

8.3 Running Times

On the case $(a, b, c) = (1, -1, 1)$; $\boldsymbol{\mu_\sigma} = (2, -2, 2.5)$, $\boldsymbol{\rho_\sigma} = (1.5, 1.5, 2)$, for 200 data, $t \in [0, 10]$, $\pm 2.5\%$ perturbations, $l = 30$, note that:

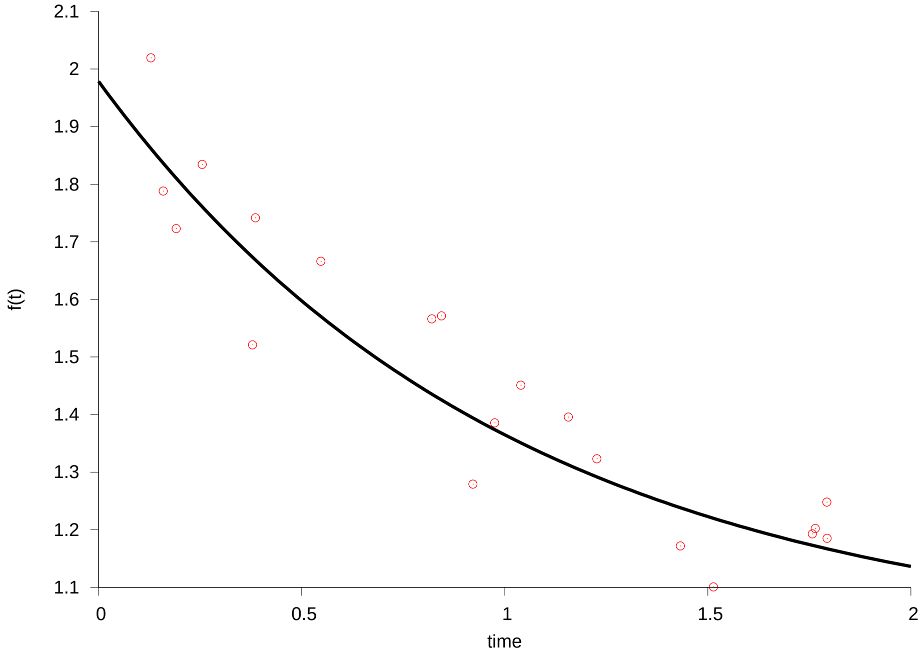
Intel(R) Xeon(R) 2 X CPU E5530 @ 2.40GHz
Classical dominant function: 545.75s
New dominant function: 67.20s

Intel(R) Pentium(R) 4 CPU 3.00GHz
Classical dominant function: 1119.16s
New dominant function: 117.38s

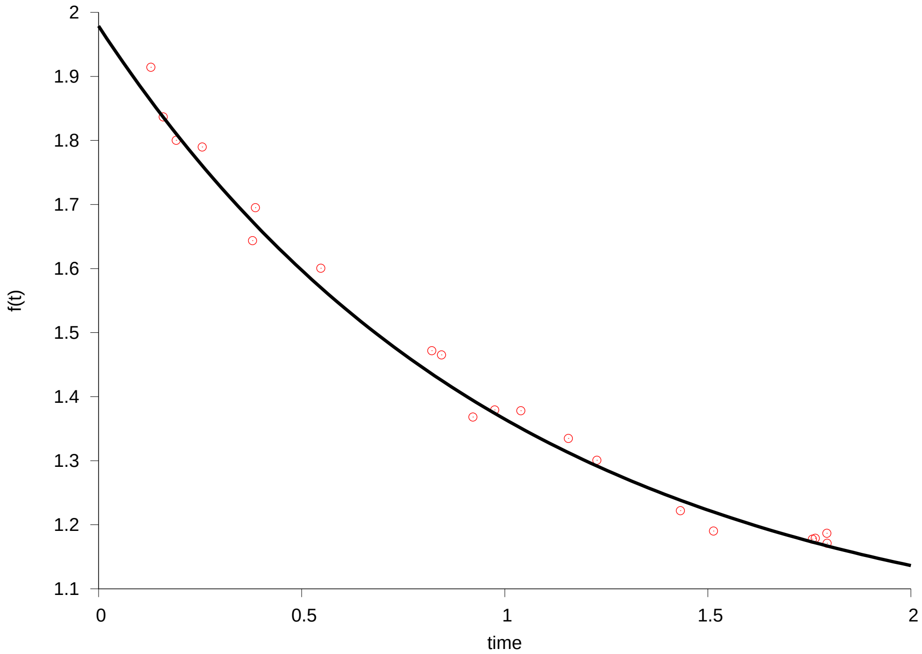
Besides the fact that the new dominant function strongly simplifies the numerical code, accuracy, these running times written above bring an immediate argument in favor of the efficiency.

8.4 Graphics

Here, we graphically illustrate some of the results presented in the previous section for $(a, b, c) = (1, -1, 1)$

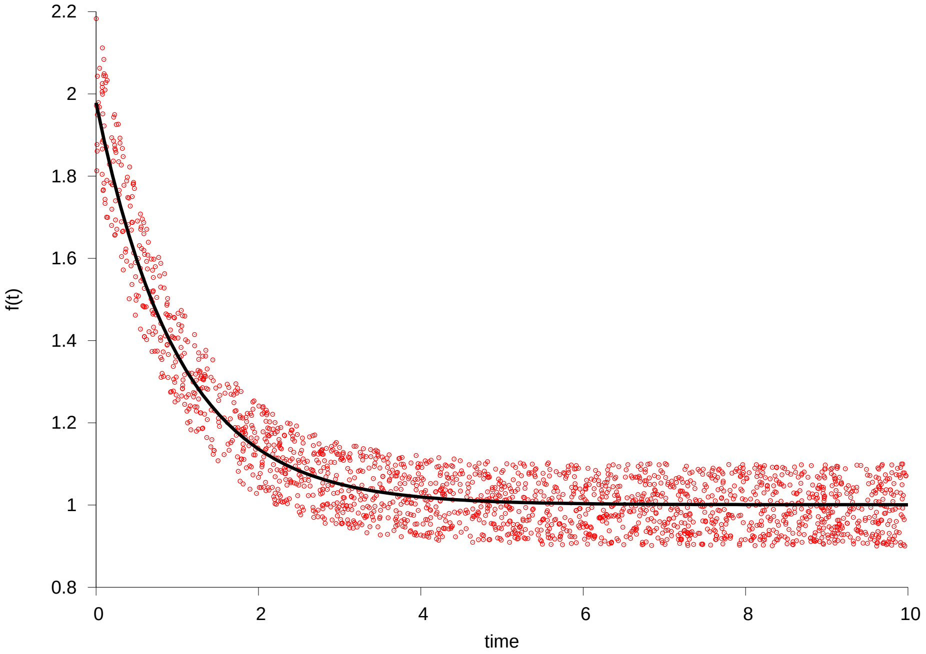


20 data, $\pm 10\%$ perturbations

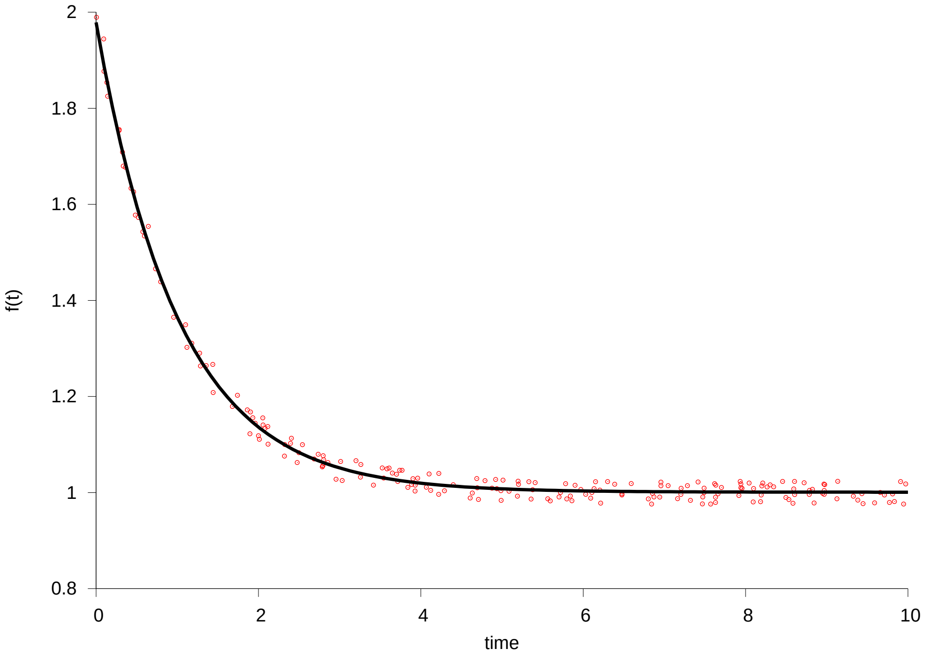


20 data, $\pm 2.5\%$ perturbations

$$(a, b, c) = (1, -1, 1)$$



2000 data, $\pm 10\%$ perturbations



200 data, $\pm 2.5\%$ perturbations

References

[1] S. Galassi, M. Gatto and B. Zanetti, *BIOCON: A program for the parameter estimation and the simulation of a simple bioconcentration model*, Environmental Software **4**, (1989) 157-161.

[2] S. N. Luoma and P. S. Rainbow *Why Is Metal Bioaccumulation So Variable? Biodynamics as a Unifying Concept*, Environ. Sci. Technol., 2005, **39(7)**, 1921-1931.

[3] K. Georg, *Improving the Efficiency of Exclusion Algorithms*, Advances in Geometry, **1**, (2001), 193-210.

[4] E. L. Allgower, S. G. Cruceanu, S. Tavener, *Application of numerical continuation to detect all the solutions of semilinear elliptic equations*, Advances in Geometry, **9**, (2009), 371-400.

[5] S. G. Cruceanu, and D. Marinescu, *Applications of cellular exclusion methods to locate solutions of non-linear systems of equations*, ROMAI Journal, 2010, to appear.

[6] S. G. Cruceanu, and D. Marinescu, *Cellular exclusion algorithm for parameter estimation with applications in biological models*, Mathematical Modelling of Environmental and Life Science Problems - Proceedings of the eight workshop, 2010, to appear.

[7] R. E. Moore, *A test for existence of solutions to nonlinear systems*, SIAM J. Numer. Anal., **14(4)**, (1977), 611-615.

[8] J. S. Zhang, W. Wang, and B. L. Chen, *A cell exclusion algorithm for finding all global minimizers of functions of several variables*, Math. Numer. Sinica, **17**, (1995), 443-455.

[9] Z. B. Xu, J. S. Zhang, and W. Wang, *A cell exclusion algorithm for determining all the solutions of a nonlinear system of equations*, Appl. Math. Comput., **80**, (1996), 181-208.

[10] Z. B. Xu, J. S. Zhang, and Y. W. Leung, *A general cdc formulation for specializing the cell exclusion algorithms of finding all zeros of vector functions*, Appl. Math.Comput., **86**, (1997), 235-259.

[11] B. L. Meng and Z. D. Xing, *A cell exclusion algorithm for finding all solutions to systems of nonlinear equations*. Pure Appl. Math. (Xian), **15**, (1999), 72-76.

[12] E. Allgower, M. Erdmann, and K. Georg, *On the complexity of exclusion algorithms for optimization*, J. Complex., **18**, (2002), 573-588.

[13] M. I. Syam, *Nonlinear optimization exclusion tests for finding all solutions of nonlinear equations*, Appl. Math. Comput., **170**, (2005), 1104-1116.