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Global optimization approaches to parameters identification in an immune competition model

Lekbir Afraites[1], Abdelghani Bellouquid[2]

[1] *Sultan Moulay Slimane University, FST, Beni-Mellal, Morroco*
lekbir.afraites@gmail.com

[2] *Cadi Ayyad University, ENSA, Marrakech, Morroco*
a.bellouquid@uca.ma

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Abstract

The identification of the parameters in a model of immune competition is treated in this paper. More precisely, an approach of inverse problems toward the identification from measurements of densities of cells population is used. The inverse problem is transferred into a parametric optimization problem using the nonlinear identification approach with a Least Square objective function. Global optimization techniques are pursued and a design procedure for global robust optimization is developed using the so-called Kriging method, optimization approaches are used to determine the global robust optimum of a surrogate model.

Keywords: `tumor immune cells competition, identification parameters, inverse problem, global optimization, Kriging method.`

AMS subject classification: `05A16, 65N38, 78M50.`

1. Introduction.

The modeling of biological systems has recently been developed by a new approach based on the kinetic theory of active particles [1,2]. Several applications have experienced, especially focusing on the modeling of immune competition [3–9]. In general, models include biological parameters that play an important role in the dynamics. Their identification is necessary to validate models. This calibration of models can be developed through an inverse problem approach, in which the unknown parameters of the model can be estimated from empirical data (observations).

Such inverse problem is difficult to solve. Moreover, the problem is ill-posed and requires, for example, the use of regularization methods. On the other hand, the use of traditional optimization methods brings us back to a local optimum and the quality of the result depends on the initial point.

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In order to deal with the issue of local optimum and the dependence of the initial point, we propose an approach based on the so-called Kriging interpolation method and its use as a technique for global optimization.

Considering that this paper deals with the identification of parameters, it is worth mentioning that a number of methods and software tools have been developed for for applications to the study of biological systems [10–15]. Amongst the existing methods, the predominant strategy consists in looking for values of the parameters that minimize the data mismatch, namely the discrepancy between the experimental observations and the simulated data. The underlying premise is that the optimal set of parameters is the one which gives rise to simulated data that match the empirical observations at the best computational approximation. Computationally, the minimization of the objective function may involve some combination of local and global minimization methods [16,17].

This work considers an integro-differential system modeling the immune competition, developed in [4,8], and presents various results obtained by analytic and computational methods.

The content of this paper is developed through six more Sections as follows: Section 2 deals with the statement of the mathematical modeling. Section 3 introduces the inverse problem and some results on the identifiability, as well as on the local stability. Section 4 is devoted to transform the inverse problem to an optimization problem, where the unknowns are parameters to be identified. The gradient of the cost function using the adjoint technique, the optimization procedure and disadvantages of this method has been presented. Section 5 describes the "Kriging" method and global optimization techniques to achieve the global optimum independently of initial point. Section 6 presents some numerical experiments with respect to the introduction of a Gaussian noise on the measurements illustrating the techniques proposed, finally Section 7 focuses on a final summary of the results of this research work.

2. Mathematical modeling and problem statement.

2.1. *The model.*

Modeling the competition between tumor cells and immune cells can be developed by tools of the generalized kinetic theory. This means that the microscopic state of the system is described by a variable u called activation (or biological function), while the evolution of the system can be described by a distribution function over the said micro-scale variable. This modeling approach was introduced in [1], and subsequently developed by various authors, see [2].

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Let us specifically consider a system consisting of two interacting populations, namely normal cells that begin to move towards states abnormal (tumor) represented by the distribution function f_1, such that for $u \in (-\infty, 0)$ cells are normal, while for $u \in (0, +\infty)$ become abnormal. The immune system is represented by the distribution function f_2.

Referring to [8], the evolution equation of the system can be written as follows:

$$
(1) \qquad \begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = n_1(t)\Big(f_1(t,u-\alpha_{11}) - f_1(t,u)\Big) \\ \qquad\qquad + n_2^A(t) f_1(t,u+\alpha_{12}) U_{[0,\infty)}(u+\alpha_{12}) \\ \qquad\qquad + f_1(t,u)\left[\beta_{11} n_1^E(t) - (1+\beta_{12}) n_2^A(t)\right] U_{[0,\infty)}(u), \\ \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t) f_2(t,u+\alpha_{21}) U_{[0,\infty)}(u+\alpha_{21}) \\ \qquad\qquad + n_1^T(t)\left[\beta_{21} - 1\right] f_2(t,u) U_{[0,\infty)}(u), \end{cases}
$$

where

$$
n_1 = \int_{-\infty}^{\infty} f_1(t,u)\,du, \quad n_2 = \int_{-\infty}^{\infty} f_2(t,u)\,du, \quad n_1^E = \int_{-\infty}^{0} f_1(t,u),\ du,
$$

$$
n_2^I = \int_{-\infty}^{0} f_2(t,u)\,du, \quad n_1^T = \int_{0}^{\infty} f_1(t,u)\,du, \quad n_2^A = \int_{0}^{\infty} f_2(t,u)\,du,
$$

and where U is the stepwise function defined by

$$
(2) \qquad U_{[a,b]}(z) : \begin{cases} U_{[a,b]}(z) = 1 \quad if \quad z \in [a;b], \\ U_{[a,b]}(z) = 0 \quad if \quad z \notin [a;b]. \end{cases}
$$

The above model (1) is characterized by two types of phenomenological parameters α_{ij} and β_{ij} which are small with respect to one, where the α_{ij}-parameters are related to conservative encounters, while the β_{ij}-parameters are related to proliferative and destructive phenomena.

In case where conservative interactions are negligible and proliferative interactions become dominant, namely $\alpha_{ij} = 0$, one obtains the following model [8]:

$$
(3) \qquad \begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = f_1(t,u)\Big(\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\Big) U_{[0,\infty)}(u), \\ \\ \dfrac{\partial f_2}{\partial t}(t,u) = \beta_{21} n_1^T(t) f_2(t,u) U_{[0,\infty)}(u). \end{cases}
$$

2.2. *The initial value problem.*

The aim of this section consists in stating some results on the qualitative analysis of the initial value problem for the mathematical model (3).

The analysis has the objective of showing the validity of the model with respect to well-posedness of the initial value problems related to its applications, and to provide the necessary framework for the simulations which will be developed later. In details, this subsection is devoted to prove existence, uniqueness, and continuity of the solutions for the Cauchy problem for the model defined in Equations (3). Such a problem can be formally written as follows:

$$(4)\qquad \begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = f_1(t,u)(\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)) U_{[0,\infty)}(u), \\ \dfrac{\partial f_2}{\partial t}(t,u) = \beta_{21} n_1^T(t) f_2(t,u) U_{[0,\infty)}(u), \\ f_i(0,u) \quad = f_{i0}(u), \quad i = 1,2. \end{cases}$$

The analysis of problem (4) needs the definition of some suitable function spaces. Specifically:
$L_1(\mathbb{R})$ is the Lebesgue space of measurable, real-valued functions which are integrable on R. The norm is denoted by $\| \cdot \|_1$.
$X = (L_1(\mathbb{R})^2 = \{f = (f_1, f_2) : f_1 \in L_1(\mathbb{R}), f_2 \in L_1(R)\}$ is the Banach space endowed with the norm

$$\| f \| = \| f_1 \|_1 + \| f_2 \|_1 .$$

$X_+ = \{f = (f_1, f_2) \in X : f_1 \geq 0, f_2 \geq 0\}$ is the positive cone of X.
$Y = C([0,T], X)$ and $Y_+ = C([0,T], X_+)$ are the space of the functions continuous on $[0,T]$ with values, respectively, in a Banach space X and X_+, equipped with the norm

$$\| f \|_Y = \sup_{t \in [0,T]} \| f \| .$$

Global Existence and uniqueness of the solution to the initial value problem are stated by the following (see [8]):

Theorem 2.1. *For any $T > 0$ there exists a unique solution $f \in C([0,T], X)$ of (4) with the initial data, $f_0 \in X_+$. The solution satisfies*

$$(5)\qquad f(t) \in X_+, \quad \forall t \in [0,T],$$

and, for some constant C_T depending on T and on the initial data,

$$(6)\qquad \sup_{t \in [0,T]} \| f(t) \| \leq C_T.$$

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3. Inverse problem.

The contents of the preceding section provide some illustrative applications concerned with problem of immune competition [8]. Focusing on the aforesaid inverse problem:

Integrating Equations (3) over the biological variable u, yields:

$$\begin{cases} \dfrac{\partial n_1^T}{\partial t}(t) = n_1^T(t)\Big(\beta_{11} n_1^E(0) - \beta_{12} n_2^A(t)\Big), \\ \dfrac{\partial n_2^A}{\partial t}(t) = \beta_{21} n_1^T(t) n_2^A(t). \end{cases} \tag{7}$$

Noting that $N_1 = n_1^T$ and $N_2 = n_2^A$, then, Equations (7) can be rewritten as follows:

$$\begin{cases} \dfrac{\partial N_1}{\partial t}(t) = N_1(t)\Big(n_1^E(0)\beta_{11} - \beta_{12} N_2(t)\Big), \\ \dfrac{\partial N_2}{\partial t}(t) = \beta_{21} N_1(t) N_2(t), \end{cases} \tag{8}$$

with the initial conditions given by $(N_1(0), N_2(0)) = (N_{10}, N_{20}) = (n_1^T(0), n_2^A(0))$.

We write Equations (8) in the following form:

$$\frac{\partial N}{\partial t}(t) = H\Big(N(t), \beta\Big), \quad \beta = \Big[\beta_{11}, \beta_{12}, \beta_{21}\Big], \tag{9}$$

where

$$N(t) = \begin{pmatrix} N_1(t) \\ N_2(t) \end{pmatrix}, \quad H\Big(N(t), \beta\Big) = \begin{pmatrix} H_1(N(t), \beta) \\ H_2(N(t), \beta) \end{pmatrix}.$$

Our main goal is the development of a method to identify the parameters β_{ij} from empirical data for the densities N_1 and N_2 solutions of Equations (8).

First, we define an appropriate space $\mathcal{P}_{ad}$ for admissible parameters:

$$\mathcal{P}_{ad} := \{(\beta_{11}, \beta_{12}, \beta_{21}) \in [0, 1]^3\}, \tag{10}$$

where setting $\beta = \Big[\beta_{11}, \beta_{12}, \beta_{21}\Big] \in \mathcal{P}_{ad}$ and we denote the solution obtained with parameter value β by $N(t) := N(t, \beta) = \Big(N_1(t, \beta), N_2(t, \beta)\Big)$. The existence and uniqueness of solution of Equations (8) are given directly by Theorem 2.1 using integration of the distribution functions f_i over the state u.

The model (8) is well-posed and the solution $N(t) = N(t;\beta)$ is well defined and is a $C^r(r \geq 1)$ function of β, it is also known as solution of the *direct problem* (**DP**).

Let us now define the observation operator:

$$F : \mathcal{P}_{ad} \to C^r([0,T],\mathbb{R}^2) \quad \beta \mapsto N(t,\beta). \tag{11}$$

The *inverse problem* that we deal with is the following:
IP: Given the measurements $m(t) = \{(m_1(t), m_2(t)), 0 \leq t \leq T\}$ of the densities $N(t)$; find the parameter β such that the observation (11) satisfies

$$F(\beta) = m(t) \quad i,e \quad N(t,\beta) = m(t). \tag{12}$$

Several questions arise on such inverse problems: does the available densities $F(\beta)$ can determine uniquely β (uniqueness or identifiability)? and if so, how does the parameter β depend of $F(\beta)$ (stability)? Is there a constructive algorithm for determining this parameter (identification)?

3.1. *Identifiability and stability.*

Identifiability is a essential property to show that the solution of the inverse problem **IP** is the solution of the optimization problem under consideration. This property consists to prove the injectivity of the operator F which means that two different parameters give two different observations. This allows to know if our inverse problem is well-posed in the following sense: if two different observations N^1 and N^2 associated with β^1 and β^2 coincide in $[0,T]$, then it is generated by the same parameter β ($\beta^1 = \beta^2$). The identifiability result is given by the following:

Proposition 3.1. *Let* $\beta^i = \left(\beta^i_{11}, \beta^i_{12}, \beta^i_{21}\right), i = 1,2$ *where* $\beta^i \in \mathcal{P}_{ad}$ *and* N^i *the solution of Equations (8) using* β^i*. Assume that* N^i_2 *is not constant in* $[0,T]$*. If the observation* $F(\beta^1) = F(\beta^2)$ *then* $\beta^1 = \beta^2$ *i.e.* $\beta^1_{11} = \beta^2_{11}, \quad \beta^1_{12} = \beta^2_{12}, \quad \beta^1_{21} = \beta^2_{21}$.

Proof. For $i = 1,2$, let $N^i = \left(N^i_1(t), N^i_2(t)\right)$ the solution of the following system:

$$\begin{cases} \dfrac{\partial N^i_1}{\partial t}(t) = N^i_1(t)\Big(C_1\beta^i_{11} - \beta^i_{12}N^i_2(t)\Big), \\ \dfrac{\partial N^i_2}{\partial t}(t) = \beta^i_{21}N^i_1(t)N^i_2(t), \end{cases} \tag{13}$$

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with $C_1 = n_1^E(0) \neq 0$. Assume that $F(\beta^1) = F(\beta^2)$, then $N_1^1 = N_1^2 = N_1$; $N_2^1 = N_2^2 = N_2$ are solutions of the following system:

$$\begin{cases} N_1(t)\Big(C_1\beta_{11}^1 - \beta_{12}^1 N_2(t)\Big) = N_1(t)\Big(C_1\beta_{11}^2 - \beta_{12}^2 N_2(t)\Big), \\ \\ \beta_{21}^1 N_1(t)N_2(t) = \beta_{21}^2 N_1(t)N_2(t). \end{cases} \tag{14}$$

As N_2 is not constant, then from (14), one has $\beta_{12}^1 - \beta_{12}^2 = 0$, and then $\beta_{11}^1 - \beta_{11}^2 = 0$ since $C_1 \neq 0$. This completes the proof. □

In order to study the continuous dependence of the parameters (β_{ij}) on the measurements (observations) $F(\beta)$, the stability of the inverse problem (**PI**) is introduced. It guarantees that a small error in the measurements causes a small error on the identified parameters. Stability is a crucial issue for numerical applications and it has been considered by many authors (see for examples [18,19]).

Let $\beta = (\beta_{11}, \beta_{12}, \beta_{21})$, $\gamma = (\gamma_{11}, \gamma_{12}, \gamma_{21})$ two elements of $\mathcal{P}_{ad}$ and h small enough such that $\beta^h := \beta + h\gamma \in \mathcal{P}_{ad}$. Let $N^h(t) = (N_1^h(t), N_2^h(t))$ solving the following problem:

$$\begin{cases} \dfrac{\partial N_1^h}{\partial t}(t) = N_1^h(t)\Big(C_1\beta_{11}^h - \beta_{12}^h N_2^h(t)\Big), \\ \\ \dfrac{\partial N_2^h}{\partial t}(t) = \beta_{21}^h N_1^h(t)N_2^h(t), \end{cases} \tag{15}$$

and

$$F(\beta^h) = N^h(t). \tag{16}$$

The following result can be obtained easily by using the definition (11) and Equations (15):

Proposition 3.2. *(Local Lipschitz stability) Let N and N^h solutions of Equations (8) and Equations (15). Assume that N_2 is not constant in $[0,T]$. If $\gamma \neq 0$, then one has:*

$$\lim_{h\to 0} \frac{\|F(\beta^h) - F(\beta)\|}{|h|} = \lim_{h\to 0} \frac{\|N^h(t) - N(t)\|}{|h|} \neq 0. \tag{17}$$

4. Optimization method (identification).

In this section, we transform our inverse problem to an optimization problem where the unknowns are parameters β. We fit our parameters to

empirical data $m(t)$ using a parameter identification methods based on optimization methods to find the best parameter values. We propose an algorithm based on the minimization of Least Squares cost function:

$$J_0(\beta) = \frac{1}{2}\|F(\beta) - m(t)\|^2_{L_2} = \frac{1}{2}\int_0^T (N(t) - m(t))^2 dt. \tag{18}$$

Consider now the following optimization problem:

$$Find \quad \beta \in \mathcal{P}_{ad} \quad such\ that \quad J_0(\beta) \leq J_0(\mu), \quad \forall \mu \in \mathcal{P}_{ad}. \tag{19}$$

Proposition 3.1 shows that the solution of the inverse problem (12) is the solution of the optimization problem (19), and one has:

Proposition 4.1. *Let $\beta \in \mathcal{P}_{ad}$ be the solution of the inverse problem (12), then it is the unique solution of minimization problem (19).*

Thanks to the above proposition, the inverse problem (12), is turned into the optimization problem (19). Furthermore, in order to use the gradient method, we compute the gradient of cost function J_0 using the adjoint technique as given by following proposition.

Proposition 4.2. *The gradient of the cost function J_0 is given by:*

$$\nabla J_0(\beta) = -\int_0^T \phi(t)^{\mathsf{T}} H_\beta(N(t), \beta) dt, \tag{20}$$

where ϕ is solution of the adjoint problem:

$$\begin{cases} \dfrac{\partial \phi}{\partial t}(t) = -H_N(N(t), \beta)^{\mathsf{T}} \phi(t) + N(t) - m(t), & t \in [0, T[\,, \\ \phi(T) = 0. \end{cases} \tag{21}$$

and, H_N (respectively H_β) is the derivative of H with respect to N (respectively the derivative of H with respect to β).

Proof. Let Introduce a Lagrange multiplier ϕ for the ODE constraint, and consider the following functional:

$$L(N(t), \beta) = \frac{1}{2}\int_0^T (N(t) - m(t))^2 dt + \int_0^T \phi(t)^{\mathsf{T}} \Big(\frac{\partial N}{\partial t} - H(N(t), \beta) \Big) dt. \tag{22}$$

For $N = F(\beta)$ solution of the initial value problem (8), the second term vanishes and we have $L(F(\beta), \beta) = J_0(\beta)$.

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Using integration by parts, then the variation δL due to variation δN, $\delta\beta$ yields

$$\begin{aligned}\delta L &= \int_0^T (N(t)-m(t))\delta N(t)dt + \phi(T)^{\mathsf{T}}\delta N(T) - \int_0^T \frac{\partial \phi}{\partial t}^{\mathsf{T}} \delta N(t)dt \\ &- \int_0^T \phi(t)^{\mathsf{T}}\Big(H_N(N,\beta)\delta N(t) + H_\beta(N,\beta)\delta\beta\Big)dt \\ &= \int_0^T \Big(N(t)-m(t)-\frac{\partial \phi}{\partial t}^{\mathsf{T}} - \phi(t)^{\mathsf{T}}H_N(N,\beta)\Big)\delta N(t)dt + \phi(T)^{\mathsf{T}}\delta N(T) \\ &- \int_0^T \phi(t)^{\mathsf{T}}H_\beta(N,\beta)\delta\beta dt.\end{aligned} \tag{23}$$

Now, let the Lagrange multiplier ϕ satisfy the so-called adjoint equation (21), then the variation δL does not depend on δN, i.e. $\delta L = L_\beta \delta\beta$, where

$$L_\beta = -\int_0^T \phi(t)^{\mathsf{T}}H_\beta(N(t),\beta)dt.$$

Additionally, we have $\delta L = \delta J_0$ (for $N = F(\beta)$) and $\delta J_0 = \nabla J_0 \delta\beta$ (by definition). Hence, we can directly read off the gradient $\nabla J_0 = L_\beta$ from (23). This complete the proof. □

4.1. *Optimization algorithm.*

An optimization algorithm based on the gradient of cost function can be presented as follows.

Algorithm 4.1 Gradient method

1: Choice of the initials parameters.
2: Calculate solution of the direct problem (8).
3: Calculate solution of the adjoint problem (21).
4: Calculate the gradient of cost function by formulate (20).
5: Update of the parameters by optimization gradient method.

This technique, based on the gradient method (see [20]), is used or numerical tests. In general, this inverse problem is difficult to solve. Indeed, the problem is ill-posed, which requires for example the use of regularization methods. Moreover, the use of traditional optimization methods brings us back to a local optimum and the quality of the result depends on the initial point. To overcome these difficulties, global optimization techniques are useful as we shall see in the next section.

5. The Kriging method and global optimization techniques.

5.1. *The Kriging method.*

The Kriging method is an exact interpolation method [21,22], developed by Matheron and Krige [23], based on the theory of regionalized variables. It is a stochastic interpolation, which has proved to be reliable when approximating deterministic behaviors [24]. Indeed, it attempts to obtain statistically the optimal prediction, namely to provide the best linear unbiased estimator. The basic premise of the Kriging interpolation method is that every unknown point can be estimated by the weighted sum of the known points. The method also provides a mechanism to estimate the interpolation error for any approximated point [25].

More precisely, given the previously computed values of the objective function $f(x_1), ..., f(x_n)$ at the data points $x_1, ..., x_n$. Estimating the value of variable x in a not sampled site by a linear combination of specific data

$$\tilde{f}(x) = \sum_{i=1}^{n} \lambda_i f(x_i),$$

where λ_i depend on the distance of the test point x from observed points. The Kriging technique is essentially a method of interpolation between known points that provides a mean prediction $\tilde{f}(x)$, as well as a measure of the variability of the prediction $s(x)$.

5.2. *Global optimization technique.*

This subsection is inspired by the work of Donald Jones et al. [26]. The idea is based on the optimization of the response surface constructed by a Kriging model. The simplest possible way would be to fit a surface to the response surface then to find the minimum of this surface. However, if we proceed that way, we can easily be lead to a local minimum, and we have no specific information on the uncertain areas of the approximated response surface. To overcome this issue, we must put some emphasis on sampling the surface where we are uncertain, this is inherently measured by the standard error of the predictor $s(x)$. To combine the search for local and global minimum and we take into account the uncertainties of the Kriging surfaces and use a criterion based of the balance between local and global search. This criterion is knows as *expected improvement*, introduced in 1978 in [27]. The expected improvement criterion is computed as follows. Let $f_{min} = min(f(x_1), ..., f(x_n))$ be the current best function value. The *improvement function* I at the point x is defined as follows:

$$I(x) = max\Big(f_{min} - F(x), 0\Big), \tag{24}$$

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where $F(x)$ is Normal $(\tilde{f}, s^2)$, i,e, F is a random variable with the mean and standard deviation given by the Kriging predictor $\tilde{f}$ and its standard error s.

The *expected improvement*, defined as the expectation of the improvement, is given by [26]:

$$E[I(x)] = \Big(f_{min} - \tilde{f}(x)\Big)\phi\Big(\frac{f_{min} - \tilde{f}(x)}{s(x)}\Big) + s(x)\Phi\Big(\frac{f_{min} - \tilde{f}(x)}{s(x)}\Big), \tag{25}$$

where ϕ is the standard normal cumulative density function, and Φ is the standard normal probability density function.

This technique of global optimization consist of finding a good balance between minimum search and global exploration. Minimum search will result in a good approximation of the global minimum if the region of the global minimum is correctly represented by the response surface, and if this surface does not introduce minima lower than the global minimum. In order to guarantee a trustworthy representation, a more or less uniform coverage of the whole domain of interest should be generated.

5.3. *Algorithm.*

The point where the value of the expected improvement is maximum gives the best point to evaluate the objective function. The expected improvement is constructed to search for both local and global minima [26]. The surrogate model is then updated to include the newest sampled point, and the operation is repeated until the sampling point does not change and the global minimum of the objective function has been found. An overview of the algorithm is given as follows:

Algorithm 5.1 Global optimization method

1: Choose a number of initial evaluation points.
2: The objective function f is evaluated for all new members of the set.
3: A Kriging surrogate model is fitted to the values of the objective function.
4: Maximization of the expected improvement objective function $E[I]$.
5: The result of the maximization (the next input point most likely to improve the objective function) is added to the set.
6: The process repeats from step 2 until a predetermined number of iterations is reached or

$$\frac{MaxE[I(x)]}{f_{min}} < \varepsilon.$$

6. Numerical experiments and results.

6.1. *Synthetic numerical results.*

In order to validate and to explain the global optimization method, we first made a test with a simple synthetic example. We consider the true function:

$$f(x) = x.sin(x) + x.cos(2x). \tag{26}$$

Our main goal is to find the global optimum of the true function (26) (the solid blue line in Figure 1). We consider that we have only few points generated by this true function (the red star in Figure 1), and we create an approximated response surface using the Kriging method (the black dotted line in Figure 1). It is associated with the standard error MSE (shown as the green line in the right of Figure 1).

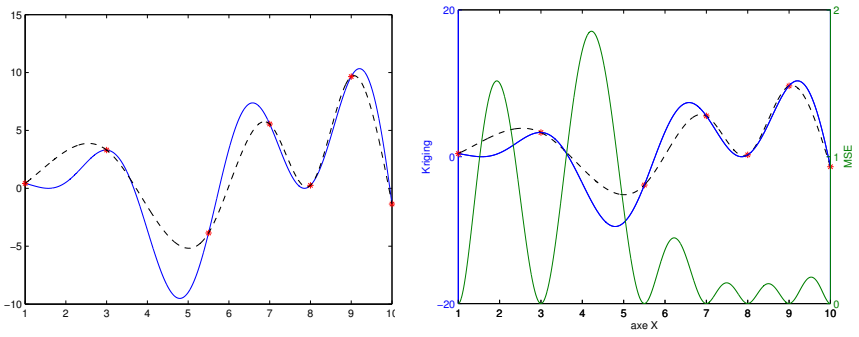

Figure 1. The true function (blue solid line), the set points used for the Kriging interpolation (red star), the surface Kriging (black dashed line) and the estimator error MSE(green solid line).

Now, we apply the global optimization algorithm described above to the problem constructed by the set of real points $\Big(f(x_1), ..., f(x_7)\Big)$(the red star in Figure 1) and the surface $\tilde{f}(x)$ obtained by Kriging (the back dotted line in Figure 1). In Figure 2, we present the Expected Improvement criterion $E[I(x)]$ (the green solid line in the left of Figure 2) and, where it reaches its maximum value, we added another point in the set (now we have 8 real points). The $f(x)$ coordinate of this point is evaluated using the true function (26) (the black triangle in the right of Figure 2).

This process was repeated until the sampling point does not change and the global minimum of the objective function has been found. The global optimization method has run using an initial sampling of 7 points to build the surrogate (the dashed line in Figure 2).

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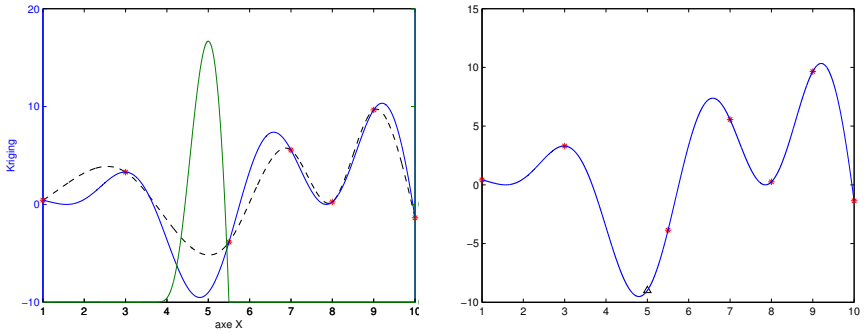

Figure 2. The true function (blue solid line), the set of points used for the Kriging interpolation (red star), the Kriging surface (black dashed line), the Expected Improvement criterion (green sold line) and the right, the true function with the add point (the triangle).

A further 5 function evaluations (the triangle in the left of Figure 3) were required to find the global minimum.

Now, we apply the global optimization method with an initial sampling of 2 points and the method is able to find reasonable solution in 13 function evaluations (see the right of Figure 3).

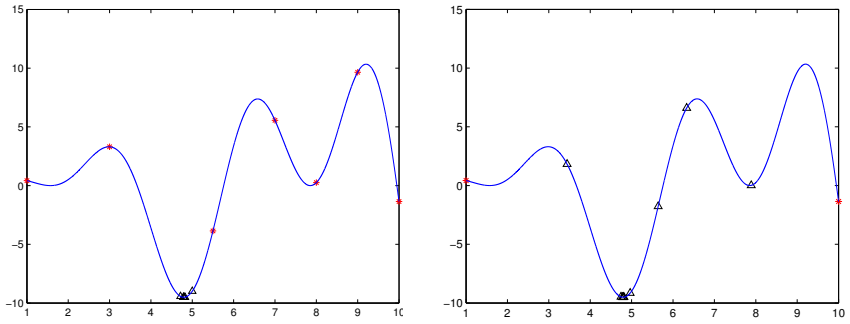

Figure 3. In the left, the convergence method with 7 points as initial set and the right, the convergence with 2 points as initial set.

6.2. *Applications of inverse problem in immune competition cells.*

Let us now consider the inverse problem in immune competition cells which consists in determining the parameters of model (8) from measurements of densities of cells population. For this, we applied the global optimization algorithm using the Least Square cost function (18) from simulated data.

First, we present the numerical solution of the direct problem (8) $\Big(N_1(t_i), N_2(t_i)\Big), i = 1, ..., n$ for different parameters values of $\beta_{11}, \beta_{12}, \beta_{21}$ (see Figure 4). The latter is solved numerically with ODE systems methods. The numerical solution is performed using the function ode45 from MATLAB, which is based on an explicit Runge-Kutta formula, and the Dormand-Prince pair.

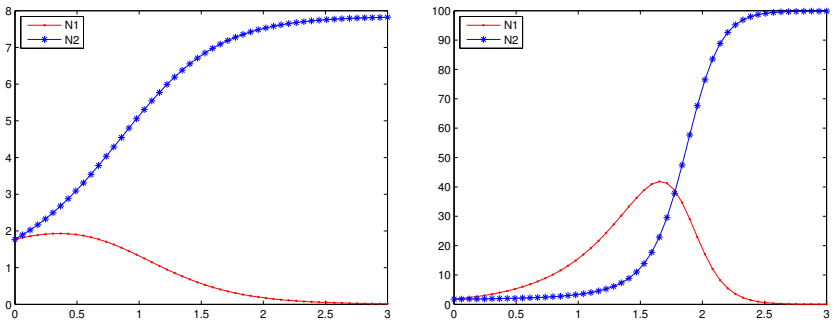

Figure 4. Evolution in time of tumor and active immune cells for the direct problem (8) with $\beta_{11} = 0.5, \beta_{12} = 0.5$ and $\beta_{21} = 0.6$ in the left and with $\beta_{11} = 0.9, \beta_{12} = 0.1$ and $\beta_{21} = 0.1$ in the right.

To identify the parameters (β_{11}, β_{12}, β_{21}), we generate simulated test data using the solution of direct problem and we apply the global optimization algorithm 5.1. For the tests with noisy data, we perturbed the numerical solutions, by a Gaussian noise with fixed amplitude.

6.2.1. *Two parameters:* $\beta_{11} = 0$, $\beta_{12} = 0.5$, $\beta_{21} = 0.6$.

In this section, we consider the case of two dimensions ($\beta_{11} = 0$), i.e. identify the two parameters β_{12} and β_{21}. We generate simulated test measurements m from the following parameters $\beta_{12} = 0.5$, $\beta_{21} = 0.6$.

In Figure 5, we present the convergence of global optimization where the initial evaluation points is 4 corners points (red star in Figure 5) and the new evaluation points (the triangle in Figure 5). The algorithm converges to $\beta_{12} = 0.4981$ and $\beta_{21} = 0.6050$ after 72 evaluations of cost functions.

In order to study the convergence of method, we present in Figure 6, the minimum f_{min} of the objective function (18), and the Maximum of the Expected Improvement $E(I)$ (25) in function of the number of iteration.

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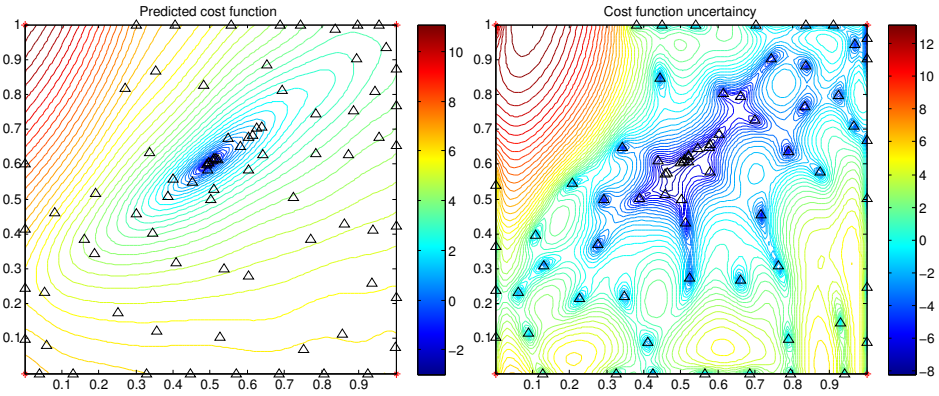

Figure 5. In the left, the evaluation of the objective function at the evaluation points, in the right, the estimator error MSE.

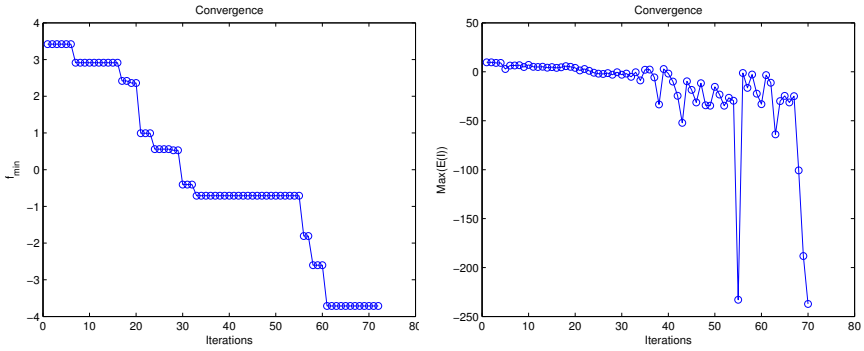

Figure 6. In the left, the convergence of cost function (18) in function the number of iterations, in the right, the maximum of expected improvement E(I).

6.2.2. *Three parameters:* $\beta_{11} = 0.5$, $\beta_{12} = 0.5$, $\beta_{21} = 0.6$.

In this section, we are interested to identify the three parameters β_{11}, β_{12} and β_{21}. We generate simulated test measurements m from the following parameters $\beta_{11} = 0.5$, $\beta_{12} = 0.5$ and $\beta_{21} = 0.6$.

In Figure 7, we present the convergence of global optimization where the initial evaluation points is the corners of admissible domain (red star in Figure 7) and the new evaluation points (the triangle in Figure 7). The algorithm converges to $\beta_{11} = 0.5080$ $\beta_{21} = 0.5012$ and $\beta_{21} = 0.6001$.

6.2.3. *Identification results.*

In the Table 1, we present the identification results by using the algorithm described in the paragraph 5.3 for different parameters. The first column in the Table 1, contains the exact parameters $(\beta_{11}, \beta_{12}, \beta_{21})$ from

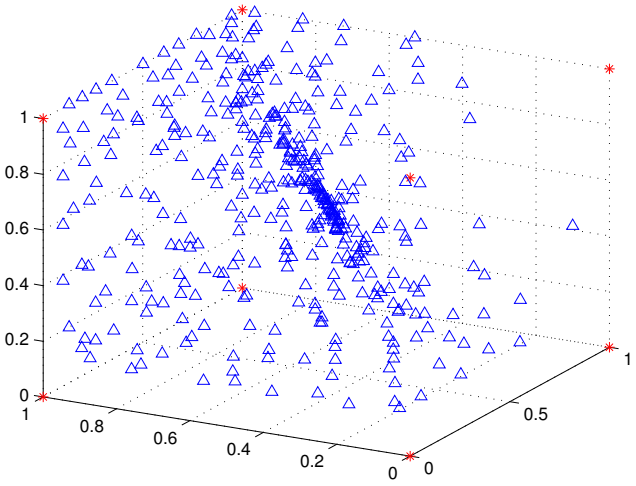

Figure 7. The convergence with the initial evaluation points is the corners of admissible domain.

which we have formed measurements m, while the second column is reserved for identified parameters by global optimization algorithm. Numerical tests have been done using the Gaussian noise fixed at 1%.

Table 1. Identification results of different parameters.

Exact parameters			Identified parameters		
0.5	0.5	0.6	0.5080	0.5012	0.6001
0.7	0.5	0.8	0.6979	0.4974	0.8028
0.8	0.5	0.6	0.8043	0.5005	0.5997
0.4	0.6	0.8	0.4096	0.6042	0.7998

7. Conclusion.

In this work, the problem of identifying parameters of an integro-differential system modeling the immune competition was studied. The Least Square cost function is used to estimate the parameters of the presented model. The optimization algorithm used is based on the global optimization and Kriging method. This technique provides a solution that does not depend on the initial points. This enhanced capability is mostly due to the fact that it is able to find the next best place to sample for a global minimum of the objective function. The algorithm is tested with synthetic and simulated data.

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