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Estimating Uncertain Parameters of a Two Compartment Model of Cancer via Homotopy Optimization Method

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Abstract

One of the restrictions for uncertain biological systems is that there are uncertain parameters which are not measurable with non-invasive instrument. A problem of interest is that proposing a method which estimates this parameter from measurable outputs of system. By declining homotopy parameter the initial problem which has the form of a high gain observer gradually transforms to a parameter estimation problem. With the gradual transform to the main problem provide the ability of finding the global value of uncertain parameter. This approach is applied for the model of cancer to illustrate the effectiveness of the homotopy method to achieve the best estimate for uncertain parameters by finding the minimum of a proposed optimization problem.

Keywords: Homotopy optimization method, Cancer system, Parameter estimation, Global minimization

1. Introduction

Cancer is one of the main causes of morbidity and mortality in the world. It refers to a set of disease where normal cells of the body lose their mechanisms which are responsible for controlling their growth and motility. Cancer cells typically proliferate in an exponential fashion, the size of the cancerous mass

is measured experimentally as a volume, though this mass is often referred to in terms of the number of cells 10^9 [1]. The growth of cancerous tumor is a complicated process involving multiple biological interactions. Also, the response of tumors to active treatments such as chemotherapy and radiotherapy is complex, but important to understand. A tumor's response to treatment depends on many factors, including the severity of the disease, the application of the treatment, and the strength of patient's own immune response.

The main factors considered in chemotherapy include the general status of the patient, the stage of the diseases, scheduling of the therapy and interaction of the drugs. The actions of the chemotherapy treatment agents are based upon an understanding of the cell cycling mechanisms. The cell cycle is a chain of phases that both normal and cancer cells undergo from their birth to death. The cycle comprises of five stages as show in Figure 1. A brief description of different stages of cell cycle is given below [1, 2]:

G_1: Post mitotic gap, the cell prepares for DNA synthesis.
S : DNA synthesis takes place in preparation for cell division (many anticancer drugs act by interfering with DNA at this stage, causing cell death).
G_2: Pre-mitotic gap, specialized proteins and RNA are synthesized in preparation for cell division.
M : Mitotic phase, cell division takes place to produce two identical daughter cells.
G_0: Resting phase, cell is quiescent, viable but unable to divide.

Mathematical modeling of this process is viewed as a potentially powerful tool in the development of improved treatment regimens. The mathematical modeling of tumor growth and treatment has been approached by a number of researchers using a variety of models over the past decades [3]. Biological systems are inherently stochastic due to unavoidable unpredictability (randomness). In such cases, a precise estimation of system properties is not possible, and the uncertainty can be characterized through ensemble averages. Mathematical models are necessarily simplified representations of the phenomena being studied and a key aspect of the modeling process is the judicious choice of model assumptions.

Parameter estimation is a key issue in the construction of a biological model. Within these models, there are a group of unknown parameters, which determine the system's characteristics. In most cases it is very difficult or even impossible to measure the parameters experimentally. However, we usually have the chance to measure some of the variables involved in the model, such as the concentrations of reaction components. This work focuses on two compartment model of cancer chemotherapy treatment presented by [4]. All constants in two compartment model are known, but some of parameters might vary in every patient. Using dynamic patient's data, it is possible to extract the values of these parameters using parameter estimation.

As it is mentioned in the previous paragraph, the problem of parameter identification can be posed as an optimization problem [5], where the arguments of the global minimum of the objective function are the identified parameters. The optimization problems are usually solved using deterministic methods, which require the solution of differential equations at each optimization step. The solution of these ODEs can be obtained using initial-value methods [6]. When deterministic approaches like the steepest descent, Gauss–Newton [7], and Levenberg–Marquardt algorithms are used in the optimization procedure, it is not uncommon to converge to a local minimum rather than the global minimum [8]. Stochastic methods, such as simulated annealing [9] can be used to find global minima, but these methods typically require a large number of iterations to converge and, thus, are timeconsuming, especially for parameter identification problems where the equations of motion are integrated at every optimization step [6].

Homotopy optimization method (HOM) is an effective algorithm for finding global minimum of optimization problems. Homotopy, as a fundamental part of topology, has a relevant place in constructing algorithms for solving systems of algebraic equations, which is referred to as the homotopy method. This method has become much more efficient and powerful since the probabilityone homotopies were proposed by Chow et al. [10], and hence was widely applied and improved to solve many problems such as nonlinear systems [11], and nonlinear constrained optimizations [12], etc. Homotopy is a powerful technique that is used in several areas of mathematics, including optimization [13] and nonlinear root finding [10]. It is also successfully applied to ARMAX models [14] for the identification of linear parameters. More details of its development and application in computational science can be found in [15].

In homotopy method, the objective function to be minimized is modified by adding another function whose optimum is known, herein referred to as the known function, and a homotopy parameter is used to transform the modified function into the original objective function. A series of optimizations is performed while slowly varying the homotopy parameter until the modified function is transformed into the original objective function [16]. A new generalized homotopy algorithm for the solving multi objective optimization problems with equality constraints have also been studied and reported upon [13], The mentioned paper gives a necessary and sufficient condition for the set of Pareto candidates to form a (k-1) dimensional differentiable manifold, provides the numerical details of the proposed algorithm, and applies the method to two multi objective sample problems.

The application of homotopy to the general parameter identification in biomedical model has not been studied in the literature yet. In this work, we present a methodology to apply homotopy to the problem of parameter identification for a two compartment model of cancer chemotherapy treatment. Also, the application of the homotopy optimization method on cancer mathematical models are shown and its uncertain parameters to be estimated.

The paper is structured as follows: In the next section, we state the mathematical model of the cancer. Next, homotopy optimization method (HOM) is presented as a parameter estimation method. The main idea of this paper and the simulation results which show the efficiency of presented algorithm in parameter estimation has been proposed section follows, ending with a set of conclusions.

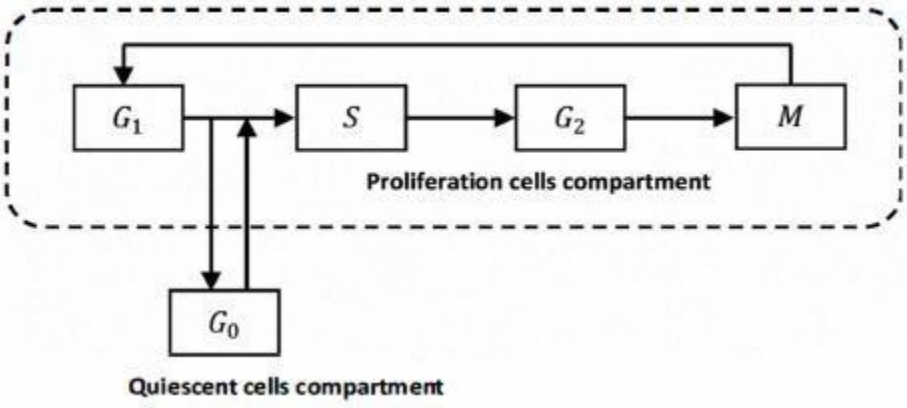

Fig. 1. Schematic diagram of the different phases of cell cycle

2. Mathematical Model

The mathematical models of tumor responses for chemotherapy are widely used to predict the tumor responses and to design the drug dosages. The models are generally developed based on a set

of differential equations. The purpose of using mathematical models of cancer chemotherapy is to predict and control the course of the disease when a treatment is used. A linear model presented in [17] describes the administration of anticancer drug for cell cycling specific chemotherapy. Figure 3 shows a two-compartment model where is P (Proliferating) present the combination of the first four stages of the cell cycle as mentioned earlier (G1, S, G2 and M) and Q (Quiescent cells) indicates stage Go. The parameters "*m*" and "*b*" express the immigrants between the proliferating cells and quiescent cells respectively. Here "*a*" indicates to the growth rate of cycling cells and "*n*" is the natural decay of the cycling cells. Based on clinical evidences [18], the population of proliferation and quiescent cells at the tumor site are assumed to be 1012 and 109 at the time of diagnoses. For two compartment model, it is generally assumed that 80% of the cell population is quiescent whereas the remaining while the remaining 20% are active proliferating cells [18]. A number of differential equations used to build a two compartment model of cancer chemotherapy treatment are explained briefly. The first equation, predicts the rate of change of proliferation cells population at the tumor site during the treatment, is as follows [4]:

$$\frac{dP}{dt} = (a - m - n)P(t) + bQ(t) - g(t)P(t) \quad (1)$$

Where P and Q represent population of proliferating and quiescent cells. Here parameters a, m, band n indicate the rate of growth of proliferation cells, immigrant from cycling to quiescent cells, immigrant from quiescent cells to cycling cells and natural death of cycling cells respectively. Parameter get) indicates the effects of drug on tumor cell which is the rate of cell killing per unit drug. Equation (2) describes the rate of change of cell population in the quiescent compartment of the tumor site during the period of treatment and equation (3) indicates the effect of chemotherapy:

$$\frac{dQ}{dt} = mP(t) + bQ(t) \quad (2)$$

The anticancer drugs affect tumor cells and normal cells as well. To reduce the toxic side effects of the chemotherapy treatment, the population of normal cell should be maintained as high as possible during the treatment. A logistic equation is used to describe the effect of chemotherapy drug on normal cells, as expressed by equation (3) below:

$$\frac{dY}{dt} = \delta Y(t)\left(1 - \frac{Y(t)}{K}\right) - g(t)Y(t) \quad (3)$$
$$g(t) = k_1 D(t)$$

Here Y (t) indicates the normal cells population whereas 0 and K present the growth rate of the normal cells and the carrying capacity of normal cells respectively. Equation (4) shows the rate of change of drug concentration at the tumor site during the treatment cycle.

$$\frac{dD}{dt} = -\gamma D(t) \quad (4)$$

γ is drug decay which is related to the metabolism of drug inside patient's body. Equation (5) shows the relationship between level of toxicity and drug concentration at the tumor site during the treatment period.

$$\frac{dT}{dt} = D(t) - \eta T(t) \tag{5}$$

The nominal values of parameters are determined by [4]:

a=0.5, m=0.218 (day^{-1}), n=0.477(day^{-1}), b=0.05(day^{-1}),
K=2*10^{12}, $\eta = 0.3$, $\gamma = 0.4$, $k_1 = 0.0084$

3. Estimation Uncertain Parameter Using Homotopy Optimization Method

3.1 Representing the Parameter Estimation in the form of an Optimization Problem

The nonlinear equations of the physical system for which the parameters must be identified are assumed to be of the following form:

$$\begin{aligned} \dot{x}_1 &= x_2 \\ \dot{x}_2 &= x_3 \\ &\vdots \\ \dot{x}_n &= f(x_1, \dots, x_n, p, t) \end{aligned} \tag{6}$$

For above system $\boldsymbol{X}(t) = [x_1(t), x_2(t), \dots, x_n(t)]^{\mathrm{T}}$ is the independent coordinates and $\boldsymbol{p}$ is a vector of parameters to be identified. The system is assumed to be nonlinear which is appears in f.

Experimental data $\boldsymbol{X}_e(t) = [x_{1e}(t), x_{2e}(t), \dots, x_{ne}(t)]^T$ of all the displacements is assumed to be available over time T. Note that it is possible to identify the system parameters with only a few components of $\boldsymbol{X}_e(t)$ since, in coupled systems, each component of $\boldsymbol{X}_e(t)$ contains information from all the parameters due to the coupling between the system equations. The aim is to estimate the parameters in the mathematical model such that the solution of the differential equations (6) closely matches the experimental data. To identify the parameters, the integral of the squared difference between the experimental and simulated states which is an error indicator should be minimized:

$$\min_p E(\boldsymbol{p}) = \frac{1}{2}\sum_{i=1}^{n}\left\{\int_0^T \left(x_{ie}(t) - x_i(t,p)\right)^2 dt\right\} \tag{7}$$

Note that a discrete summation can be used in place of the integral in this equation. Given the initial estimates of the parameters, we can use Gauss-Newton [7] which is a fast gradient base optimization method to minimized (7). Using Gauss-Newton algorithm, parameter p is updated according to (8):

$$p^{r+1} = p^r + d^r \tag{8}$$

Where $\boldsymbol{d}^r$ is the search direction, which can be obtained from the following relation [16]:

$$H(p^r)d^r = -G^T(p^r) \tag{9}$$

In (10), $\boldsymbol{G}$ and $\boldsymbol{H}$ are the gradient and the approximate Hessian of the objective function, which can be calculated through (10) and (11) by neglecting the higher order terms:

$$G(p) = \frac{\partial V}{\partial p} = -\sum_{i=1}^{n}\left\{\int_0^T \left(x_{ie}(t) - x_i(t,p)\right)\frac{\partial xi}{\partial \boldsymbol{p}}\,dt\right\} \tag{10}$$

$$H(p) = \frac{\partial^2 V}{\partial p^2} \approx \sum_{i=1}^{n}\left\{\int_0^T \frac{\partial xi}{\partial \boldsymbol{p}}^T \frac{\partial xi}{\partial \boldsymbol{p}}\,dt\right\} \tag{11}$$

The sensitivity data $\frac{\partial xi}{\partial \boldsymbol{p}} = [\frac{\partial xi}{\partial p_1}, \frac{\partial xi}{\partial p_2}, \ldots, \frac{\partial xi}{\partial p_m}]$ can be obtained by solving the sensitivity differential equations, which can be derived by directly differentiating (6), with respect to the individual parameters:

$$\frac{\partial \dot{x}_1}{\partial p_j} = \frac{\partial x_2}{\partial p_j}$$
$$\frac{\partial \dot{x}_2}{\partial p_j} = \frac{\partial x_3}{\partial p_j}$$
$$\vdots$$
$$\frac{\partial \dot{x}_2}{\partial p_j} = \frac{\partial f(x_1, x_2, \ldots, x_n, p, t)}{\partial p_j} + \frac{\partial f(x_1, x_2 \ldots, x_n, p, t)}{\partial x_1}\frac{\partial x_1}{\partial p_j} + \frac{\partial f(x_1, x_2, \ldots, x_n, p, t)}{\partial x_2}\frac{\partial x_1}{\partial p_j} + \cdots + \frac{\partial f(x_1, x_2, \ldots, x_n, p, t)}{\partial x_n}\frac{\partial x_1}{\partial p_j} \quad (12)$$

We will briefly explain how homotopy is applied to a simple algebraic minimization problem. Let $F(\boldsymbol{p})$ be the objective function. We are interested in finding parameters $\boldsymbol{p}^*$ at which *F* has a global Minimum.

3.2 Parameter Estimation Using HOM

We now discuss how the homotopy method can be applied to the problem of parameter identification. To modify the objective function, the experimental data is coupled to the mathematical model as follows:

$$\dot{x}_1 = x_2 + \lambda K_1(x_{1e} - x_1)$$
$$\dot{x}_2 = x_3 + \lambda K_2(x_{2e} - x_2)$$
.
.
$$\dot{x}_n = x_n + \lambda K_n(x_{ne} - x_n) \quad (13)$$

Initially, when $\lambda = 1$, the coupling term acts as a high-gain observer [19], and if sufficiently high values of *Ki* are used, the experimental data and simulated response will synchronize. Note that λ is introduced to the traditional definition of a high-gain observer so as to construct the homotopy transformation. Also note that the sensitivity equations (12) must be modified to account for the added coupling term. For very large Ki, the cost function becomes a flat surface with a very small magnitude, and the experimental data x_{1e} and simulated response $\boldsymbol{x}1$ will reach together in the last step. We decrease λ by a small amount $\delta\lambda$ and minimize the objective function (7), treating (13) as the mathematical model. We then decrease λ further to $\lambda - \delta\lambda$; since the parameter guesses have been refined. At each stage in this process, we use the converged result from the previous stage as the initial guess for $\boldsymbol{p}$. This process is repeated until λ = 0 and (13) has transformed into (6). In summary, the homotopy optimization approach follows the path of minimal error as the observer gain is decreased. We ensure that the error is close to zero in the last stage, with the hope that the refined parameter guesses at the final stage are sufficiently close to the global optimum of the original problem. The process of applying the homotopy method to the problem of parameter identification is summarized in Algorithm 1.

4. Simulation & Discussion

In this paper, HOM is applied to estimate uncertain parameters of a cancer model which is defined in section two. The state space model of such system is:

$$\dot{x}_1 = -0.195x_1 + 0.05x_2 - 0.0084x_2x_3$$
$$\dot{x}_2 = 0.218x_1 + 0.05x_2$$
$$\dot{x}_3 = -0.4x_3$$
$$\dot{x}_4 = x_3 - 0.3x_4$$
$$\dot{x}_5 = P\left(x_5 - \left(\frac{x_5^2}{2*10^{12}}\right)\right) - 0.0084x_3x_5 \quad (14)$$

Where P is an uncertain parameter. We consider an experimental model with nominal value of P=0.8. Using the state of experimental model (x_{ie}) we construct the cost function as follows:

$$E(\boldsymbol{p}) = \frac{1}{2}\sum_{i=1}^{3}\left\{\int_0^T \left(x_{ie}(t) - x_i(t,p)\right)^2 dt\right\} \quad (15)$$

To estimate the uncertain parameter we use the proposed algorithm 1 for system below:

$$\dot{x}_1 = -0.195x_1 + 0.05x_2 - 0.0084x_2x_3 + \lambda K_1(x_{1e} - x_1)$$
$$\dot{x}_2 = 0.218x_1 + 0.05x_2 + \lambda K_2(x_{2e} - x_2)$$
$$\dot{x}_3 = -0.4x_3 + \lambda K_3(x_{3e} - x_3)$$
$$\dot{x}_3 = x_3 - 0.3x_4 + \lambda K_4(x_{4e} - x_4)$$
$$\dot{x}_3 = P\left(x_5 - \left(\frac{x_5^2}{2*10^{12}}\right)\right) - 0.0084x_3x_5 + \lambda K_5(x_{5e} - x_5) \quad (16)$$

The simulation results of optimization algorithm for different values of initial point of P are illustrated in figure 2. For $\lambda = 1$ the described system (16) has the structure of a high gain observer. In this observer we consider large values of K gain which forced the system states to track their related experimental data. This leads to dramatic decline of $E(p)$ as it is shown in figure 2. By decreasing the λ value, the structure of (16) transforms to a parameter dependent equation. Considering the E(p) value for small values of λ shows that the presented algorithm efficiently estimation the uncertain parameter P=0.8, and the accuracy of parameter estimation is not depends on the initial guess of P. The process of estimated P convergence to its nominal value by decreasing λ and with different initial values of the uncertain parameter is defined in table 1. To indicate the efficiency of algorithm 1, we employ the algorithm for three different initial guess ($p = 10,20,30$). For each fixed value of λ, we consider $m = 3$. According to table 1, estimated p, with each initial value, converges to its actual value as λ converges to zero in 5 iteration and the error ($E(p)$) reach to the zero in 7 iteration.

Considering this example shows that HOM algorithm is an effective method for estimating uncertain parameters of biological model. Independence on initial value of P is one of the main advantages of this method.

Algorithm 1 Parameter Identification Using Homotopy

Input: Experimental data ($\boldsymbol{x}_{1e}$),
Output: Identified parameters ($\boldsymbol{p}$)
Initialize
while $\lambda \geq 0$ **do**
for *i=1: m*

Solve ODEs for $\boldsymbol{x}1$ and $\partial \boldsymbol{x}1\ \partial pj\ \forall j$ Minimize $V(\boldsymbol{p}) = \frac{1}{2}\sum_{i=1}^{n}\left\{\int_0^T (y_{ie}(t) - y_i(t,p))^2 dt\right\}$
Solve $\boldsymbol{H}(\boldsymbol{p})\ \boldsymbol{d} = -\boldsymbol{G}T(\boldsymbol{p})$ for $\boldsymbol{d}$
$\boldsymbol{p} = \boldsymbol{p} + \boldsymbol{d}$
end for
$\lambda = \lambda - \delta\lambda$
end while
return ***p***

5. Conclusions

In this work, we have presented a new methodology for applying the homotopy optimization method to the parameter estimation. As it was seen in pervious sections, this method could find the global optimization of the uncertain parameter and this estimation is equal to the nominal value of the parameter. The proposed homotopy method can successfully find global minima given a wide domain of initial parameter guesses. The efficient of the proposed method for parameter estimation has been demonstrated by applying to cancer model. The authors are currently investigating the use of HOM to apply to other biological systems and set the controller up to these systems and identification parameters with controller as next works.

Table. 1. Convergence to the nominal value with the difference initial value of the parameter P and decrease the error.

Number of Iteration	**Test 1**		**Test 2**		**Test 3**	
	P	E(p)	P	E(p)	P	E(p)
Iter. 1.	30	3.6669e+016	20	8.7379e+013	10	5.4090e+12
Iter. 2.	0.0147	1.7990e+010	0.2878	7.7915e+009	0.5546	1.8195e+09
Iter. 3.	0.8209	1.3490e+007	0.8137	5.7366e+006	0.8065	1.3157e+006
Iter. 4.	0.7994	1.1826e+004	0.7996	5.0316e+003	0.7998	1.1546e+003
Iter. 5.	0.8000	10.3830	0.8000	4.4174	0.8000	1.0136
Iter. 6.	0.8000	0.0091	0.8000	0.0039	0.8000	8.8987e-004
Iter. 7.	0.8000	1.0128e-005	0.8000	4.3090e-006	0.8000	9.8874e-007

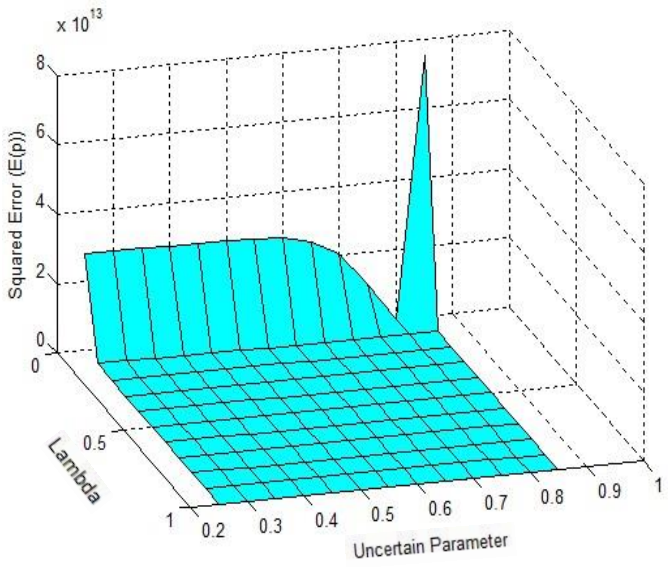

Fig. 2. Simulation results of optimization algorithm for different values of initial point of P and λ

References

[1] R. Martin, and K. Teo, Optimal control of drug administration in chemotherapy tumour Growth. l ed. 1994: World Scientific. 95- Ill.

[2] P. Dua, V.Dua and N. Pistikopoulos, Optimal delivery of chemotherapeutic agents in cancer. Computer and Chemical Engineering, 200S. 32 : p. 99-107.

[3] L.G. de Pillis and A. Radunskaya. A mathematical model of immune response to tumor invasion. Computational Fluid and Solid Mechanics, 2:1661{1668, 2003.

[4] S. Algoul, M. SAlam, M. A. Hossain, "Feedback control of chemotherapy drug scheduling for phase specific cancer treatment", IEEE Fifth International Conference on Bio-Inspired Computing: Theories and Applications (BIC-TA), 1443 – 1450, 2010

[5] L. Ljung, T. Söderström, *"Theory and Practice of Recursive Identification".* MIT Press, Cambridge, 1983.

[6] T.J. Gordon, R. Hopkins, *"Parametric identification of multibody models for crash victim simulation"* Multibody Syst. Dyn. 1, 85–112, 1997.

[7] S.S. Rao, "*Optimization: Theory and Applications".* Wiley, New York, 1983.

[8] P. Eberhard, W. Schiehlen, D. Bestle, *"Some advantages of stochastic methods in multicriteria optimization of multibody systems".* Arch. Appl. Mech. 69, 543–554, 1999.

[9] H.E. Romeijn, R.L Smith, *"Simulated annealing for constrained global optimization",* J. Glob. Optim. 5, 101–126 , 1994.

[10] S.N. Chow, J. Mallet-Paret, J.A. Yorke, *"Finding zeroes of maps: homotopy methods that are constructive with probability one"* , Math. Comput. 32 887–899, 1978.

[11] L.T. Watson, *"Globally convergent homotopy algorithms for nonlinear systems of equations"*, Nonlinear Dyn. 1, 143–191, 1990.

[12] L.T. Watson, *"Theory of globally convergent probability-one homotopies for nonlinear programming"* , SIAM J. Optim. 11 (3) 180–761, 2000.

[13] C. Hillermeier, *"Generalized homotopy approach to multiobjective optimization"*, Optim. Theory Appl. 110, 557–583, 2001.

[14] J. Hu, K. Hirasawa, *"A homotopy approach to identification of ARMAX systems"*, Trans. Inst. Electr. Eng. Jpn. 119, 206–211, 1999.

[15] L.T. Watson, "*Probability-one homotopies in computational science"*, Comput. Appl. Math. 140, 785–807, 2002.

[16] D.M. Dunlavy, D.P. O'Leary, *"Homotopy optimization methods for global optimization"* . Sandia National Laboratories Report SAND2005-7495, 2005.

[17] J. Panetta and Adam, A Mathematical Model of Cycle-Specific Chemotherapy. Math. Comput Modelling, 1995.22 (2): p. 67-S2

[18] P. Dua, V.Dua and N. Pistikopoulos, Optimal delivery of chemotherapeutic agents in cancer. Computer and Chemical Engineering, 200S. 32 : p. 99-107.

[19] A. Chatterjee, J.P Cusumano, *"Asymptotic parameter estimation via implicit averaging on a nonlinear extended system".* J. Dyn. Syst. Meas. Control 125, 11–18, 2003.