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Analogies between  
Astrodynamics and  
Cancer Immunotherapy

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*'We choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard, because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one which we intend to win, and the others, too...Many years ago the great British explorer George Mallory, who was to die on Mount Everest, was asked why did he want to climb it. He said, Because it is there. Well, space is there, and we are going to climb it, and the moon and the planets are there, and new hopes for knowledge and peace are there. And, therefore, as we set sail we ask God's blessing on the most hazardous and dangerous and greatest adventure on which man has ever embarked.'*

J.F.Kennedy, May 25, 1961



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# Chapter 1

## Introduction

The term *model* is used in several senses indicating an essential scheme of physical phenomena. It can be seen as tool to simulate these phenomena [51].

In space applications, but also in many other technological fields, there is a huge use of models. This aspect is related to the impossibility to work on prototypes or from an economic point of view their development is always less expensive [51]. These simulation models can be used to design the control strategy and also to simulate it before the implementation on the real system. Regarding the relationship between a model and theory, it can be observed that often models are considered the first stage of an investigation in order to have depth knowledge of a wide range of phenomena and mechanisms before the experimental step. The formulation of a mathematical model follows an interpretation of the real phenomena. The model is a translation of these aspects into mathematical and physical variables. This work focus its attention on the mathematical modeling and optimal control of tumor growth, its interaction with the immune system and the therapeutic treatment. This simulations can be viewed as potentially powerful tools in the development of a therapy [36].

### 1.1 Cancer Immunotherapy

Cancer is one of the five leading causes of death in all age groups among both males and females. Cancer is the leading cause of death among women aged 40 to 79 years and among men aged 60 to 79 years. Cancer is the leading cause of death among men and women under age 85 years<sup>1</sup>.

Patients with metastatic melanoma or renal cancer cell have a life expectancy of less than five years in 95% of the cases [42]. No effective chemotherapies are available for regression of the tumor as for prolonging survival.

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<sup>1</sup>Source: US Mortality Data, 2005, National Center for Health Statistics, Centers for Disease Control and Prevention, 2008.

Tumors despite the general mechanism of origin is unique, they may experience a very wide range of changes and symptoms. In all, however, there is a continuous increase in the number of cancer cells, due to the increased rate of cell division. In this way a greater number of tumor cells multiply and fewer of them die, while those who survive are increasing. Usually the growth of a tumor follows a geometric law: it is very slow at first, but accelerates with increasing mass of the tumor. The critical size of a tumor is about 1 cubic centimeter: the tumor reached such a dimension starts to grow very quickly and lead to the early symptoms, and becomes detectable by medical examinations and analyses [36, 38, 42].

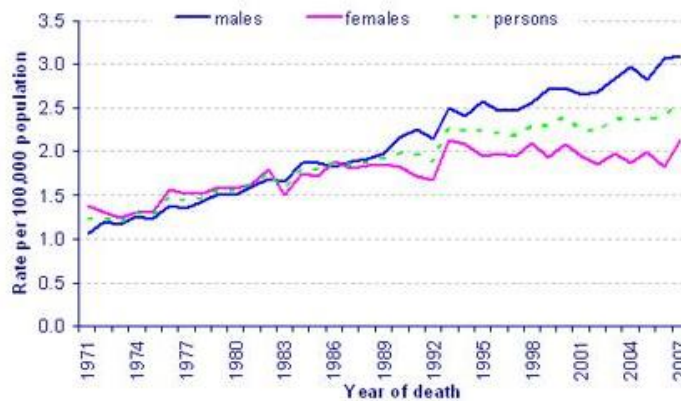


Figure 1.1: Mortality rates of patients with metastatic melanoma, UK (source cancer research institute UK)

The number of melanoma cases worldwide is increasing faster than any other cancer and remains one of the most treatment-refractory cancers. Despite decades of clinical trials testing chemotherapy, a standard first line treatment has not yet been established. The disappointing results with single and multiple agent chemotherapy led to the evaluation of alternative treatments. The relationship between melanoma and the immune system has been recognized for decades [6, 37]. Case reports of spontaneous tumor regression in patients with metastatic melanoma have suggested that immunotherapy can influence the regression of the tumor growth [37]. There are still many unanswered questions about the mechanisms that regulate the interaction between these two populations. In particular one of the main difficulties is determine which components of the immune system play significant roles. The development of models that will describe in a detailed way the phenomenon will lead to a better understand of the different interactions and the governing mechanisms. The next step is the definition of therapy protocol that will be able to defeat the tumor in a permanent way. The numerical simulation aims to be a valid tool that will be able to provide guidance

on the direction to follow in clinical trials [36]. As a matter of fact, especially in the medical field, testing must follow strict rules and results of simulations can be taken to justify the clinical researches. However, on the one hand, the theoretical predictions made with the numerical simulation must be validated experimentally, on the other side testing it is necessary in order to obtain reasonable estimates of the parameters considered in the model.

## 1.2 Optimal Control

The theory and framework of optimal control, often referred also as dynamic optimization, allows analysis of problems, in which a dynamic system is to be controlled in an optimal manner according to some performance index. The dynamics describes the evolution of the system's state and how the controls affect it. The performance index is a functional of the state and the control and gives the cost to be minimized or utility to be maximized. The history of optimal control reaches back to the Brachistocrone problem [8, 18], proposed by John Bernoulli in the 17th century, and calculus of variations, from which optimal control theory is developed [17]. Calculus of variations leads to the Euler-Lagrange equations, which are first order necessary conditions of optimality for a function to minimize or maximize a functional. In problems for which the dynamics evolves in discrete steps, the name dynamic programming problem is often used. The term also refers to the solution method developed by Bellman [4]. The method is based on the principle of optimality, which states that 'On an optimal path each control is optimal for the state at which it is executed, regardless of how that state was arrived at', and is valid for continuous as well as for discrete time problems. The dynamic programming method, when extended to continuous time problems, leads to the Hamilton-Jacobi-Bellman equation [4] [12], which is a partial differential equation defining the optimal cost to go function, i.e., performance index value from current time to the end, on the optimal trajectory.

For continuous time optimal control problems the necessary conditions of optimality are provided by the Pontryagin maximum principle [35], which relates the optimality of the control to minimizing or maximizing the Hamiltonian function of the problem at each time instant by the control value subject to control constraints. These necessary conditions define a two point boundary value problem for the dynamics of the system and the adjoint states also known as co-states. Analytical as well as indirect numerical methods of solving optimal control problems are based on the maximum principle [9].

The solution of an optimal control problem can be found either by solving the boundary value problem formulated by the optimality conditions of the maximum principle, by application of dynamic programming or direct optimization of the

objective functional. For example, if the dynamics of a discrete time problem with finite number of time steps is given in state space form, the problem can easily be written as a parameter optimization problem with the state transition equations as constraints, or the dynamics can be inserted into the objective function, so that only controls are to be chosen. For a continuous time problem the solution can be found in an approximative way by representing the state and control functions by a finite number of parameters, and thus transcribing the problem into a parameter optimization problem, (see [24]). Finding a solution in closed form for an optimal control problem, by any method, is usually possible only for very simple problems [9]. Also, the solution is often available only in the form of open loop control, i.e., the solution applies only to a given initial state instead of being in feedback form in which the control is related to the current state. A special situation is if the dynamics is linear, the objective functional is quadratic, and there are no constraints, except for fixed initial state. Then, a closed loop formulation of the control is available, it is a linear function of the state, and the problem and solution are referred to as linear quadratic (LQ) problem and control [9]. Dynamic programming provides the solution in feedback form but is in practice limited by the size of the problem [4]. The term curse of dimensionality refers to the fact that the computational and memory requirements of using dynamic programming increase exponentially with the size of the problem. An approximate method to generate a feedback formulation is by receding horizon approach, where the problem is re-solved at each (discrete) control instant and only the part of the solution before the next control instant is used. The principle of optimality still holds in the sense of expected or average objective value, and the method of dynamic programming leads to the solution. These techniques have been developed in the aerospace field and in these years they have been applied with success in different areas. The fields in which optimal control is applied ranges from industrial engineering and military applications to economics, medicine, biology and electromagnetism. In industrial application, as an example, optimal control serves the management of a distillation process. Military applications are focused in context of aircraft trajectory optimization. In economics, optimal control is applied, e.g., in real option pricing and management of resources. Design of effective medical treatments is formulated as an optimal control problem. Many biological and ecological systems are dynamic and, e.g., [21] studies airflow in breathing while [27] considers flight paths of flying fish. For example these techniques is applied to the optimal control of electromagnetic and acoustic waves propagation [5].



## 1.3 Principal aim and contents of the thesis

This work aims to create a wide overview of optimal control problems. The attention is focused on the tools used in modelisation and in the resolution of such kind of problems.

A wide discussion about the different methods with the analysis of the advantages and disadvantages is presented. An algorithm to solve optimal control problems will be proposed and will be then applied to a biological system. This method can be also applied to any ODE system models without modification of the algorithm by the users. The user will be able to solve various problems only defining the parameter of the problem and defining some setting of the algorithm. This aspect is used as a demonstration the versatility of this approach in different research fields.

Obviously the core of the work is the application of these techniques on a cancer immunotherapy problem. The goal is to identify an optimal drugs administration protocol that will decrease or completely defeat the tumor. The therapy will be analyzed taking into consideration the actual clinical applicability and the side effects related to the protocol.

In order to do this, in the early chapters a background on the optimal control theory and immunotherapy field will be created. In this way it is possible to better understand the biological models that will be presented in the following chapters. The theory of optimal control is introduced in Chapter 1. After analyzing the formulation of a general constrained problem of control, direct and indirect methods are discussed.

The numerical techniques are analyzed in order to have a subsequent conscious and rational use of the algorithms used. The basics of the technique of nonlinear programming and genetic algorithms will be analyzed. To get a complete overview, after introducing the ingredients of the technique of optimal control, a problem is analyzed to verify and test the algorithms.

Chapter 2 describes cancer immunotherapy. In particular all the aspects related with immune system response will be analyzed. The immune system defense and the tumor growth phase are considered in this section. In order to compare the results of our optimized treatment, the actual clinical strategy that has been tested on humans will be reported highlighting the positives and negatives. A knowledge of the variables described in the mathematical models presented subsequently leads to a physical evaluation of the results obtained from simulations, so allowing developing a critical maturity.

In Chapter 3 the Kirschner-Panetta model is analyzed. It is the first mathematical models of interaction between the immune system and cancer cells; it represents a necessary step before undertaking the analysis of more complex models. After the dynamic characterization of the system, the optimal control problem is con-

sidered. Continuous and discrete solutions will be presented, using both direct and indirect methods described in Chapter 1. The model is a simple representation of the dynamic interaction between the tumor cells and the immune system, because as described in Chapter 2 there are many actors that take part in the immune response.

Chapter 4 presents the Castiglione-Piccoli model. This is an improved model of the previous one that consider various kinds of immune system cells, but it takes into account only vaccine treatment. As done for the previous model, after analyzing the dynamics of the system, the optimal control of both the continuous and discrete problem is considered. Discrete control is analyzed starting from the solution evaluated with the continuous control problem, and also with a genetic algorithm. The final solution obtained by minimizing the final concentration of tumor cells will be obtained by trying to optimize the dose, the schedule and the number of drugs injections. A test of robustness of the control solution has been made using a Monte Carlo methods and considering a modification of the basic model. At the end of the chapter a comparison of the results obtained with the different resolution strategy has been analyzed.

Chapter 5 describes the problem of an optimal control of satellite trajectory. In fact, while these methods are used consistently for the optimization of trajectories, only in recent years they are applied to problems in the dynamics of the immune system and pharmacokinetics. A brief overview of the n-body problem will be given and then a series of model approximation will be presented. Interplanetary transfers will form a basis of comparison between the resolution of problems inherent astrodynamics and immunotherapy. The optimal control problems are solved using the same algorithm used in immunotherapy problems. The idea is to create a perfect analogy between the two fields of research.

In conclusion further development of the algorithm and of the immunotherapy models will be proposed analyzing the main advantages that could be obtained.

# Chapter 2

## Optimal Control Problem

Optimal control theory deals with the analysis and design of complex dynamical systems, in details with the definition of the optimal way to guide or control such systems. In aerospace field, problem of satellite guidance, design of trajectories, shape optimization and many others can be stated as optimal control problems. This chapter describes briefly the theory associated with optimal control problem formulation and its following transcription into a nonlinear programming problem, together with its more efficient solution techniques. It is possible to assert that the optimal control theory is an extension from the calculus of variation [7, 9, 17]. In this section the optimal control is presented using the variational approach, leaving at the next section the discussion about the algorithm used in the numerical approach. The scheme followed in the discussion describes the development of a classical optimal control problem as an extension of the calculus of variation called dynamical programming.

In particular OCP applied to time-continuous differential systems is treated as an expansion of a nonlinear programming NLP problem, with an infinite number of variables.

We start considering a simple constrained non linear optimal control problem OCP. The problem consists in finding a continuously differentiable or a piecewise continuous function  $\mathbf{u}(t)$  that minimize a given functional cost with different constraints on the state and control variables. These constraints contain boundary conditions and the state equations that define the dynamic system:

$$\dot{\mathbf{y}}(t) = \mathbf{f}(\mathbf{y}(t), \mathbf{u}(t), t) \quad (2.1)$$

where  $\mathbf{y}(t_i)$  is given and  $t_i \leq t \leq t_f$ .

The number of the constraints is generally different from the number of problem variables, this leads to a non single defined solution. It is worth noticing that the constraints can be both continuous and discrete.

In fact the solution of optimal control problems can be inexistent, unique or it is possible to find different solution that depends from the starting guess solution.

This aspect is strictly related with the system controllability in the classical control theory. If the system is uncontrollable it is not possible to transfer from any initial state to any desired final state in a desired time.

The functional cost is a performance criterion used in order to evaluate the performance of a system. There are different forms that should be used; the most general is the Bolza form

$$J := \Phi(\mathbf{y}_{t_f}, t_f) + \int_{t_0}^{t_f} F(\mathbf{y}(t), \mathbf{u}(t), t) dt \quad (2.2)$$

Lagrange form consists only in the integral term, while the Mayer form is represented with the first term of the functional. The three formulations are theoretically different but it is possible to translate the functional from a form to another with simple operations. In order to maintain more generality the Bolza form will be considered in the following discussion.

Considering a functional cost with boundary conditions at the end of the time interval defined as

$$\phi(\mathbf{y}_{t_f}, \mathbf{u}_{t_f}, t_f) = 0 \quad (2.3)$$

and subject to state equations, it is possible to form an augmented performance index

$$\hat{J} := [\Phi + \nu^T \phi]_{t_f} + \int_{t_0}^{t_f} \{F(\mathbf{y}(t), \mathbf{u}(t), t) + \lambda^T(t) [\mathbf{f}(\mathbf{y}(t), \mathbf{u}(t)) - \dot{\mathbf{y}}]\} dt \quad (2.4)$$

where  $\lambda$  and  $\nu$  are multiplier functions.

In order to use a standard convention the Hamiltonian is a scalar function defined as

$$H(\mathbf{y}(t), \mathbf{u}(t), \lambda(t), t) = F(\mathbf{y}(t), \mathbf{u}(t), t) + \lambda^T(t) \mathbf{f}(\mathbf{y}(t), \mathbf{u}(t)) \quad (2.5)$$

The necessary conditions for the optimum are obtained after integrating the right hand side of (2.4) and they are identified setting the variation  $\delta \hat{J} = 0$ . These conditions are always referred as Euler-Lagrange equations.

$$\begin{aligned} \delta x = 0 &\Rightarrow \dot{\lambda}^T = -\frac{\partial H}{\partial x} \\ \delta u = 0 &\Rightarrow \frac{\partial H}{\partial u} = 0 \end{aligned} \quad (2.6)$$

The first one is the adjoint equation that describes the dynamics of the adjoint variables, while the other are algebraic equations for the control functions. The problem is completed with the so called transversality equations defined as:

$$\begin{aligned} \lambda(t_f) &= [\Phi + \nu^T \phi]_{t_f} \\ 0 &= H + \partial[\Phi + \nu^T \phi] / \partial t \\ 0 &= \lambda(t_i) \end{aligned} \quad (2.7)$$

The problem, as stated previously, is known as two-point boundary-value problem, TPBVP, and the complete set of necessary conditions consists of a differential-algebraic (DAE) system.

## 2.1 Numerical solution of optimal control problems

Solving simple problems with a functional cost and constraints is a hard task. With the development of computer it is now possible to solve complicated problems in a reasonable computational time. The methods used are generally classified in three categories: dynamic programming, direct methods and indirect methods.

Dynamic programming computes recursively a feedback control. In continuous problem this approach leads to the solution of Hamilton-Jacobi-Bellman PDE. This method have several difficulties and limitation such as the restricted small state dimensions required.

The numerical solution of the Euler-Lagrange equations is the basis of the so-called indirect methods. Indirect methods lead to the solution of a boundary value problem (BVP). A TPBVP consists essentially in the process of solving a set of differential equations whose solution has to satisfy initial and final boundary conditions [2]. Solving TPBVPs is computationally intensive, because the simple integration from initial conditions almost fails to reach an adequate solution that respects the final conditions [2, 7, 8]. The techniques involved in solving this problem is often trial-and-error in nature. The numerical solution of the TPBVP is mostly performed by shooting techniques or by collocation.

The two major drawbacks are that the differential equations obtained are often difficult to solve due to strong nonlinearity and instability and also define a guess initial solution for the Lagrangian multiplier. As a matter of fact these variables do not have a physical meaning, this leads to problems in the definition of an initial guess solution to start the algorithm. Another problem that it is necessary to take into account in the resolution of a BVP is that the existence and uniqueness of solution is not guaranteed as in an initial value problem [10]. Each problem may have a unique solution, several solutions or no solution at all.

Indirect methods have been largely used for the solution of optimal control problems in the past when the computation performances are not enough to solve complex problems. Nowadays the trend [8] is to use direct methods that generally require more computational effort but they do not require the solution of the Euler-Lagrange equations. A direct method attempts to converge at the minimum of an objective function  $F$ , in contrast to an indirect method that look for the minimum finding the root of the necessary condition  $F' = 0$ . The solution of

a direct method can avoid the resolution of a BVP using nonlinear programming, in fact they transform the original infinite problem into a finite dimensional nonlinear programming problem. One of the main advantages of these methods is that they can easily treat constraints. All the direct methods are based on the discretization of the control variables and differs in the way the state trajectory is handled.

### 2.1.1 Direct transcription and nonlinear programming

The basic idea of the direct transcription involves a discretization of the state and the control space in a continuous problem [7]. This means that the method leads to an approximate solution, in fact the technique allows converting an optimal control problem into a nonlinear programming problem.

This involves different steps:

- transcription: formulation of the continuous problem with a finite-dimension set of variables;
- solution: computation of the value of the unknowns through a parametric optimization approach;
- verification: evaluation of the accuracy of the discrete approximation of the problem.

The first phase requires knowledge about the basic elements and the solution of a nonlinear programming problem. The solution of the optimal control problem will be an easy extension of this method.

Direct transcription is a direct methods that implies, as said in the previous section, to find  $\mathbf{x}^T$  such that the function  $F(\mathbf{x})$  is a minimum. The solution of the problem starts with a Taylor approximation of the cost functional about the point  $\mathbf{x}$ :

$$F(\bar{x}) = F(x) + \mathbf{g}^T(x)(\bar{x} - x) + \frac{1}{2}(\bar{x} - x)^T H(\bar{x} - x) \quad (2.8)$$

Where  $\mathbf{g}(x)$  is the gradient of the functional and  $H$  is the Hessian matrix. Defining the search direction as  $p = \bar{x} - x$  the Taylor expansion can be written as

$$F(\bar{x}) = F(x) + \mathbf{g}^T(x)p + \frac{1}{2}p^T Hp \quad (2.9)$$

$\hat{x}$  is the minimum point if the objective function in all the neighboring points is larger, that means that the directional slope must be zero in all the directions at  $\hat{x}$ .

$$\mathbf{g}^T(\hat{x})p = 0 \Rightarrow \mathbf{g}(\hat{x}) = 0 \quad \forall p \neq 0 \quad (2.10)$$

This condition is necessary but not sufficient to define the stationary point  $\hat{x}$  as a strong local minimum. The required condition is that the curvature in the direction  $p$  is positive definite that means

$$p^T H p \geq 0 \quad (2.11)$$

The previous formulas simply define the application of the Newton method to a generic minimum problem. An addition to this method is the optimization of an objective function subjected to equality constraints.

The equality constraints are defined as  $\mathbf{c}(\mathbf{x}) = 0$ . Using the Lagrange multipliers as in the classical variational approach it is possible to define the Lagrangian as

$$L(x, \lambda) = F(x) - \lambda^T c(x) \quad (2.12)$$

In analogy with the consideration 2.10 the minimum necessary conditions on the gradients are:

$$\nabla_x L = 0 \quad (2.13)$$

$$\nabla_\lambda L = 0 \quad (2.14)$$

In order to define a complete set of necessary and sufficient conditions the Hessian of the Lagrangian must be positive definite in order to distinguish a minimum stationary point.

Considering the constraint vector  $\mathbf{c}$  a linear approximation at  $\bar{x}$  is defined as

$$c(\bar{x}) = c(x) + G(\bar{x} - x) \quad (2.15)$$

where  $G$  is the Jacobian matrix of the constraint vector. Solving for  $c(\bar{x}) = 0$  it is possible to evaluate the search direction with this linear system

$$Gp = -c(x) \quad (2.16)$$

The analogous approximation step is required for the gradient respect to direction  $x$ . The gradient is defined as

$$\nabla_x L = g - G^T \lambda \quad (2.17)$$

Expanding 2.17 about  $x$  and  $\lambda$  through a Taylor expansion

$$0 = g - G^T \lambda + Hp - G^T(\bar{\lambda} - \lambda) \quad (2.18)$$

This equation with the linear approximation of the constraints lead to the Karush-Kuhn-Tucker KKT linear system

$$\begin{bmatrix} H & G^T \\ G & 0 \end{bmatrix} \begin{bmatrix} \Delta x \\ \Delta \lambda \end{bmatrix} = \begin{bmatrix} -g \\ -c \end{bmatrix} \quad (2.19)$$

An equivalent definition of the search direction  $\mathbf{p}$  derives from the minimization of the quadratic function

$$\mathbf{g}^T \mathbf{p} + \frac{1}{2} \mathbf{p}^T H \mathbf{p} \quad (2.20)$$

subjected to the constraints

$$G \mathbf{p} = -\mathbf{c} \quad (2.21)$$

If the constraints of the problem are inequalities it is possible to extend what we have previously stated.

The nonlinear problem can be solved using several methods that are available: Collocation, Shooting Techniques, Legendre Pseudospectral Method [43] [30]. In section 2.1.1 we will analyze the first two approaches.

In this thesis we will use numerical techniques that consider initial value problems IVP instead of BVP. This because the techniques for solving IVP are well established and can be divided into two categories: one-step or multistep integrators. Among the first, the classic Runge-Kutta RK scheme reads:

$$y_{n+1} = y_n + h \sum_{i=1}^s b_i k_i \quad (2.22)$$

where  $k_i$  is defined as

$$k_i = f \left( t_n + c_i h, y_n + h \sum_{j=1}^s a_{ij} k_j \right) \quad (2.23)$$

$s$  is the number of scheme stage, and  $a$ ,  $b$ ,  $c$  are the method coefficients.

The other class of integration methods are the multistep schemes, which have the following general form:

$$y_{i+1} = \sum_{j=0}^{k-1} \alpha_j y_{i+1} + h \sum_{j=0}^k \beta_j f_{i+j} \quad (2.24)$$

With respect to the specific coefficients of the methods (either one-step or multi-step), the schemes may be explicit or implicit. In any case, for a boundary value problem any scheme becomes effectively implicit. In this work both methods are used, the first will be used as verification of the solution because of their high order of convergence, while the latter will be implemented in the algorithm to describe the dynamics.

## 2.1.2 Trajectory optimization problem

A trajectory optimization problem must be reformulated so as to be easily implemented in a numerical algorithm. This section aims to present the general



procedure to translate this kind of OCP into NLP.

The problem time domain is divided into  $K$  intervals, called phases, and for each  $k$  phase the dynamics of the system is described by the following variables:

$$\mathbf{z} = [\mathbf{y}^k(t), \mathbf{u}^k(t)] \quad (2.25)$$

that for a system with  $n$  states and  $m$  controls is a vector made up by  $(n + m)(K + 1)$  elements. In addition, there is the  $bk$ -dimensional parameter vector  $\mathbf{p}$ , which is not a function of the independent time variable  $t$ . From now on, for sake of clarity, the phase-dependent notation is omitted, without losing validity. The differential equations of the problem are defined as

$$\dot{\mathbf{y}} = \mathbf{f}[\mathbf{y}(t), \mathbf{u}(t), \mathbf{p}, t] \quad (2.26)$$

while the initial and final conditions are stated as

$$\begin{aligned} \psi_{il} &\leq \psi[\mathbf{y}(t_i), \mathbf{u}(t_i), \mathbf{p}, t_i] \leq \psi_{iu} \\ \psi_{fl} &\leq \psi[\mathbf{y}(t_f), \mathbf{u}(t_f), \mathbf{p}, t_f] \leq \psi_{fu} \end{aligned} \quad (2.27)$$

where the subscript  $l$  and  $u$  defines respectively a lower or an upper bound.

In addition, the solution is subject to the following path constraints

$$\mathbf{g}_l \leq \mathbf{g}[\mathbf{y}(t), \mathbf{u}(t), \mathbf{p}, t] \leq \mathbf{g}_u \quad (2.28)$$

together with simple bounds on state variables:

$$\mathbf{y}_l \leq \mathbf{y} \leq \mathbf{y}_u \quad (2.29)$$

and on the control variables:

$$\mathbf{u}_l \leq \mathbf{u} \leq \mathbf{u}_u \quad (2.30)$$

The determination of the control vector history  $\mathbf{u}^{(k)}(t)$ , and of the parameters  $\mathbf{p}^{(k)}$ , that minimize the following performance index:

$$J = \psi[\mathbf{y}(t_i^1), \mathbf{u}(t_i^1), \mathbf{y}(t_f^1), \mathbf{u}(t_f^1), \mathbf{p}_i, \dots, \mathbf{y}(t_i^{K+1}), \mathbf{u}(t_i^{K+1}), \mathbf{y}(t_f^{K+1}), \mathbf{u}(t_f^{K+1}), \mathbf{p}_f] \quad (2.31)$$

corresponds to the basic optimal control statement.

According to the formalism associated with the concept of a phase partition of the time domain, the dynamics equations cannot change within a phase, but may change from one to another. This idea can be used considering combined therapy, e.g. chemotherapy together with immunotherapy. It is possible to consider different set of differential equations that describes the different treatment. In aerospace problems this idea is widely used, as it makes possible to use different sets of differential equations during a complicated interplanetary transfer.

The performance index 2.31 can be written in Mayer, Lagrange or Bolza form. The last two forms contain an integral that in order to be translated in the algorithm is approximated using a numerical method.

### 2.1.3 Collocation

The standard collocation methods discretize the time domain into  $N$  equal segments

$$t_0 = t_1 < t_2 < \dots < t_N < t_{N+1} = t_f \quad (2.32)$$

with the endpoints of each segment being the grid points. A vector  $\mathbf{p} \in \mathbb{R}^{(N+1)(N+M)}$  is defined as

$$\mathbf{p} = \{\mathbf{x}^T(t_1), \dots, \mathbf{x}^T(t_{N+1}), \mathbf{u}^T(t_1), \dots, \mathbf{u}^T(t_{N+1})\} \quad (2.33)$$

whose elements are the values of the state and control variables at grid points. The vector  $\mathbf{p}$  is the independent variable that will be determined in the optimization process. Hence the performance index and all of the constraints should be transcribed with  $\mathbf{p}$ . The set of differential equation that describes the dynamics are approximated using an approximate scheme that use as points for the evaluation those belonging to vector  $\mathbf{p}$ . The number of points in this way strictly determines the accuracy of the dynamics representation, because in order to have the real solution the dimension of the NLP variables must be infinite. This method is useful when considering a continuous control, while in the other case it is better to consider a single or multiple shooting approach in order to reduce the number of variables and correctly integrate the dynamics.

### 2.1.4 The simple shooting method

As written previously, the global optimization problem is a BVP, while in general numerical methods for solving initial values problem IVP are relatively well established than the techniques for solving BVP [10].

The basic idea is to determine the IVP that produce the solution of the BVP. A general BVP in the interval  $[a, b]$  read as

$$\mathbf{r}(\mathbf{y}(a), \mathbf{y}(b)) = \mathbf{0} \quad (2.34)$$

Function  $\mathbf{r}$  depends on both initial and final values. The evolution of this nonlinear system can be demanded to the solution of an IVP. The final state values are obtained following this dependence  $\mathbf{y}(a) = \mathbf{s} \Rightarrow \mathbf{y}(b) = \mathbf{y}(b, \mathbf{s})$ . Consequently we obtain the nonlinear system

$$\mathbf{r}(\mathbf{y}(a), \mathbf{y}(b)) = \mathbf{r}(\mathbf{s}, \mathbf{y}(b, \mathbf{s})) = \mathbf{0} \quad (2.35)$$

The problem is now demanded to find the zero of the function  $F(\mathbf{s}) = \mathbf{y}(b, \mathbf{s}) - \mathbf{y}(b)$ , which it is also called discrepancy vector. Starting with an initial approximation  $\mathbf{s}^0$  it is necessary to compute the iteration

$$\mathbf{s}^{i+1} = \mathbf{s}^i - \frac{F(\mathbf{s}^i)}{F'(\mathbf{s}^i)} \quad (2.36)$$

The iteration stops when the norm of  $F$  is in a sufficiently small neighborhood of zero, condition that is necessary and sufficient to translate the BVP into an IVP. The major difficulties in this procedure is that highly nonlinear system are very sensitive on initial solution, this leads to a hard convergence in the iterative procedure [10]. Other serious problem with the convergence lead to the selection of an initial solution  $\mathbf{s}$  not close to the real value. To sum up the simple shooting method is not a very practical method [23].

The application of this procedure to indirect methods leads to the propagation of a guess unknown initial values of the Lagrange multiplier using the optimal control. The use of a gradient method to adjust the initial solution and respect the final boundary constraint often does not converge. These because the sensitivity of the Lagrange multipliers on initial conditions, and also often the system is unstable.

For sake of clarity, assuming a single phase problem, the complete set of NLP variables becomes

$$\mathbf{x} = \{\mathbf{y}(t_i), t_i, \mathbf{y}(t_f), t_f, \mathbf{p}\} \quad (2.37)$$

The associated constraint and objective function associated with the NLP formulation are quantities evaluated at both ends of the trajectory. Therefore the constraint vector is organized as follows

$$\mathbf{c}(\mathbf{x}) = \{\psi_i[\mathbf{y}(t_i), t_i, \mathbf{p}], \psi_f[\mathbf{y}(t_f), t_f, \mathbf{p}]\} \quad (2.38)$$

### 2.1.5 Multiple shooting method

It is possible to extend the previous method by dividing the time domain into subdomains and using for each of them the single shooting approach. In the multiple shooting methods one selects the unknown parameters  $\mathbf{s}$  at the initial time just like in the simple shooting method, but does not integrate all the way to the final time. Instead the distance from a corresponding point on a preselected grid is checked continuously as the integration proceeds. The goal is to match-up the discontinuous trajectory segments. In this way the nonlinear effects of the continuity conditions are distributed over the whole time horizon. It combines some of the advantages of simultaneous methods as collocation and the simplicity of the single shooting approach. This approach starts discretizing the control on

a grid  $u(t) = q_i$  for  $t$  that resides in the interval  $[t_i, t_{i+1}]$ . The algorithm proceeds solving the ODE problem on each interval independently, starting with an initial guess solution  $\mathbf{s}_i^0$ :

$$\dot{\mathbf{y}}_i(t) = \mathbf{f}(\mathbf{y}_i(t), q_i) \quad (2.39)$$

$$\mathbf{y}_i(t_i) = \mathbf{s}_i^0 \quad (2.40)$$

The objective is to evaluate the control law in order to satisfy the dynamics and the initial and final conditions written in the form

$$\psi_i[\mathbf{y}(t_i), \mathbf{u}(t_i), t_i, \mathbf{p}] = 0 \quad (2.41)$$

$$\psi_f[\mathbf{y}(t_f), \mathbf{u}(t_f), t_f, \mathbf{p}] = 0 \quad (2.42)$$

The algorithm procedure is similar to that presented in the collocation approach. The trajectory is divided into  $N$  segments as in 2.32 and the vector of NLP variables is defined as in 2.33. If necessary, it is possible to append as additional variables  $t_i$  and  $t_f$ .

The difference with the collocation approach is the solution of dynamics. As in the simple shooting an approach IVP is solved by means of a given integration scheme. In this work a RK method of the seventh order has been used.

The satisfaction of the global dynamics of the problem is obtained joining together the time segments at their boundaries with the conditions

$$\eta_j = \Phi(\mathbf{y}_j, \mathbf{p}, t) - \mathbf{y}_{j+1} = 0 \quad (2.43)$$

where  $\Phi$  is the flow representing the dynamics.

These conditions can be modified for consider a discrete impulsive control at each grid point  $j$  as

$$\eta_j = \Phi(\mathbf{y}_j, \mathbf{p}, t) - \mathbf{y}_{j+1} + \mathbf{u}_j = 0 \quad (2.44)$$

where  $\mathbf{u}_j$  is a vector that contains the impulsive controls. Obviously its structure depends from the problem equations and it should be not completely full.

Finally the complete constraint vector is assembled in the following form

$$\mathbf{c}(\mathbf{x}) = \{\psi_i[\mathbf{y}(t_i), t_i, \mathbf{p}], \eta_1, \dots, \eta_{N-1}, \psi_f[\mathbf{y}(t_f), t_f, \mathbf{p}]\} \quad (2.45)$$

As far as it concerns the multiple shooting approaches, the size of the NLP increases with respect to simple shooting. Fortunately the Jacobian matrix is sparse thanks to the fact that the variables of the problem are uncoupled, i.e. variables playing an active role in the first part of the trajectory do not influence the constraints at the end of it.

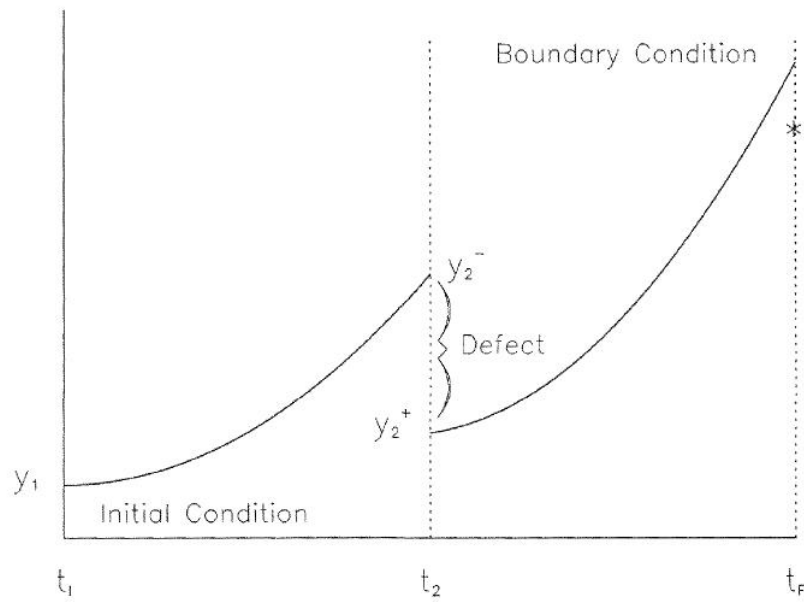


Figure 2.1: Multiple shooting technique [7]

## 2.2 Simple example

As an exercise we consider the example described in [17] at page 181. The problem statement as follows:

minimize

$$F(u) := \int_0^1 (x_1(t)^2 + x_2(t)^2 + \rho u(t)^2) dt \quad (2.46)$$

subject to

$$\begin{aligned} \dot{x}_1(t) &= x_2(t) \\ \dot{x}_2(t) &= -x_2(t) + u(t) \end{aligned} \quad (2.47)$$

with the initial conditions  $x_1(0) = 0$  and  $x_2(0) = -1$  and the following inequality constraints

$$x_2(t) + 0.5 - 8(t - 0.5)^2 \leq 0 \quad (2.48)$$

$$-20 \leq u(t) \leq 20 \quad (2.49)$$

This problem is a good test on the algorithm implemented because it contains both equality and inequality constraints. The formulation of the problem leads to a resolution of an optimal control problem using the direct collocation nonlinear programming DCNLP.

### 2.2.1 Direct transcription formulation using collocation

It is possible to solve the optimal control problem with a discretization of the solution into a grid of  $N$  points. For each  $N - 1$  intervals it is possible to identify a vector of variables that includes the  $n$  states and also the  $m$  controls. For the problems in the example the vectors looks as follows:

$$\mathbf{x}^T = \{x_1^{(1)}, x_2^{(1)}, u^{(1)}, \dots, x_1^{(N)}, x_2^{(N)}, u^{(N)}\} \quad (2.50)$$

The cost functional must be discretized for every phase with the trapezoidal method.

Obviously considering high order integration scheme such as Hermite-Simpson or Runge Kutta methods will lead to a more accurate approximation of the system trajectory. In the problem considered in this thesis the trapezoidal scheme is not used out of this example. Considering the Lagrangian defined as

$$L(x_1, x_2, u, t) = x_1(t)^2 + x_2(t)^2 + \rho u(t)^2 \quad (2.51)$$

The integral approximated with the numerical scheme is:

$$\sum_{i=1}^{N-1} \frac{L(x_1^{(i)}, x_2^{(i)}, u^{(i)}, t^{(i)}) + L(x_1^{(i+1)}, x_2^{(i+1)}, u^{(i+1)}, t^{(i+1)})}{2} h \quad (2.52)$$

As we have previously described it is necessary to translate the dynamics into nonlinear equality constraints using discrete approximations.

The differential equations that describes the system are replaced with a finite difference approximation using Euler method. For each phase it is possible to determine  $n$  defects equations for a total number of  $n(N - 1)$

$$s_k = \mathbf{y}_{k+1} - \mathbf{y}_k - h_k \mathbf{f}_k \quad (2.53)$$

where  $\mathbf{y}$  is the  $n = 2$  rows vector of the system variables, and  $\mathbf{f}_k$  is the right-hand-side of the system equation evaluated at each time  $k$ .

Initial boundary conditions must be defined in this vector adding several rows as the number of the conditions. For the example it is possible to define a vector  $\Phi_I = [g_1, g_2]$  where  $g_1 = x_1^{(1)} - x_1(0)$  and  $g_2 = x_2^{(1)} - x_2(0)$ . The nonlinear equality vectors can be written as:

$$\mathbf{c}(\mathbf{x}) = [s_1, \dots, s_{N-1}, \Phi_I]^T \quad (2.54)$$

The problem contains also inequality constraints. These are very common in several optimization problems, because often the variables can vary in a specific range.

The inequalities with the state  $x_2$  is defined using a vector:  $\mathbf{c}(\mathbf{x}) \leq 0$ . For each phase the  $\mathbf{c}(\mathbf{x})$  is defined as

$$c(\mathbf{x})_k = x_2^{(k)} - 0.5 - 8(t^{(k)} - 0.5)^2 \quad (2.55)$$

The inequalities on the control can be written defining upper and lower bounds for the variable  $\mathbf{y}$  with the following structure:

$$\begin{aligned}\mathbf{l}_b &= [-\infty, -\infty, -20]^T \\ \mathbf{u}_b &= [\infty, \infty, 20]^T\end{aligned}\quad (2.56)$$

It is also possible to consider these limits as inequalities and add two rows to vector  $\mathbf{c}(\mathbf{x})$  changing the inequality sign as specified in the definition. These alternatives lead to an inequality constraint vector defined for each phase as:

$$c(\mathbf{x})_k = [x_2^{(k)} - 0.5 - 8(t^{(k)} - 0.5)^2, u^{(k)} - 20, -u^{(k)} - 20]^T \quad (2.57)$$

### 2.2.2 Optimization results

The results obtained with one hundred phases are shown in the figures 2.2 and 2.3.

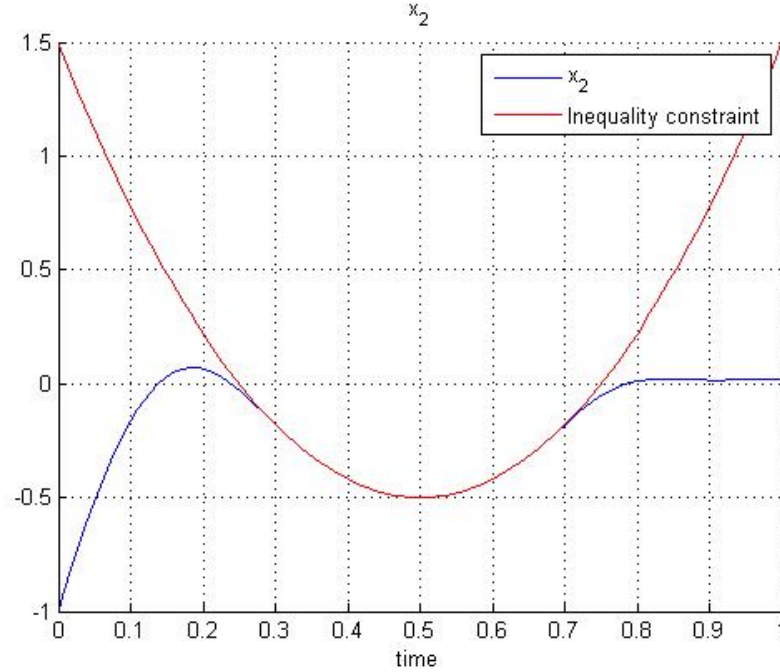


Figure 2.2:  $x_2$  with  $\rho=5e-3$

The solution is obtained following a mesh refinement from a coarse mesh with a technique that will be described in the next section. The comparison of the solution for  $x_2$  and its inequality constraint shows that equation 2.55 is solved as equality (constraint active) for the major part of the integration time.

### 2.2.3 Verification

The transcription method translates the optimal control continuous problem into a finite dimension nonlinear programming problem. The last necessary step is to

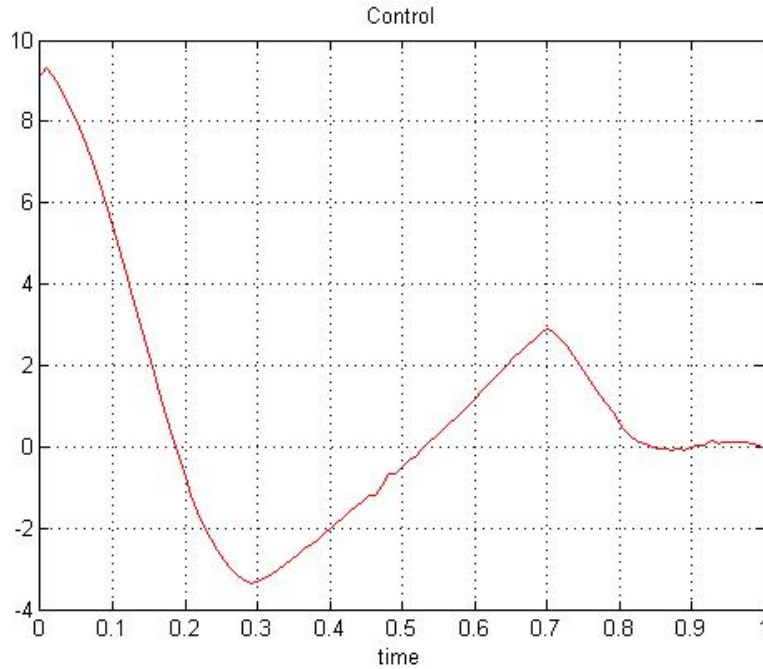


Figure 2.3: Control variable with  $\rho=5e-3$

verify the results obtained in comparison from those obtained from the starting problem. In this way it is possible to evaluate the respect of the accuracy constraints and, if necessary, repeat the optimization varying different parameters of the discretization. The discretized control vector must be interpolated with a cubic spline and consequently an integration of the system equations must be performed. The integration scheme is Runge-Kutta. The tolerance has been fixed for the state variable  $\mathbf{x}$  at the end of the time interval as

$$\|\mathbf{x}(t_f) - \mathbf{x}_N\| \leq \epsilon \quad (2.58)$$

In order to reduce the error between the solution obtained through the real integration and those evaluated with the approximate integration scheme and satisfy the tolerance in 2.58, we use a progressive enrichment of the grid. This method is known in literature as nested iteration [1] and it is the most ancient and even the most intuitive method that use a hierarchical grid. The process consists in the resolution of the model in a coarse grid and in an iterative way interpolate the results on an accurate mesh with an increased number of grid points. The meshes can be uniform or not and the process can be adaptive in the sense that the algorithm will increase the number of points in critical part of the solution. In this work we consider only uniform non adaptive mesh refinement, this will provide a simple algorithm that can give several advantages to the simulation. The respect of the fixed tolerance proves the consistency between the solution of the discretized problem and that of the original continuous time problem. The



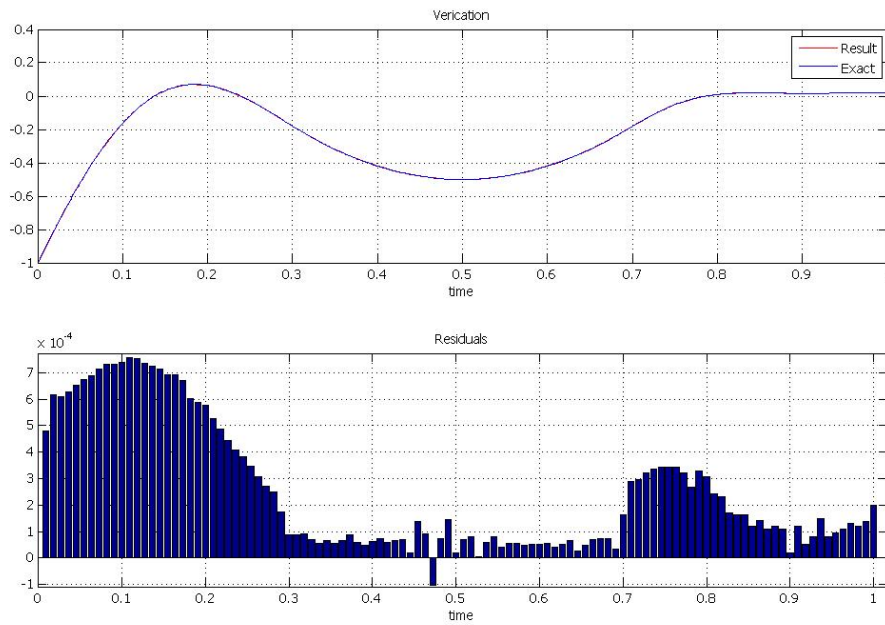


Figure 2.4: Verification results comparison

solution of the old mesh is interpolated in the new grid points and used as a guess solution of the optimization. In this way it is possible to accelerate the convergence of the optimization algorithm. This method may guarantee a good initialization for the refined mesh necessary to have the convergence to the optimal solution.

As a general consideration for direct methods a larger mesh size is always linked with an improvement of accuracy required. In order to capture the irregularities in the control and in the state variables a mesh refinement is necessary. Usually the common solution is to increase the number of grid points and in this way increase the computational time. There is also another opportunity that is related with the distribution pattern of grid points.

Figure 2.4 shows the comparison between the solution obtained with the trapezoidal integration method and the real solution that it evaluated using a 7/8th Runge Kutta scheme. The residuals are  $O(10^{-4})$ , this value can be decreased using a high order integration scheme such as Hermite-Simpson.

## 2.3 Genetic algorithm optimization

Methods that are based on deterministic calculations, which are the subject of numerous theoretical studies and applications, trying to get the local extreme by solving a nonlinear system of equations, often through the application of the gradient method. In fact all methods starting from the condition that the gradient

of the function exists (differentiability of the functional) make an approximation sufficiently accurate and numerous evaluations (through discretization of an adjoint equation, with automatic differentiation or finite difference). These methods have the advantage of having a high speed of convergence (asymptotically) if the initial guess solution is sufficiently close to the optimum or the functional is convex [33].

The methods that are based on random search do not require knowledge of the gradient and they are based solely on the evaluation of the functional. These methods are more robust in identifying a global optimum for their lower sensitivity to initial conditions. For this reasons, these methods have a remarkable success in solving coupled problems where the classical assumptions of differentiability and convexity are not justified [33].

Evolutionary algorithms (EAs) are optimization procedure that search for the solution that minimizes or maximizes a given function in a prescribed space.

There are different kind of EAs [44]: differential evolution, particle swarm optimization, genetic algorithm. In our work only genetic algorithm (GA) are used. These represent a robust parameter optimization techniques based on the Darwinian concept of evolution that use selection and specific recombination of a chromosome-like data structure [22]. These mechanisms are selection operators and they are based on reproduction, mutation, recombination, natural selection, and survival of the fittest.

We have focused our attention on GA because this is a pseudo-aleatory method in which a random generation of the variables is guided by an intelligent method of exploration of the search space. The advantage is that GAs algorithm well suited to optimization of nonlinear problems and/or where traditional methods are not very robust.

One of the main problems related to Genetic algorithm is the implementation of the constraints [50]. The solution proposed consists in using the Augmented Lagrangian Genetic Algorithm (ALGA) in order to solve a nonlinear optimization problem with nonlinear constraints, linear constraints, and bounds. In this approach, bounds and linear constraints are handled separately from nonlinear constraints. A subproblem is formulated by combining the fitness function and nonlinear constraint function using the Lagrangian and the penalty parameters. A sequence of such optimization problems are approximately minimized using the genetic algorithm such that the linear constraints and bounds are satisfied.

This method born in the 1970s [22] and it is a current research issue. The algorithm starts with a random initial population. This population consists in individuals that show a genotype, or chromosome, based on the variables to be optimized.

The procedure for the generation of a new population can be divided into two phases [22]. In the first one selection is applied to the current population generat-

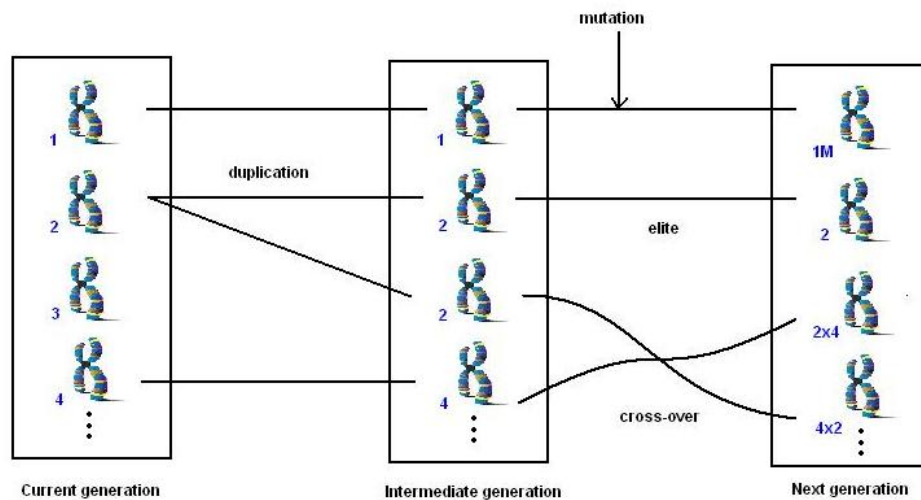


Figure 2.5: Scheme for the creation of a new generation

ing an intermediate population. The probability that an individual is duplicated and placed in the intermediate population is proportional to its fitness value. Recombination and mutation are then applied to the intermediate population in order to generate the next population. Cross-over consists in a random selection of a point in the chromosome of two individuals. The fragments obtained splitting the chromosome in two parts from the point selected are then swapped between the two parents. Mutation children are created by a random change in the genes of the individual parent. The other children taken into account are the so called elite children. These ones are the individuals that survive unchanged between two different generations. The principle of elitism is used to avoid the loss of good individuals with high fitness score. One generation of the algorithm is obtained after the processes of evaluation, selection, and recombination. In our algorithm the process is repeated until the change in the fitness function between the current generation and the next generation is less than a tolerance of  $1e-6$ . The result is a direct consequence of the survival of the fittest, the final population consists in individuals that are better suited to the environment as in natural adaptation.

To sum up a genetic algorithm is essentially based on:

- A chromosomal representation of solutions of the problem;
- An evaluation that plays the role of the environment: it classify the solution as function of their fitness;
- Genetic operators that define the transmission mechanisms of the genotypes

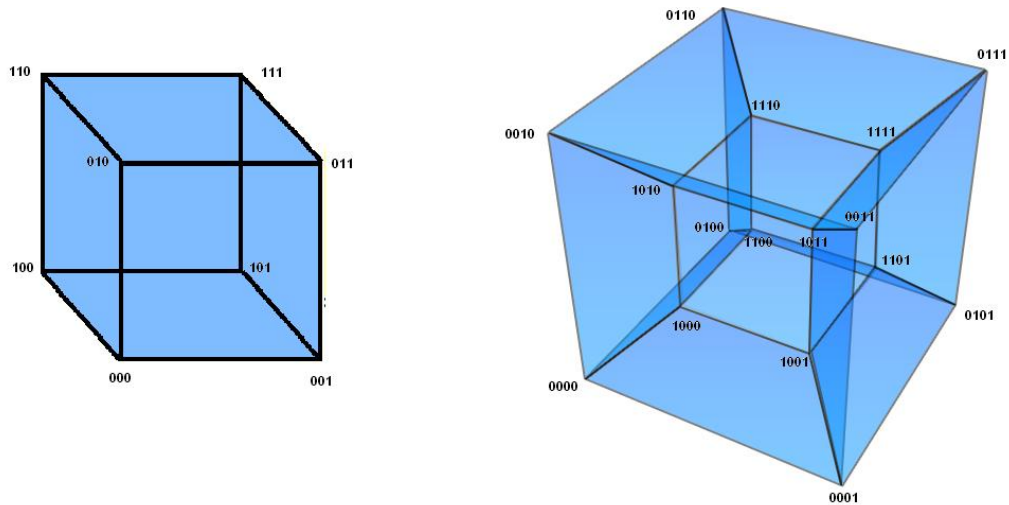


Figure 2.6: Hypercube and 4D hyperspace

alleles from parents to descendant;

- The value of the parameters used in the algorithm (Population size, number of generations, genetic operator percentage).

GAs search from multiple points in the design space simultaneously and stochastically, this lead to the fact that GAs can be processed in parallel [33]. In our work GAs run in parallel on two 1.66 MHz Intel core.

In order to understand how it is possible that the solution obtained via GA is a form of optimization, we consider a simple modelisation used by Holland in its work [22]. The genetic algorithm is a search method on hyperplane partitions of the search space. We consider a chromosome that consists in a string of 3 bits. Each of these bits can assume the value 0 and 1. These chromosomes can be represented in the 3 dimensional space. A cube with corners numbered by bit strings that differ by 1 bit is the geometrical representation of the global search space.

The front plane of the cube shown in figure 2.6 contains all the solutions that begin with 0. This plane can be identified as  $0^{**}$ , and it is also called hyperplane of order 1. In general a hyperplane of order  $n$  contains  $n$  bits with a definite value. A chromosome matches a particular hyperplane if its bit strings can be constructed from the label of the hyperplane by replacing the symbol ‘\*’ with the appropriate bit value. Every chromosome belongs to  $2^L - 1$  different hyperplanes, where  $L$  is the number of the value that a single bit can assume. The total number of hyperplane partitions of the search space is  $3^L - 1$ . When the algorithm evaluate a chromosome many hyperplanes are sampled ( $2^L - 1$ ) and evaluated in an implicit parallelism.

Implicit parallelism implies that many hyperplane competitions are simultaneously solved in parallel. The theory suggests that through the process of reproduction and recombination the competing hyperplanes increase or decrease their representation in the population according to the relative fitness score of the strings that lie in those hyperplane partitions [47]. Setting cross-over and mutation at low level maximizes the preservation of hyperplane samples obtained in the intermediate generation, while this aspect minimizes the disruptive effect of cross-over and mutation. It is important to consider always mutation in order to prevent a premature convergence. In fact it is possible that after several generations all the bit of a string will converge to the same value, causing the permanent loss of an allele and a not satisfactory solution. Without mutation it is impossible to reintroduce the bit value.

## 2.4 Hybrid algorithm

Gradient search methods efficiency in reaching global optimum relies on the users in providing right initial guess. A hybrid algorithm overcomes this limitation with a simultaneous exploitation of the gradient method's capability to quickly converge to the local optimum and GA's capability to explore the entire design space [46].

If the choice of the initial guess is the right one a gradient based method will converge effectively to the global minimum. In a hybrid algorithm GA guides to explore the promising good initial guesses spread over design space, while gradient based methods GBM identifies the global optimum.

GAs algorithm are not efficient in solving constrained problems, but with this kind of procedure the solution can be useful also if the constraints are not satisfied. The respect of the constraints is delayed to the following gradient based algorithm that can permit an easy implementation of these conditions.

The hybrid algorithm starts using the genetic algorithm that begins its search with a random solution. The GA optimization explore the entire design space and can be terminated at convergence of the fitness function. The best individual of the final population is then passed to the GBM as the initial solution of a NLP. The NLP problem must be carried out until it reach the convergence to the minimum.

This method as we will demonstrate in the work is a robust and efficient optimization algorithm capable of locating global optimum.

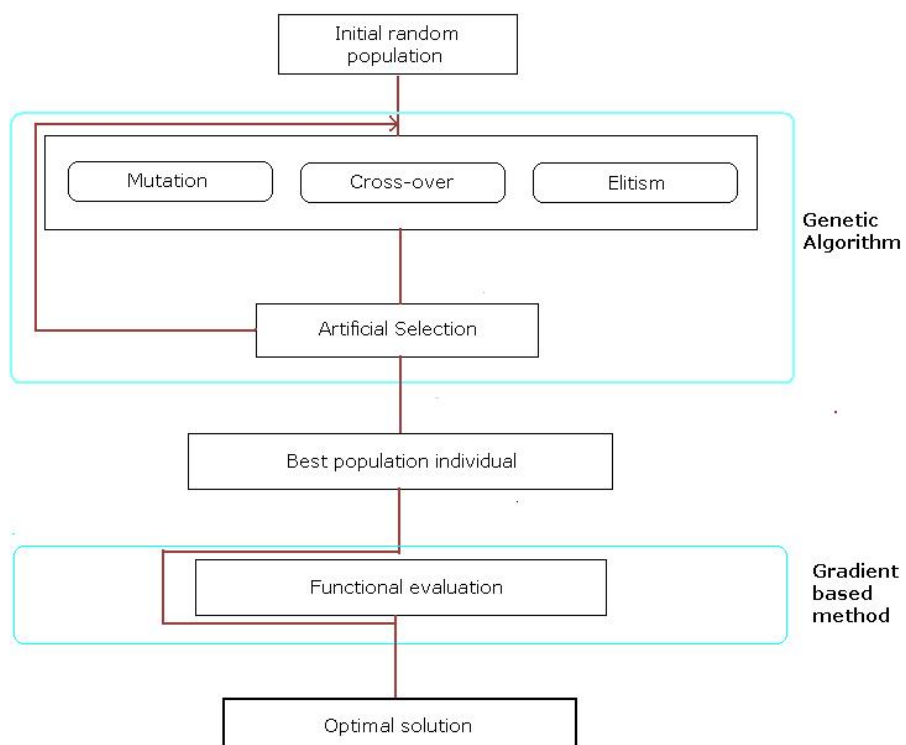
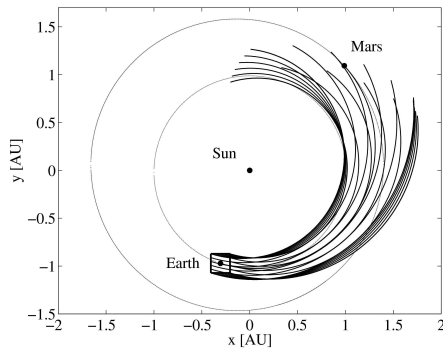
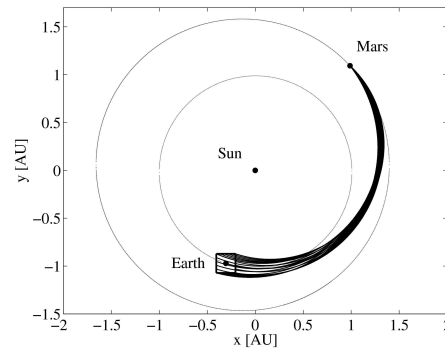


Figure 2.7: Hybrid algorithm flowchart



2.8.1: Evolution without corrections



2.8.2: Evolution with velocity corrections

Figure 2.8: Evolution of the boundary points[20]

## 2.5 Uncertainties analyses

One of the main aspect that have to be taken into account analyzing non linear systems is the uncertainty on boundary conditions and on the parameter set of the model considered. In this research highly non-linear systems are considered and one of the major obstacles is the accurate definition of the initial conditions. It is therefore necessary to attach to the nominal solution evaluated with the reference parameters and boundary conditions, a check in order to prevent mistakes in real scenarios. It is then possible to evaluate corrective scenarios in order to achieve the targets.

In the spacecraft trajectory design the lack of knowledge of the initial configuration of the system, the lack of available data, refer to a certain level of uncertainty. To prevent failure in real scenarios we can follow two strategies. The first refers to statistic and Monte Carlo methods, while the second one leads to differential algebra, no longer based on the evaluation of functions at specific points, but working on the function rather than its mere values [20].

In carrying out the research methods from the first class will be taken into account for problems related to immunotherapy, while the similar analysis for the optimization and design of interplanetary trajectories consider results obtained through differential algebra.

Considering the interplanetary transfer problem presented in the last section, it is possible to analyze a general statement that refers to the classic Lambert's problem. Given the initial position and the final position desidered the goal is to identify the conic arc that connects the two positions in a given time. Assuming an uncertainty on the initial position vector involving a maximum displacement of 0.1AU in [20] the propagation of the error is analyzed. Figure 2.8 shows the evolution of the error box without corrective actions and with correction

on velocity. This demonstrate that the application of the nominal solution into real scenarios can leads to solution that violate the constraints also in a simple TPBVP.



# Chapter 3

## Cancer immunotherapy

Tumor depends from the uncontrolled proliferation of clones of transformed cells and their diffusion in the entire organism (metastasis). The process starts from an evolutionary process which may give rise to abnormal DNA when a cell duplicates its genome due to defects in tumor suppressor or DNA mismatch repair genes [6]. The therapeutic task is to eradicate these diseased cells without any side effects on the healthy tissues. Conventional therapies against cancer (surgery, chemotherapy and radiotherapy) have gradually evolved over the years. These techniques increase the survival of patients, however, the percentage of patients treated not exceed the total of 45-50% [38, 39, 40, 41, 42].

In the last years the research is directed towards new less invasive techniques. Innovative anticancer strategies that, alone or combined with conventional, leading to enlargement of therapeutic possibilities. One possible strategy is the exploitation of the immune response. In 1909 Paul Erlich first suggested that the immune system defend organism from developing tumors, otherwise they would have been much frequent [37]. Until the end of the 20th century there was no concrete evidence of the cancer antigens existence or any measurable immune system response against cancer. Recently evidence has been shown in different situation[49]:

- spontaneous remissions of cancer without external treatment;
- the presence of immune system cells (monocytic, lymphocytic and plasmatic cells) in the neoplasia mass;
- the increased tumor growth in immunosuppressed patients.

The immune system is able to promote a response that can recognize, destroy cancer cells and maintain long-term memory, provided that the tumor antigens are recognized efficiently. Immunosurveillance is the term that describes the tendency of the immune system to prevent neoplasia.

The immune system acts with two different strategies against the guest: innate immune response and the adaptive or acquired immune response [37, 36].

Innate immune response is rapid but less specific than the second technique. In this category are included physicochemical barriers (e.g. skin and mucosa), blood proteins, phagocyte cells (macrophages, Dendritic cells [DC] and natural killer cells [NK]) and cytokines.

Adaptive immunity is more specific and consists in the ability to remember the previous existence of the pathogen and differentiate from self to non self. In this way the response to a repeated external agent attack can be more active and vigorous. In this category are included B and T cells. B cells are less important than T cell for the immune response. Scientific evidence supports the role of these cells [39]. Mice lacking the major components of the adaptive immune response (T and B cells) have a high rate of spontaneous tumors. In particular two major classes of T lymphocytes are involved in the dynamic interaction between cancer cells and immune system: CD8 and CD4 cells. CD4 are necessary to activate and sustain the survival of CD8 cells. The innate and the adaptive strategies are not mutually exclusive, but they can influence each other and they can work in parallel. Immune responses can be also divided into active response, induced by an exogenous antigen, or passive response. In the last case the foreign antigen is transferred through serum or lymphocytes from an immunized individual. The passive response typical of the models that will be presented later is unable to confer memory. The immune response is provided by different actors: lymphocytes, lymphokines/cytokines and antigen presenting cells. This differentiation is the most important in the analysis of the tumor immune system models, because several models describe the population concentration of these different categories. The effector cells or lymphocytes that act specifically against cancer are T cell, natural killer NK cells, Lymphokine activated cells LAK and K cells.

The lymphokines or cytokines are biological response modifiers or growth stimulating substances biosynthesized by certain immune cells. In particular Interleukin 2 is biosynthesized by a subset of the T cell called helper T cells.

The antigen presenting cells are responsible for presenting cancer antigens to T cells in order to control the immune activity. Tumor infiltrating lymphocytes TIL are an antitumor population that infiltrate in the growing cancer. The proliferation of the TIL cells is regulated through IL2.

### 3.1 Tumor development. Interaction between the immune system and cancer cells

In this section the development phase of the tumor is described. A knowledge on this topics permits an accurate analysis of the parameter that will be introduced in the control strategies. In particular it is possible to select initial guess solution taking into account the therapeutical limits. Considering the physical processes described through the equations it is possible to evaluate the dynamic behavior of the system.

The first step is the development of cancer cells in the human anatomy. In order to consider the most general phenomenon these cells could be immunogenic or non-immunogenic.

The cancer cells proliferate despite the immuno-surveillance activity provided by Natural Killer (NK) cells (which can kill cancer cells whether immunogenic or not).

The cancer cells grow above the subclinical threshold of  $10^3$  cells and reach  $10^9$  cells that is the X-ray detectable threshold [42]. During this period of development the unique contrast activity is provided by the immune system. When antigen-presenting cells, particularly macrophages, encounter the cancer cells they act in order to eliminate the foreign agent. They internalize the cancer cells and dissolve them into fragments called epitopes. These epitopes bear the cancer-associated antigens. The macrophages then exhibit the cancer antigens on their surfaces and circulate into the vicinity of helper T-cells and increase their awareness about the antigens. The antigen-sensitized helper T-cells then release the immunostimulatory growth substance called IL-2. The stimulus to the cytotoxic T-cell to mature and proliferate is given by IL-2. These subset of the T-cell are the direct responsible for the cancer killing.

The other important contribution made by Interleukin-2 is the enhancement of the proliferation of NK and LAK cells. These activated lymphocytes acts together in a search-and-destroy anticancer activity.

From clinical studies it appears evident that despite the response of the immune system there are other mechanisms or other phenomenon that can permits the growth of the neoplasia [40]. This aspect depends from several factors due to tumor and lymphocytes characteristics. Tumor should produce immunosuppressive factors or can show low antigenicity. The antitumor T cells should be insufficient, inadequate, tolerated by the tumor cells or they cannot enter inside the tumor (TIL cells).

We have identified the phase that describe the development of the immune system response. Focusing the attention on the tumor cells, their development follows four major phases according to [16]: the first phase occurs when normal cells mutate into tumor cells and begin dividing out of control; the second phase is

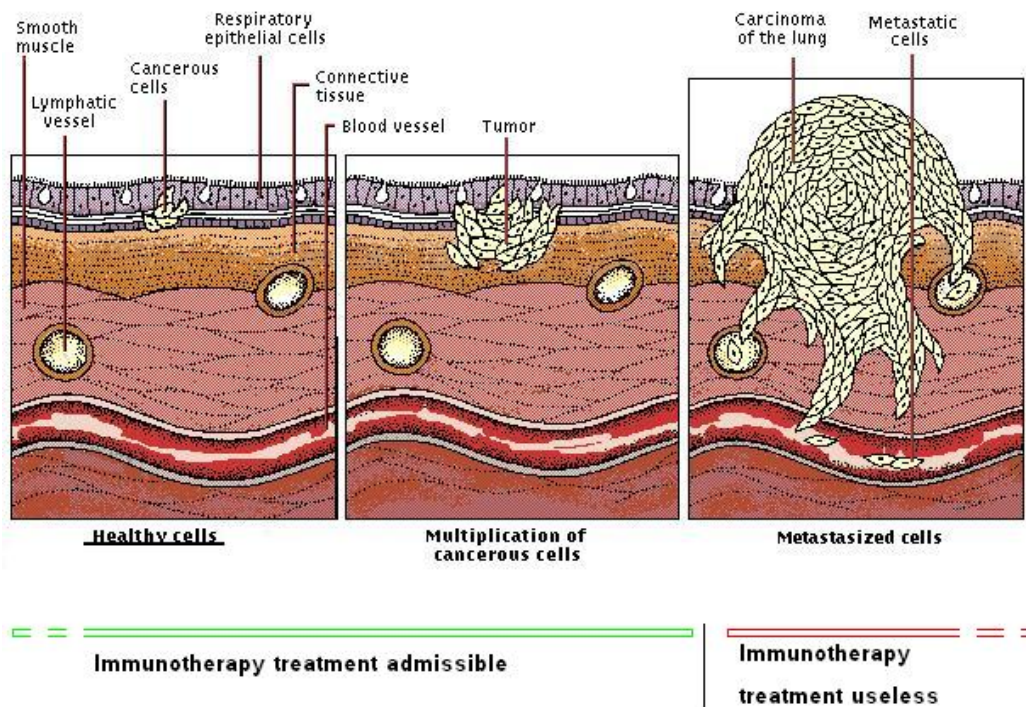


Figure 3.1: Melanoma development phases [modified from livingdhealth.com]

called carcinoma in situ and is classified by the presence of a tumor mass that has not yet invaded other tissues. This phase is limited by the nutrient flow to the tumor; if blood vessels can be induced to grow into the tumor (angiogenesis), the tumor will progress to the next phase, called the invasive stage; metastasis, or dissemination to other tissues, is the final phase.

### 3.2 Immunotherapy from dream to reality

The prospects of immunotherapy for clinical cancer have been kept bright for almost a century by promises and pretences that this notion indulges in people. Nowadays trends can be explained with two quotations from Dr. Weiss ‘The central hypothesis underlying all attempts at immunological intervention in neoplastic disease is today in danger of falling’ and ‘It is forbidden to despair’. These techniques must be not only a tool that restores the depression state of patient familiar, giving them a false hope to believe.

The section aims to identify the major steps in the cancer immunotherapy research. The progress in immunobiology and immunogenetics associated with experimental confirms about the existence of tumor antigens (TAA) are the precursors of the hypothesis of immunosurveillance [37]. This theory explain that the immune system constantly control the host cells in order to prevent malignant transformations.

The specific tumor antigens should stimulate the immune system that identifies the growing neoplasia and then it should eradicate these cells. This fact is due to an evolutive necessity as for the other common infections [37]. The immune system evolves recognizing the different cells and it takes actions to survive.

According to Thomas [37], also the organisms have evolved mechanisms of protection from cancer, similar to those that mediate allogenic rejection, thus maintaining the tissue homeostasis in complex multicellular organisms. The following considerations are natural consequences of this theory:

- The number of potential cancers is much higher than those that reach clinical observation
- The reducing at the current level is an output of the work of immunity cells
- Tumors that grow up becoming clinically obvious are cases in which the immune system have not worked

A series of experiments has been performed from the '70 in order to confirm this hypothesis. Initially experimental models of induced immunosuppression have been used [37] in order to explore the relationship between an immune system suppressed and the development of the tumor cells (figure 3.2).

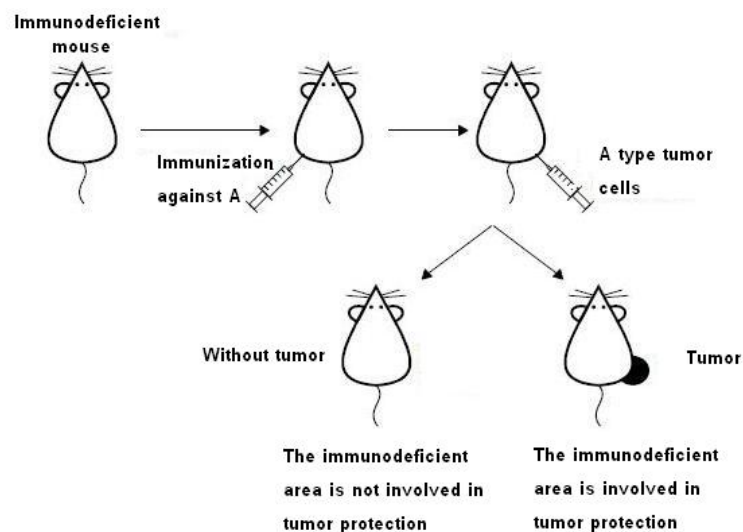


Figure 3.2: Experimental strategies with immunosuppressed animals [modified from [37]]

Results are discordant and show only that those animals which are immunocompromised have a greater susceptibility to infectious agents and, consequently, to tumors of viral origin and into tumors caused by stimulation due to chronic

lymphocytic deficiencies, but not to spontaneous tumors. Immunodepression has several effects also on human body. The human immunodeficiency can be congenital or acquired. In general in immunosuppressed patients does not change the impact of the "big killers" (colon carcinomas, lung, breast, prostate), but increases the incidence of lymphoid neoplasms and of viral origin tumors.

### 3.2.1 Clinical and experimental therapies

Immunotherapy can be viewed as an external help to the immune system in order to stimulate it and increase its performances. The immune system coordinates the interaction between the host cells and the protective cells when foreign cells are encountered. The purpose of the immune response is to restore the homeostasis state.

Unfortunately often the body natural defense not leads to a complete immune response, despite the presence of specific antigen. There are significant barrier to an effective antitumor immunity by the host. Many tumors can grow in immunocompetent hosts as can be seen from the number of people affected to advanced cancer state.

In order to decrease the immune tolerance to the tumor, in the last decades several immunotherapy approaches have been tried [38, 42]. In the first trials to increase the antitumor response, vaccines were made up of tumor cells killed, irradiated or also infected with the virus to increase its immunogenicity. Results were overall poor.

Since the eighties the knowledge on cytokines and the ability to dispose of recombinant products permit the study of their possible use as therapeutic agent [42]. The results encourage the research in this field despite the clinical limits.

Cancer immunotherapy can be referred with the use of cytokines usually together with an adoptive cellular immunotherapy (ACI). Cytokines are hormones that control the immune system.

Some cytokines biological activities can be used in tumor therapy such as:

- Enhancing the immune response against the tumor, through induction of antigen processing or stimulation of cells of innate and specific immunity.
- Inhibition of tumor angiogenesis.
- The proliferation stop of tumor cells, or the modulation of their profile of expression of membrane antigens

Unfortunately, this approach was accompanied by unacceptable toxic effects. As a result immunotherapeutic strategies focus their attention on the local admin-

istration of low amounts of cytokines [39], obtaining a high concentration in the only site of tumor growth.

Since the beginning of the nineties, with the improvement of knowledge about gene transfer, the concept of obtaining cell vaccines through the transduction of cytokine genes into cells tumor has evolved. These vaccines are expected to achieve a high local concentration of cytokines, maintaining low systemic concentration. The results have actually shown that toxic effects associated with this strategy are scarce, if not entirely absent [39]. In several models, both experimental and clinical, transduction of cytokine genes use as recipient normal cells, as tumor-infiltrating lymphocytes (TIL) or the same cells tumor [36].

The most obvious application of this approach is the therapeutic vaccination of patients already carrying the tumor to elicit an immune response able to eliminate it. Since it is known that the effectiveness of immune response is limited to small tumors, the best strategy could be the therapeutic vaccination of patients with minimal residual disease.

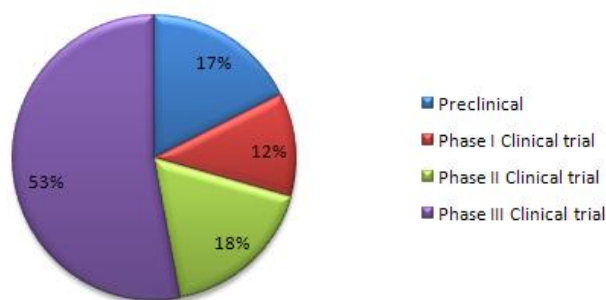


Figure 3.3: Immunotherapy drugs development [Source Informa UK 2006]

A number of successful immunotherapeutic agents are now under development (Fig 3.3); however, the majority are primarily in the early stages. Additional forms of experimental immunotherapy for stage IV patients with immune stimulant such as interleukin-2 are under studies. One of these is Proleukin a high-dose IL- 2-only regimen for the treatment of stage IV melanoma. Several experimental melanoma vaccines are also being tested in clinical trials in stage III and IV patients.

### IL-2 monotherapy

During the eighties several preclinical and clinical studies underscored sporadic but impressive tumor regression following the repeated and systematic administration of massive doses of cytokines such as interleukin 2 [42]. IL-2 has not

an active action on the cancer cells, but it is one of the major regulators of the immune reactions.

IL-2 is responsible for stimulating antigen-sensitized NK cells, cytotoxic T cells and LAK cells to develop into mature antitumor effector lymphocytes and also provides the growth stimulus for these lymphocytes to proliferate and create an effective attack against the tumor cells.

The results of the first clinical treatment with the administration of this cytokine were published in 1985. Two hundred eighty three patients with metastatic melanoma or metastatic renal cells who had failed standard treatment have been treated with a high dose of IL2 from 1985 to 1992 [42]. These clinical results presented in table 3.1 led to the approval of the interleukin treatment for metastatic melanoma or kidney cancer. A high dose IL-2 therapy can produce positive responses for 15-20% of metastatic melanoma and renal cells carcinoma with a durable complete response in 5-10% of patients. The treatment consists in the administration of IL2 intravenously every 8 hours with a concentration of 720000 cells/kg [42] [26]. This concentration was chosen to avoid exceeding certain levels of toxicity tolerated by the human organism.

Each treatment consists of 2 courses containing a maximum of 15 doses of IL2 drugs separated by 10 days of holiday. If after 40-50 days from the end of the cycle the patient shows a regression no further therapy are administered, and if the disease is stable the protocol is discontinued.

Diagnosis	Total	Complete regression	Partial regression
Melanoma	182	12	16
Renal cell cancer	227	21	22
Total	409	33	38

Table 3.1: Response of patients treated with interleukin 2 [40]

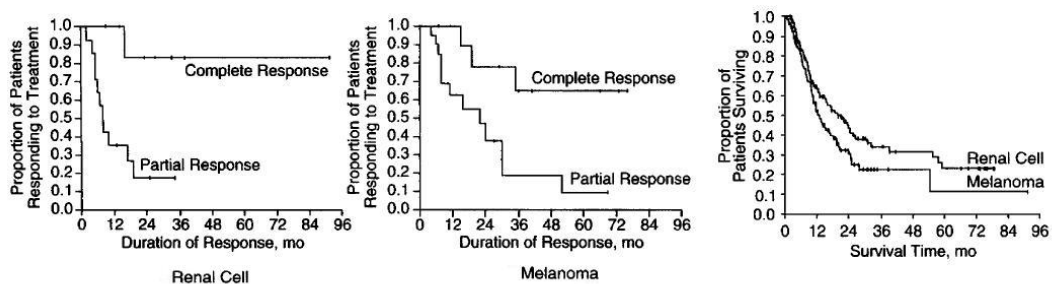


Figure 3.4: Duration of the response and proportion of patients surviving [42]

Figure 3.4 shows that the percentage of the patients that survive after 5 years is increased by 500% compared to the values mentioned in the introduction. Nowa-



day chemotherapy is the basic approach for cancer treatment. It acts reducing the growth factor of the tumor cells, but some tumors are considered highly resistant to this treatment. In fact some natural cells have high growth rate, such as the skin, the stomach, and mouth, these cells can be adversely affected by chemotherapy. Important clinical evidence states that the types of tumors for whom immunotherapy shows the best results are those resistant to chemotherapy. Administration of interleukin can be performed in combination with chemotherapy. Several studies have been made to optimize the combination of these two treatments with good results [26]. The choice to not consider the chemotherapy is mainly due to the fact that the treatment protocol is closely dependent on the patient and so the response. This makes unreliable and not generalizable the dynamic simulation.

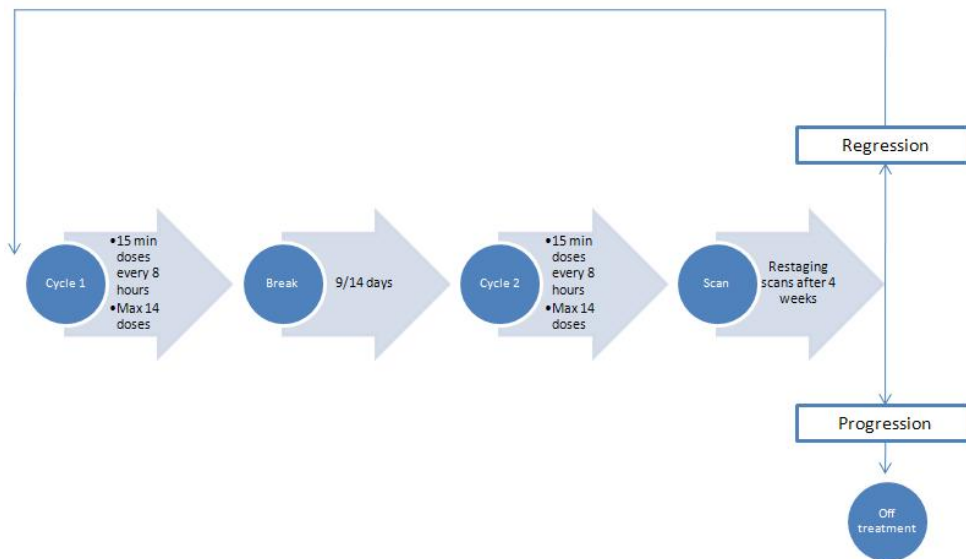


Figure 3.5: Typical IL-2 therapy standard treatment

Immunotherapy should be the primary choice for patient that can sustain high dosage of IL-2. The immune system stimulation can mediate the regression of the tumor mass. The major problem of this treatment is linked with a significant toxicity and no trascurable side effects. These side effects consist in cardiac problems that lead to hypotension, pulmonary edema, anemia, altered mental status, arrhythmias. Despite the toxicity of this treatment, it has led to a mortality of 0.7% [42] and all the side effects are reversible in the short period. It is to emphasize that few can tolerate the maximum dosage and administration so close together. It thus appears the need to propose a new protocol of treatment widely supported by the patients that exploit the knowledge of the dynamics of the phenomenon. Some studies have shown that administration of lower doses of IL2 can lead to regression of tumor cells. ”“There have been considerable efforts aimed at reducing the frequency and severity of IL2, and these will require further

clinical investigation before they can be recommended”[36].

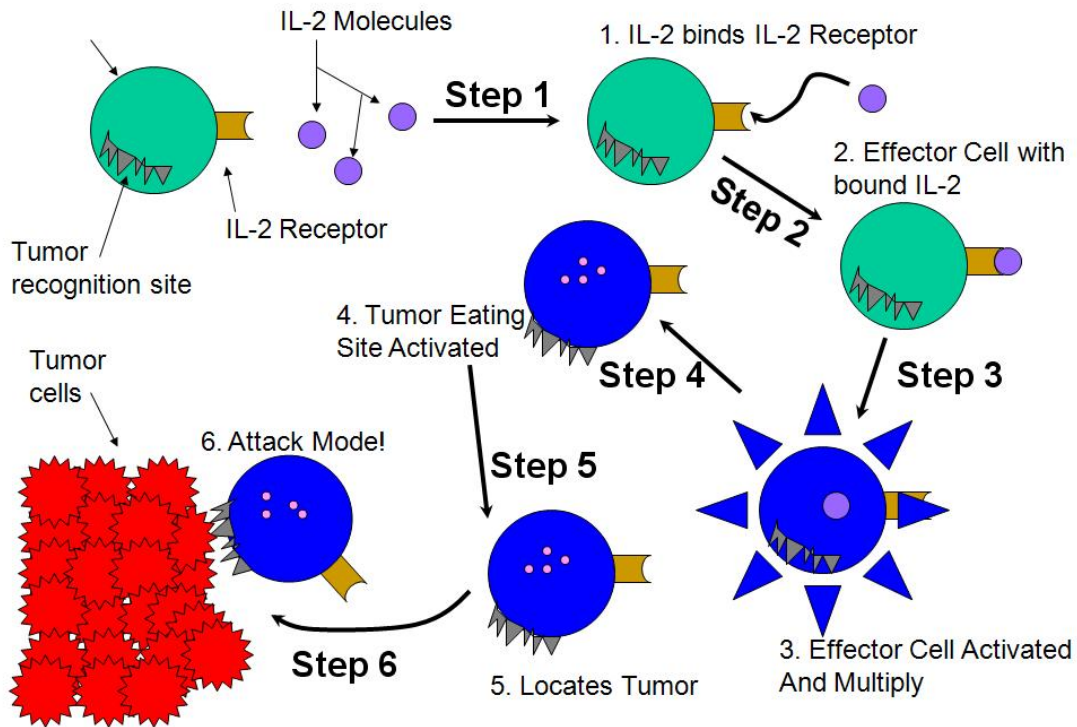


Figure 3.6: Immunotherapy process

### Cell transfer therapy

This therapeutic technique consists in the infusion in the patient of in vitro selected lymphocytes that show a high sensibility to the specific tumor. In particular these lymphocytes are genetically modified in order to express anti-tumor T cell receptors

This kind of passive therapy do not depends upon the activation properties of the tumor (tumor antigenicity activate the immune system response). The cytokine administration and the cells transfer are not mutually exclusive; indeed it is possible to encourage the development of highly specific cells in an IL2 environment. The standard IL-2 protocol is similar to the previous described in the high dose monotherapy. Different studies analyzed a low dose treatment in order to decrease the side effects [39]. The amount of cells that a patient receive during the entire treatment is  $> 10^{10}$ .

It has been demonstrated experimentally [38, 40, 39] that a lymphocytes depleting chemotherapy pretreatment eliminates lymphocytes near the tumor site that are contrary to the transplanted cells. In this way the rate of survival of specific cells transferred increases significantly. These suppressive factors limit the effectiveness of stimulants such as IL-2 and probably are the causes of ineffective cancer vaccines. As a matter of fact IL-7 and IL-15 detectable near the tumor

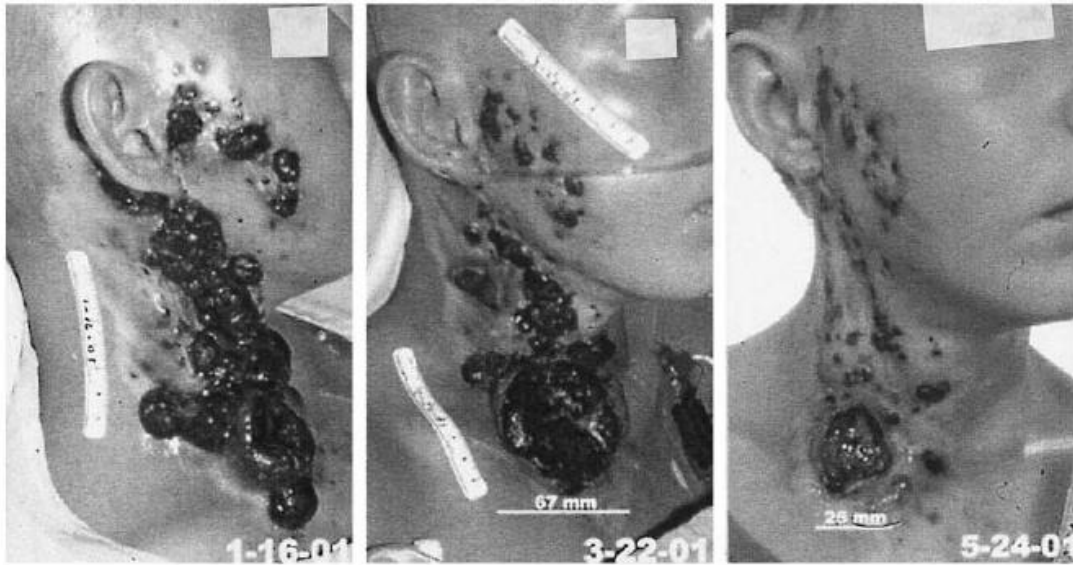


Figure 3.7: Regression of cutaneous metastases following sequential treatments in a patient with melanoma [40]

site act in a sort of competition. The presence of a huge number of T cell near the tumor site is not sufficient to determine a tumor regression. This aspect is strictly dependent on the local tumor microenvironment and in particular on down regulation mechanisms that are not clear nowadays [41]. Many mechanisms regulating the interaction between the immune system, cancer growth and therapeutic control strategy are closely dependent on mechanisms not described in the dynamic models considered. Although this it is possible to obtain a valid simulation considering as initial condition a state of lymphodepletion that means low concentration of the immune system cells.

The number of the objective response depends from the previous treatment of lymphodepletion but at least 30% of the patients have an objective durable response [39].

A future development of the dynamic models must take into account the use of the adoptive cell therapy, not only because this is nowadays the best treatment for patients with metastatic melanoma [39], but because this therapy should be applied to many different kind of cancer. This treatment is very effective in the control and regulation of the tumor regression in 50-70% of the cases [41], doubling the percentage obtained with IL2 monotherapy.



# Chapter 4

## Panetta-Kirschner model

The research in the immunotherapy modelisation is a continuous balance between clinical and experimental data and the construction of a mathematical model capable of representing the real behavior of the system. With this tool it is possible to study and analyze in depth the phenomenon, predicting the real life observation and define possible therapeutic strategies that can lead to the results required. One of the first attempts to consider the effects of the interaction between tumor-immune system-immunotherapy was made by Panetta and Kirschner [28]. Before starting in the description of the dynamics model, it should be stressed that all the models considered can be valid only for early stages of tumor growth when the processes of invasion and metastasis are not of critical importance.

Panetta-Kirschner model takes into account the interactions between three different populations:

- Activated immune system effector cells  $x(t)$ ;
- Tumor cells  $y(t)$ ;
- Cytokine Interleukin-2  $z(t)$ ;

The model is as follows

$$\begin{aligned}\frac{dx}{d\tau} &= cy - \mu_2x + \frac{p_1xz}{g_1+z} + s_1 \\ \frac{dy}{d\tau} &= r_2y(1 - by) - \frac{axy}{g_2+y} \\ \frac{dz}{d\tau} &= \frac{p_2xy}{g_3+y} - \mu_3z + s_2\end{aligned}\tag{4.1}$$

The immunotherapy is studied considering the inflow of both IL-2  $s_2$  and adoptive cells  $s_1$ .

The first equation describes the effector cells population. The growth of these cells are stimulated by the presence of the tumor and by the stimulation by IL-2. The tumor influences the rate of change of the effector cells with its antigenicity

Parameter	Description	Value	Unit
$c$	antigenicity of the tumor	[0-0.05]	days <sup>-1</sup>
$\mu_2$	Inverse of the effector cells lifespan	0.03	days <sup>-1</sup>
$p_1$	Effector cells proliferation term	0.1245	days <sup>-1</sup>
$g_1$	Michaelis constant	$2 \times 10^7$	vol
$g_2$	Michaelis constant	$10^5$	vol
$r_2$	Logistic equation parameter	0.18	days <sup>-1</sup>
$b$	Logistic equation parameter	$10^{-9}$	vol
$a$	Strength of the immune response	1	days <sup>-1</sup>
$\mu_3$	loss/degraded rate of IL-2	10	days <sup>-1</sup>
$g_3$	Michaelis constant	$10^3$	vol

Table 4.1: Parameters of Panetta-Kirschner model

( $cy$ ). The stimulation by IL-2 is described with a term of Michaelis-Menten<sup>1</sup> form that takes into account the saturation of the immune system.  $s_1$  represents the control term that describes the injection of effector cells such as LAK or TIL cells. LAK cells are obtained from in vitro culturing of blood leukocytes removed from patients with high concentration of IL-2, while TIL cells are obtained from lymphocytes recovered from the patient tumors, which are then incubated with high concentration of IL-2 in vitro. The natural death of these cells is represented through a term that depends from the inverse of the average life of the effector cells ( $\mu_2 x$ ).

The second equation describes the tumor cells behavior. A logistic term describes the rate of change of tumor cells. The interaction between the tumor and the immune system response is described with a Michaelis-Menten term that depends from the strength of the immune response ( $\frac{axy}{g_2 + y}$ ). This term indicates the limited immune system response.

The third equation describes the rate of change for the concentration of IL-2. The tumor cells stimulate the effectors cells to produce IL-2. This aspect is described with another Michaelis-Menten term that takes into account the self limiting production of IL-2 ( $\frac{p_2 xy}{g_3 + y}$ ). As for the effectors cells there is a term that describes the degradation rate.  $s_2$  is the treatment term that consists in the external input of IL-2.

The model behavior strictly depends on the antigenicity of the tumor. Antigenicity is the property of a substance to act as an antigen and in this way to stimulate the immune system and activate effectors cells. In a patient that shows low antigenicity the response of the organism tends to a tumor regime state. The growth

<sup>1</sup>Michaelis-Menten equation describes enzyme catalytic reactions in physiological process [source wikipedia]

of the tumor cells is rapid and the trend is monotone with a magnitude near its carrying capacity. Setting  $c = 0.02$  a stable limit cycle is shown in figure 4.2. The tumor is detectable only during some small time intervals. The magnitude of this case is in order of 10% of the tumor carrying capacity.

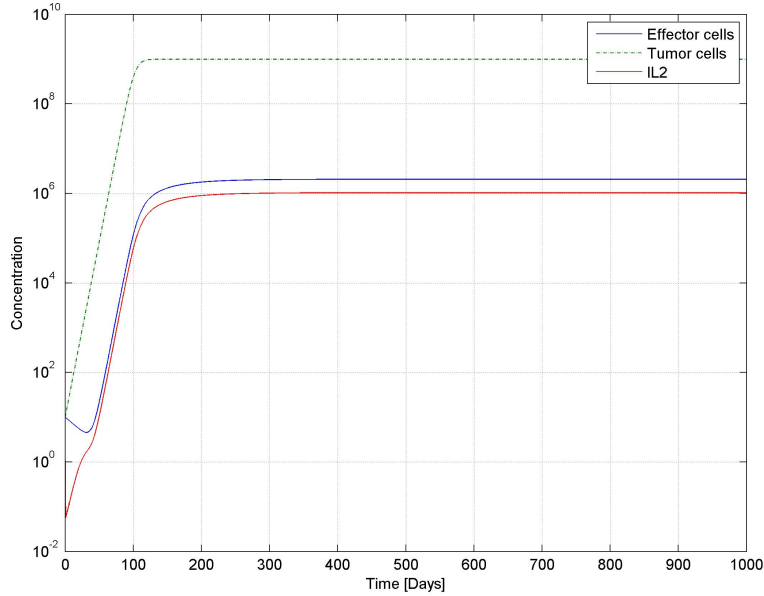


Figure 4.1: System variables without controls. Tumor carrying capacity is scaled to  $1e+5$ . Antigenicity is set as  $c=5e-5$

With value of the antigenicity set to 0.035 the oscillations of the system become small and damp out quickly. The system appears hard to control in the cases with low antigenicity, because growth is rapid and takes place from the early days even when the tumor is not detectable.

The dynamics of the system is strictly dependent on the parameters choice. The parameters vary not only for the specific cancer considered, but also from one individual to another. The parameters used in the following analysis are the most typical [28] and are reported in table 4.1. The solution of the optimal control problem has been evaluated in a nominal condition, and only with a statistic analysis on the variation of both the initial values and on the parameter it is possible to evaluate the robustness of the strategy.

A sensitivity analysis has been done on the model parameters in order to identify the component of the model that influences most significantly the final tumor concentration after a system evolution of 100 days. Each parameter was perturbed from the nominal value by 1%, and the variation of the final tumor concentration was evaluated. In the nominal condition the value of the antigenicity has been set at the value  $5e-5$ . The results of this parameter sensitivity analysis are shown in figure 4.4. The system is most sensitive on the parameter of the logistic equation

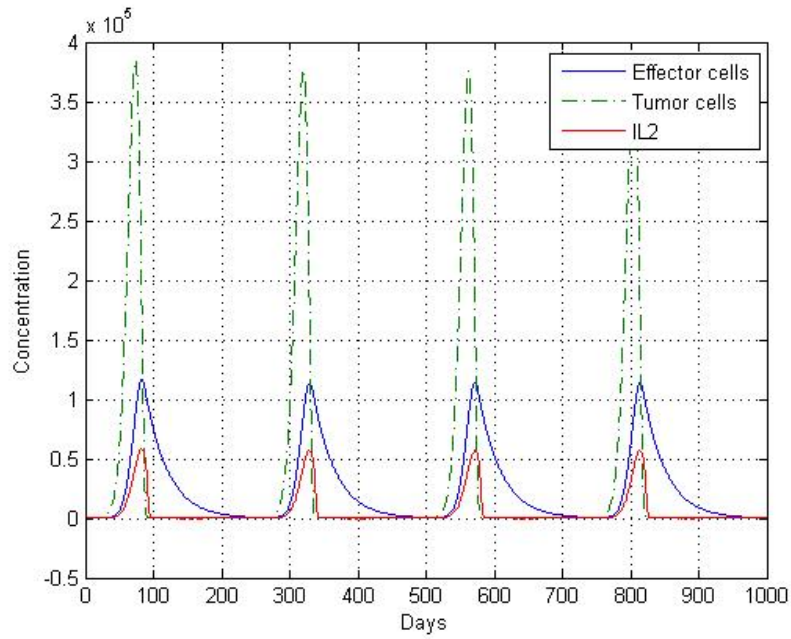


Figure 4.2: System variables without controls. Tumor carrying capacity is scaled to  $1e+5$ . Antigenicity is set as  $c=0.02$

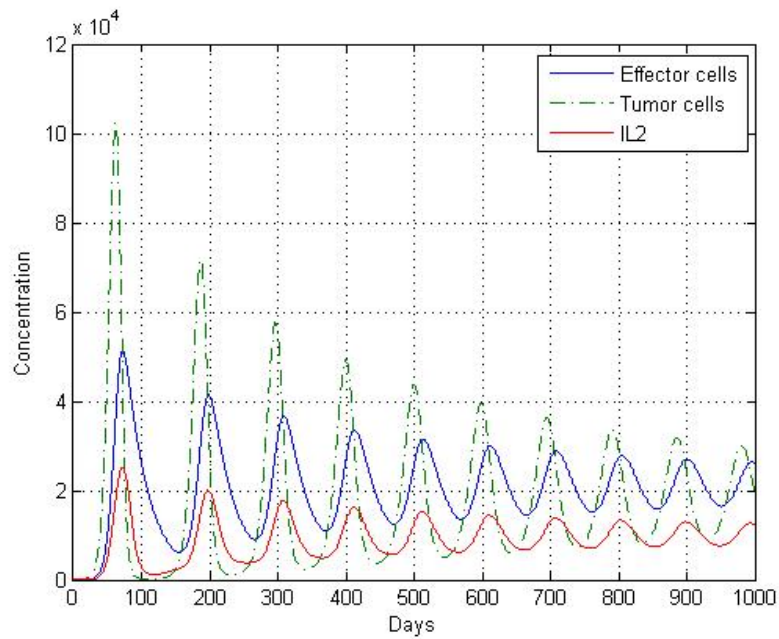


Figure 4.3: System variables without controls. Tumor carrying capacity is scaled to  $1e+5$ . Antigenicity is set as  $c=0.035$





Figure 4.4: Parameters sensitivity analysis

that represents the growth model of the tumor. This aspect suggests that the aggressiveness of the tumor is the main factor that influences the clinical therapy. Less important appear the factors representing the immune response. The system is not sensible to small variation of the tumor antigenicity, thus in contrast with high variation that can determine a completely different dynamic behavior of the system if sufficiently far from bifurcation points.

The previous figures show the behavior of the system without control, it is also important to analyze the system dynamics considering the actual standard treatment therapy (see figure 4.5). Analyzing an IL2 monotherapy with doses of 720000 I.U/kg administered following the scheme presented in figure 3.5 the results are shown in figure 4.6 et 4.7.

In presence of a tumor with antigenicity less than the value 0.02, the treatment is inefficient. The results are essentially side effects due to toxicity of the drug and the tumor shows a stable progression. The standard treatment appears to be ineffective in stimulating the immune system. It is necessary to evaluate different treatment strategies to obtain favorable results. These strategies will then be subsequently verified experimentally, but certainly a numerical evaluation can also serve as a spin off to study new therapeutic strategies.

Despite these results the outcome are completely different for a patient with antigenicity higher than the value 0.02. After the first treatment cycle the tumor cells reach their maximum peak of concentration and then in the break period they start a rapid decreasing. The second cycle is useless, because the immune system reach the concentration required to eradicate the tumor.

The standard therapy appears to be effective for patients with higher value of antigenicity, and the structure of the treatment appears related with the tumor-immune system dynamic. To sum up the result shows two completely different biological outcomes:

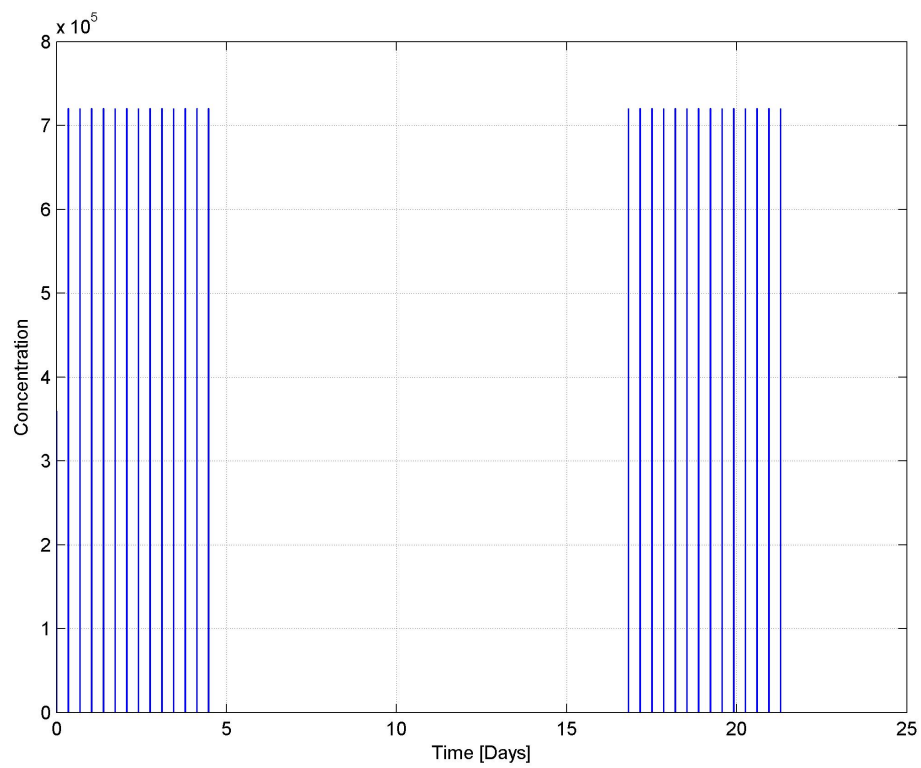
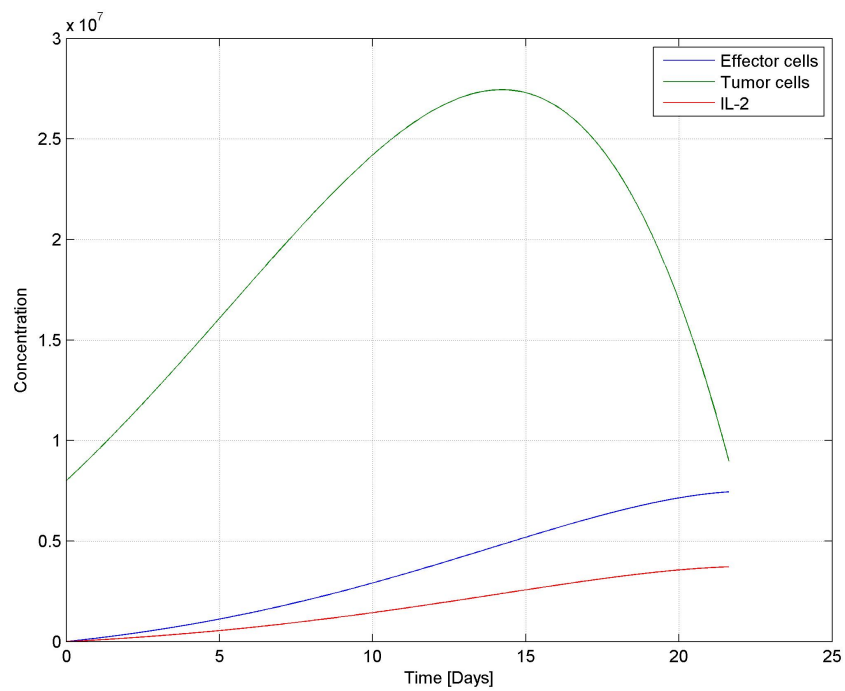


Figure 4.5: Standard drugs therapy

Figure 4.6: System dynamics with standard treatment therapy. High antigenicity  $c=0.035$

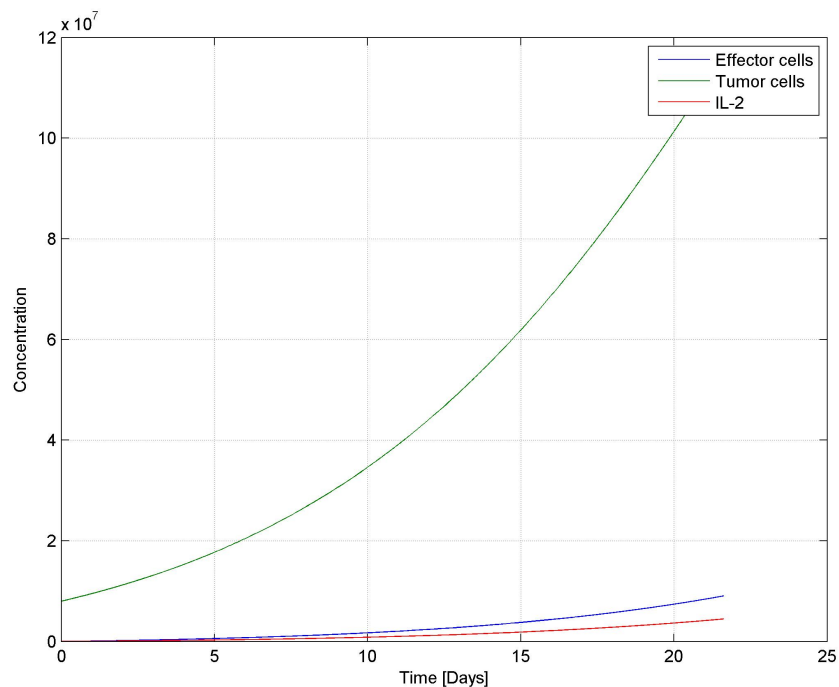


Figure 4.7: System dynamics with standard treatment therapy. Low antigenicity  $c=5e-5$

- the effective action of the immune system ends up with the destruction of the aggressive host;
- the ignition of the immune system ends up with an uncontrolled growth of the immune system cells concentration.

Particular attention is required for low value of antigenicity. These cases must be analyzed in order to define a strategy that can permit the eradication of the neoplasia or in the worst cases an increment of the expected life time. In Panetta-Kirschner the dynamics of the controlled system is considered, and one of the main considerations about monotherapy is that if IL-2 administration is low, there is no tumor free state. However if the IL-2 input is high, the tumor can be cleared but the immune system grows without bounds. This aspect is related with a constant rate of administration. The following analysis aims to clear the tumor limiting the immune system growth. An optimal control therapy will be presented, but only as a prologue for the next chapter in which a more detailed model will be analyzed. In fact the PK model was developed in order to analyze the tumor dynamics and not specifically for describe the immunotherapeutic therapy and an optimal control problem.

## 4.1 Equilibrium points

This section aims to identify the dynamic properties of the PK system. In particular the attention is focused on the existence of equilibrium points. From the therapeutical point of view the existence of stable free tumor state equilibrium leads to a permanent response to the therapy protocol. This aspect may not only increase the expectancy of life, but it can also means a complete tumor regression. The first step is the identification of the equilibrium points. A generic nonlinear system could have a number of equilibrium points starting from zero to infinity [10].

In order to identify all the variety of equilibrium point of  $\mathbf{F}(\bar{\mathbf{y}}(t), \mathbf{u}(t), t) = \mathbf{0}$  a numerical procedure has been implemented. An initial values grid has been created. This one respect the condition  $\mathbf{y}_0 \in D$  where  $D$  is the admissible domain. In this way it is possible to explore all the attraction regions. The equilibrium points vector  $\bar{\mathbf{y}}$  must be positive definite in order to respect the physics of the problem. The positivity of the solution is due to the Yang lemma [5] if the initial solution  $\mathbf{y}_0$  is such that  $\mathbf{y}_0 \in \mathbb{R}_+^3$ .

The roots of the equation  $\mathbf{F}((t), \mathbf{u}(t), t) = \mathbf{0}$  has been evaluated using a solver that is an implementation of the Trust-Region Dogleg Method. In brief this technique aims to increase the robustness of the Newton method when starting far from the solution and it consists in the minimization of a functional cost that evaluate if the solution obtained at the current iteration is better than the previous. An example of this functional implemented in the Matlab function `fsolve` is

$$\min_d f(d) = \frac{1}{2} F(x_k + d)^T (F(x_k + d)) \quad (4.2)$$

In order to identify the dynamic properties of the system we have to identify the analytic Jacobian matrix, in this way the next step is the evaluation of the stability of the equilibrium points indentified. The Jacobian matrix of the PK system is

$$\mathcal{J} = \begin{pmatrix} -\mu_2 + \frac{p_1 y_3}{g_1 + y_3} & c & \frac{p_1 y_1 g_1}{(g_1 + y_3)^2} \\ -\frac{\alpha y_2}{g_2 + y_2} & r_2 (1 - 2b y_2) - \frac{\alpha y_1 g_2}{(g_2 + y_2)^2} & 0 \\ \frac{p_2 y_2}{g_3 + y_2} & \frac{y_1 p_2 g_3}{(g_3 + y_2)^2} & -\mu_3 \end{pmatrix}$$

In order to evaluate the stability of the system we have to evaluate the eigenvalues of the Jacobian matrix at each equilibrium points. In particular the analysis has been made for different values of the parameter  $c$  as specified in [28]. As the parameter change the trivial solution is always a saddle point. It is possible to divide the dynamical behavior of the system in three relevant cases:

1.  $c = 5e-5$ . In this case two different unstable areas are identified with different physic characteristics. The variable that represents the tumor cells

assumes values at the extreme of the domain. These ones represent the two main states: tumor free or tumor regime. A stable region is localized with high value of the tumor cell concentration (major than 0.98) near the carrying capacity. The initial grid must be accurate enough to identify this singular point.

2.  $c = 0.025$ . With this value of the parameter all the stable regions disappear. All of the unstable singularities are in the region tumor free.
3.  $c = 0.04$ . The unstable region remains similar as with the previous value of the parameter. There is a stable region with high values of the three variables; this means a tumor regime state.

From the results (Figures 4.8 - 4.10 ) we cannot say anything about the future evolution from the unstable points. It is impossible to say a priori that starting from an unstable equilibrium point we will reach a tumor-free or a tumor-regime state.

A condition required for the presence of free-tumor equilibrium states can be evaluated considering planar equilibrium.

In particular the x-z planar equilibrium is

$$\left( \frac{s_1 (g_1 \mu_3 + s_2)}{\mu_2 (g_1 \mu_3 + s_2) - p_1 s_2}, 0, \frac{s_2}{\mu_3} \right) \quad (4.3)$$

and exists if

$$\mu_2 > \frac{p_1 s_2}{g_1 \mu_3 + s_2} \quad (4.4)$$

A simple consideration leads to the fact that with the IL-2 monotherapy ( $s_2 = 0$ ) it is possible to reach a tumor clear state, while considering a general therapy no further considerations can be done. Another important consideration from the planar equilibrium with tumor free state is that it is possible to have equilibrium with zero tumor cells different from the trivial solution in case of therapeutic treatment.

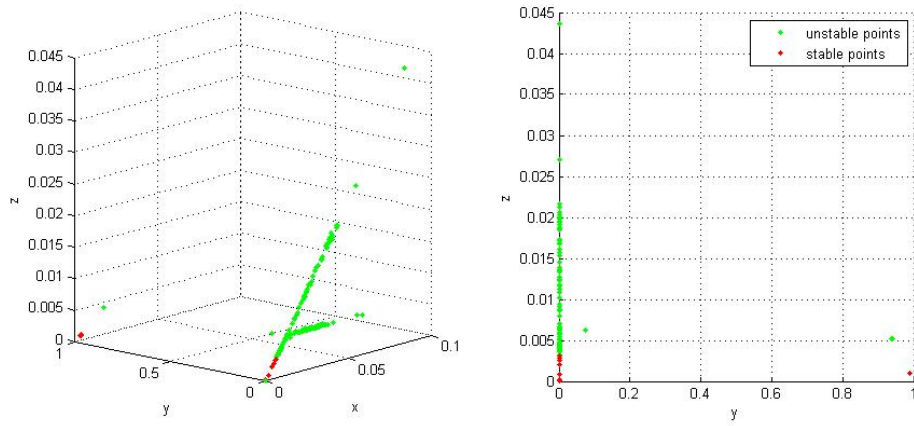


Figure 4.8: Equilibrium points  $c= 5e-5$  with an initial grid of  $50^3$  points

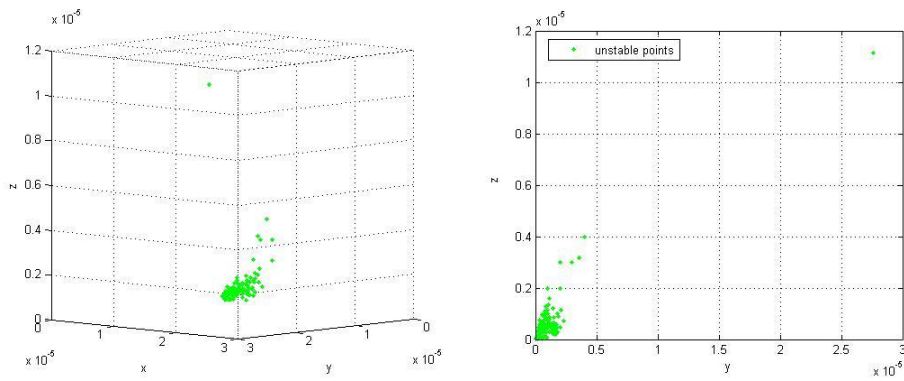


Figure 4.9: Equilibrium points  $c= 0.025$  with an initial grid of  $10^3$  points

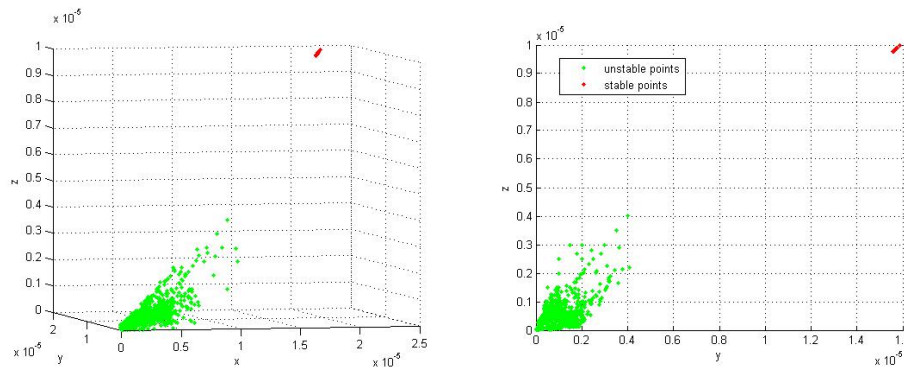


Figure 4.10: Equilibrium points  $c= 0.04$  with an initial grid of  $20^3$  points

## 4.2 Optimal control Problem

The goal of the control is to identify the correct scheduling and dose of the drugs in order to decrease the tumor mass. The dynamics of the PK model in a compact explicit form is written as

$$\dot{\mathbf{y}} = \mathbf{f}(\mathbf{y}(t), \mathbf{u}(t)) \quad (4.5)$$

where  $\mathbf{f}$  stands for the vector field of the PK system,  $\mathbf{u} = \{s_1, s_2\}^T$  is the drugs injections and  $\mathbf{y} = \{x, y, z\}^T$ . We need to identify a functional cost  $F$ . The first step is to use Mayer form trying to minimize the final tumor concentration

$$F = \Phi(y(t_f)) \quad (4.6)$$

where  $\Phi(y(t_f))$  is equal to  $y(t_f) - \rho = 0$  and  $\rho$  is equal to zero.

This solution poses no limits on the controls and contains no costs related to the dynamic evolution of the systems. The solution prescribed in [14] defines costs related with the treatment process and considers a running cost on the tumor cells aims to make the control active against the tendency of a uncontrolled tumor to growth to its tumor regime state.

We consider this performance index as a first step of the optimization, because both the constraints and the problem are well-posed. Analyzing the results obtained with this cost, which identify the primary target, we can improve the cost to be minimized after an accurate analysis of the results obtained from 4.6.

### Boundary conditions

In general in a minimization problem we have to define initial and final conditions. In particular almost every astrodynamics trajectories design problems defines an initial orbit, e.g. LEO parking orbit, thrust arc, and a final target orbit. This final condition must be satisfied in order to accomplish the mission. Think about a rendez-vous problem the accuracy of the final position is one of the main targets. In an immunotherapy optimal control problem this aspect is a little more different. The initial conditions are defined by the healthy state of the patient. These initial conditions can be also defined as an output of a previous treatment. Clearly every patient has different initial conditions and the final optimal protocol in general is not good if considering a different subject. We select a possible scenario in which the patient have an amount of  $8 \times 10^6$  tumor cells after a surgical treatment as in [26]. The other conditions are left free to the optimization; this because this model does not describes the dynamics of the different types of immune system cells. It considers only a term that describes only in general the dynamic behavior of the immune system. With this level of approximation is not required to define an accurate initial condition, while in the following model we will impose all the

values from literature. The formalization of the initial boundary condition can be written as

$$\phi_i : y(0) - 8 \cdot 10^{-6} = 0 \quad (4.7)$$

where  $\phi_i$  is a scalar.

As a difference from a classical astrodynamics problem in trajectory design the final conditions are not specified. This because the final tumor condition has to be minimized, and the other state variables can assume every values that are in their admissible domain  $\mathcal{D} \in [0, 1]$ . This assumption is verified with the introduction of lower and upper bounds on the state  $\mathbf{y}$ . The vector of lower and upper bounds for the adimensional problem is respectively a vector of zeros and a vector of ones.

### 4.2.1 Direct transcription formulation via collocation

The optimal control problem can be view as a time discretization of the continuous problem. Time is divided with a grid of N points in order to define N-1 intervals. For each phase it is possible to define a vector of variables defined as

$$\mathbf{x}^T = (x^{(1)}, y^{(1)}, z^{(1)}, s_1^{(1)}, s_2^{(1)}, \dots, x^{(N)}, y^{(N)}, z^{(N)}, s_1^{(N)}, s_2^{(N)}) \quad (4.8)$$

The respect of the differential equations of the system can be reached with an approximation. We use the Hermite-Simpson method in order to define n(N-1) defects equation :

$$\varsigma_k = \mathbf{y}_{k+1} - \mathbf{y}_k - \frac{h_k}{6} \left( \mathbf{f}_k + 4\hat{\mathbf{f}} + \mathbf{f}_{k+1} \right) \quad (4.9)$$

where  $\mathbf{y}$  is the n=3 rows vector of the system variables, and  $\mathbf{f}_k$  is the right-hand-side of the system equation evaluated at each phase k.  $\hat{\mathbf{f}}$  is defined as

$$\begin{aligned} \hat{\mathbf{y}} &= \frac{\mathbf{y}_{k+1} + \mathbf{y}_k}{2} + \frac{h_k}{8} (\mathbf{f}_k - \mathbf{f}_{k+1}) \\ \hat{\mathbf{f}} &= \mathbf{f}(\hat{\mathbf{y}}, t_k + h_k/2) \end{aligned} \quad (4.10)$$

Considering the initial boundary condition we can define a nonlinear constrain vector as:

$$\mathbf{c}(\mathbf{X}) = \{\phi_i, \varsigma_1, \dots, \varsigma_{N-1}\}^T \quad (4.11)$$

As said previously, one of the advantages of the direct transcription method is that it can be carried out avoiding the explicit derivation of the necessary conditions for the optimality. Such feature makes the method appealing for complicated applications and assures versatility and robustness. Furthermore, this procedure, in contrast to indirect methods, does not need to deal with the Lagrange multipliers, whose lack of physical meaning makes very difficult to find appropriate initial guess solutions.



In summary the NLP problem states to find the optimal vector  $\mathbf{x}$  that is the solution of

$$\min F(\mathbf{x}) \quad (4.12)$$

subject to  $\mathbf{c}(\mathbf{x})=0$ .

Where  $F(\mathbf{x})$  is the objective function translated in the formalism of the direct transcription as

$$F(\mathbf{y}) = y_N - 0 \quad (4.13)$$

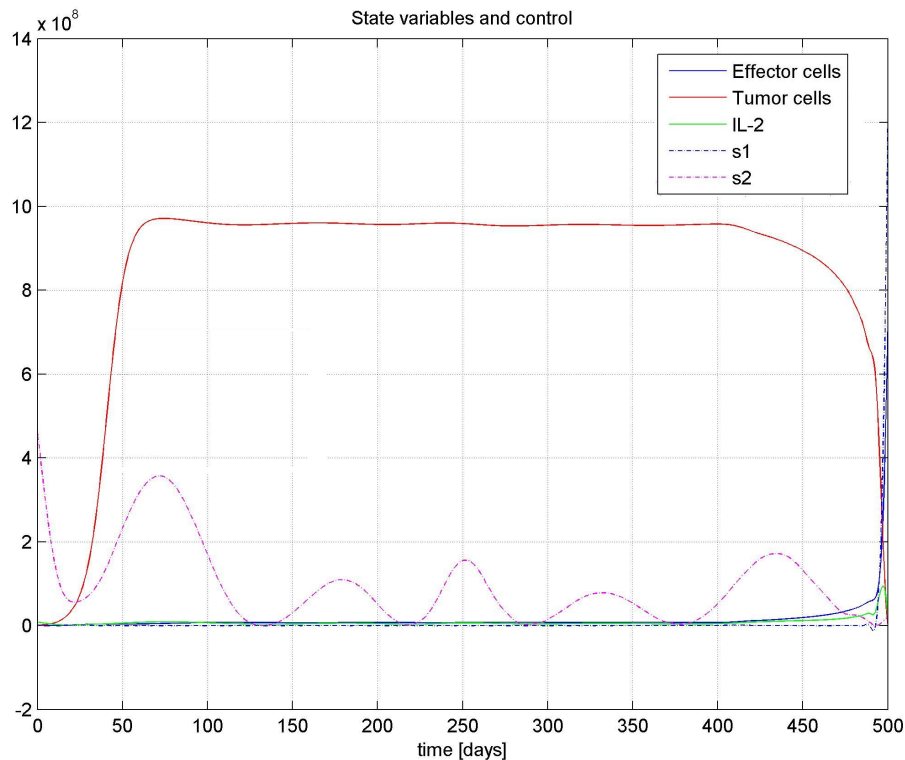


Figure 4.11: States and controls. Minimization of tumor cells at therapy conclusion.

Figure 4.11, obtained with a uniform mesh of 133 points, confirms the results predicted in [28]. The case analyzed is a low antigenicity tumor with  $c=5e-5$ . The choice of this value for the antigenicity is due to the fact that this is the worst condition possible. From the figures that show the trend of the free system dynamics this is the worst scenario for the control. Low input of controls are not sufficient to contrast the tumor growth and to decrease the final tumor mass. With large amounts of administrated IL-2, the tumor is cleared but the immune system grows unbounded as the IL-2 concentration reaches a steady-state value. The optimization does not have any constraints on the control maximum values and this aspect can be seen in the final period of treatment. This uncontrolled growth of the immune system represents a side effect explained in the previous

section. The control acts with success only at the end of the treatment, leaving the cancer constant for the most part of the protocol. This is related to the path constraints on the system variables that limit their growth.

It seems that without an adequate concentration of LAK or TIL cells injected, the IL-2 administration during the first stage of the treatment is not sufficient to defeat the tumor. Recent studies [39] are in perfect agreement with this result, confirming that the best immunotherapeutic treatment consists in the cells transfer. With the functional 4.13 the optimal solution tends to increase the concentration of effector cells to infinite. The solution obtained is due only to the fact that this variable is limited, and a solution that leads to a growth of these immune system cells at the beginning or in the middle of the treatment tend to be an unfeasible solution. The goal is to limit these effects in order to reach a real minimum. The solution obtained, despite it leads to zero the final tumor cells concentration, appears to be completely unsatisfactory.

In order to reduce this side effect a term that takes into account the total amount of drugs administered during the therapy has been added to 4.13.

The new performance index can be defined as:

$$F(\mathbf{x}) = \Phi(y(t_f)) + w \int_{t_f}^{t_0} \mathbf{u}(t)\mathbf{u}^T(t)dt \quad (4.14)$$

where  $w$  is a weight that can tune an appropriate balance between the two contrasting objective.

Considering Lagrange formulation of the functional leads to an integral computation by numerical quadrature once the controls  $u_j$ ,  $j = 1, \dots, N$  are given.

Using as initial guess solution the one obtained with the previous functional, figure 4.12 and 4.13, show the dynamic behavior of the controlled system and the control variables respectively.

The tumor in the first phase of therapy from the initial concentration underwent a considerable decrease. In this period the initial population of cells of the immune system performs this task. In fact, the aid provided by the external control is minimal.

When the cells of the immune system cannot effectively carry out their action of contrast, cancer cells start to grow. As a result, the control, in particular the administration of LAK or TIL cells begins to increase. Their action is only useful when the tumor cells have reached a concentration approximately equal to half the initial one.

The treatment protocol begins a new period lasting 200 days, in which the control action performs the task of maintaining nearly constant the concentration of tumor cells. The tendency to growth of the tumor is countered by a further increase of adaptive cells implanted.

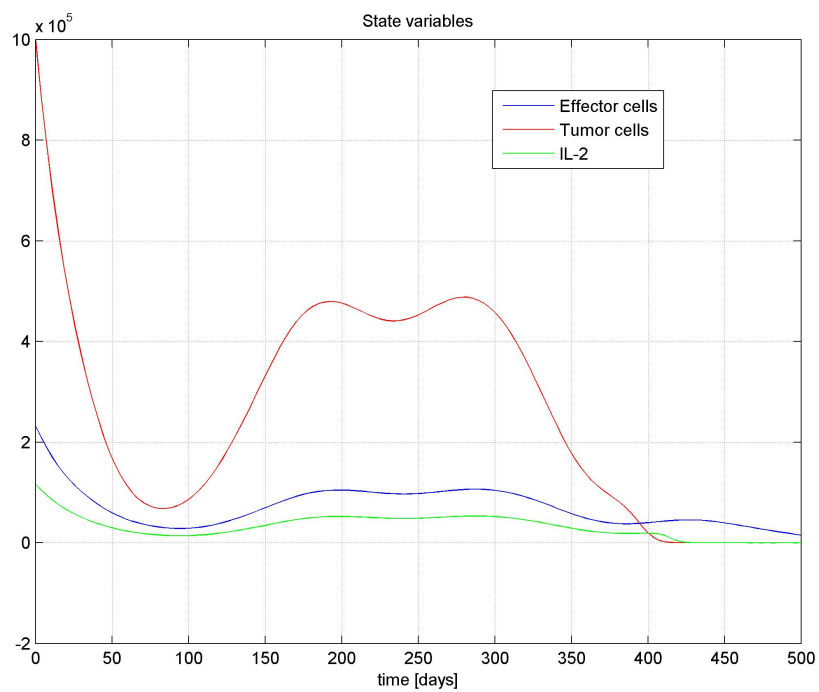


Figure 4.12: State variables. Minimization of tumor cells at therapy conclusion and minimize drugs assumption.

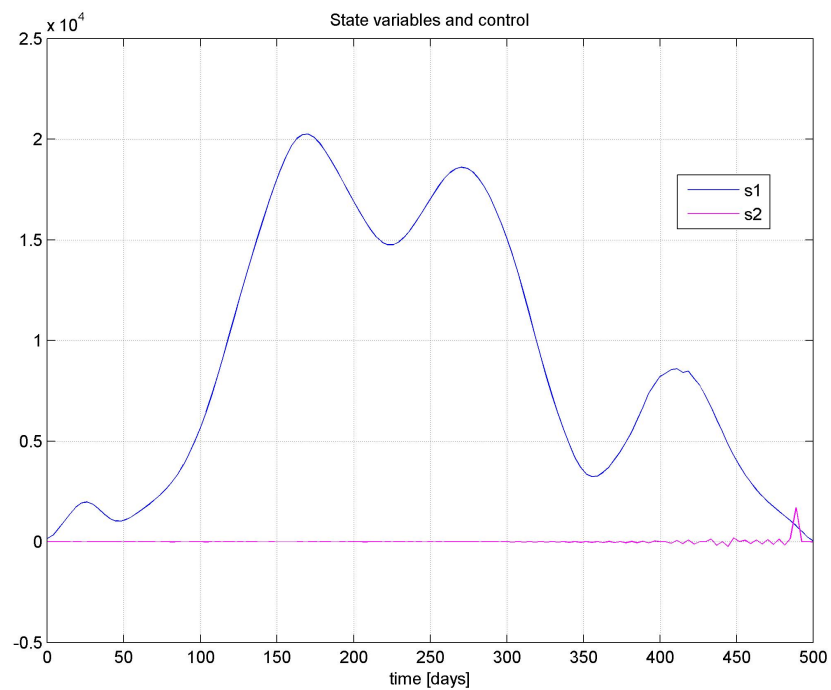


Figure 4.13: Control variables. Minimization of tumor cells at therapy conclusion and minimize drugs assumption.

After an interval of 300 days, the control is able to reverse the trend of the tumor to reach a state of high concentration tumor-regime.

The PK model has been developed to describe the dynamic characteristics of the tumor, in particular it manages to describe states in which the cancer is dormant and the tendency of oscillatory growth. This is what happens in the third and final phase of treatment. The decrease of tumor cells is the cause of the decrease of the control actions required. Further reductions would lead to a regime state for the concentration of tumor cells, or given the concavity to a further increase in the population.

For this reason, further increasing of the concentration of LAK or TIL cells leads to the presence of an inflection in the evolution of the cancer population that ultimately leads to a complete regression.

The main control action is carried out by adaptive cells that remain throughout the processing of an order of magnitude higher than the dose of IL-2. They start to increase their dose when the Effector cells population reaches concentration values higher than those of the neoplasia.

The greater relevance of the action taken by the administration of LAK or TIL cells is to confirm that at present is the most effective treatment in immunotherapy.

The constraints on the drugs assumption permits a solution with injections diffused over the entire period with doses less than three orders than the first solution.

As we have seen in the first optimization this aspect is of primary importance in order to prevent side effects. The growth of the immune system cells remain constant, but with an increase rate limited.

### 4.3 Hybrid Algorithm optimization

The strategy we adopted is continuous type and can be administered through an elastomeric or electronic pump. Current practice, as we have seen in the previous chapter, consists of treatments at discrete time intervals. More significant is to evaluate improvements in what has already been tested at the clinical level. Furthermore, the pumps have a range of flows defined and therefore they cannot be used to administer arbitrary dose. It is therefore necessary to analyze a strategy involving discrete doses of drug.

The purpose of the analysis of the optimal control problem on this model is that of being the prologue to the subsequent analysis of a more complex model developed specifically to analyze the treatment. We leave to a subsequent analysis, the analysis of how to make the matching problem between continuous and discrete approach. Indeed we are not going to use the solution to the problem continuing

to do some initial considerations on the solution of the discrete problem, but the hybrid method we have developed. Before analyzing the algorithm it is necessary to reformulate the problem through the multiple shooting approach.

The time domain is always divided into intervals. Unlike the formulation through collocation, the number of intervals does not affect the accuracy of the dynamic that is assessed accurately through a Runge-Kutta integration of 7-8th order. The number of intervals must however define the structure of the multiple shooting approach and it is closely linked to the number of injections. The time domain is in fact divided into  $m + 1$  intervals, where  $m$  is the number of the injections.

$$t_0 = t_1 < \dots < t_{m+1} = t_f \quad (4.15)$$

The optimization variables can be written as

$$\mathbf{x}^T = (s_1^{(1)}, s_2^{(1)}, \dots, s_1^{(m)}, s_2^{(m)}, \Delta t^{(1)}, \dots, \Delta t^{(m+1)}) \quad (4.16)$$

where  $s_1^{(i)}$  and  $s_2^{(i)}$  are the control at each period  $i$  and  $\Delta t^{(i)}$  is the drug holiday. We have chosen to administer at the same moment both the adaptive cells and IL-2, in this way the drugs holiday intervals are the same. Considering different intervals of administration lead only a doubling of  $\Delta t^{(i)}$  variables.

At every interval the free dynamics are integrated starting from the state variable  $\mathbf{y}_+^i$  at the previous interval and obtaining

$$\mathbf{y}_-^{i+1} = \phi(\mathbf{y}_+^i, t^{i+1}, s_1^{(i)} = 0, s_2^{(i)} = 0) \quad (4.17)$$

where  $\phi$  is the flow of the PK system at time  $t^{i+1}$ .

The impulsive control at each interval lead to a new state  $\mathbf{y}_+^{i+1}$  defined as

$$\mathbf{y}_+^{i+1} = \mathbf{y}_-^{i+1} + I\mathbf{u}^i \quad (4.18)$$

where  $\mathbf{u}_i = \{s_1^{(i)}, 0, s_2^{(i)}\}^T$ .

The algorithm starts from  $i=1$  and with  $\mathbf{y}_+^i$  equal to the initial healthy state of the patient.

The hybrid algorithm does not require an initial guess solution. Each individual of the population is generated with a random procedure. This aspect makes unnecessary to provide an initial solution a priori, and also combined with the characteristic of genetic algorithms to search on the entire space, allows the evaluation of a global optimal solution and avoid the fallout on local minima.

An extensive search in the space of solutions is guaranteed by the average distance between individuals. This value should not be too high because the algorithm would not find an optimal solution and should not be too low because it would lead to fall on a local optimum solution. Figure 4.14 shows how the set of parameters allows us to have a good diversity among individuals in the initial generations

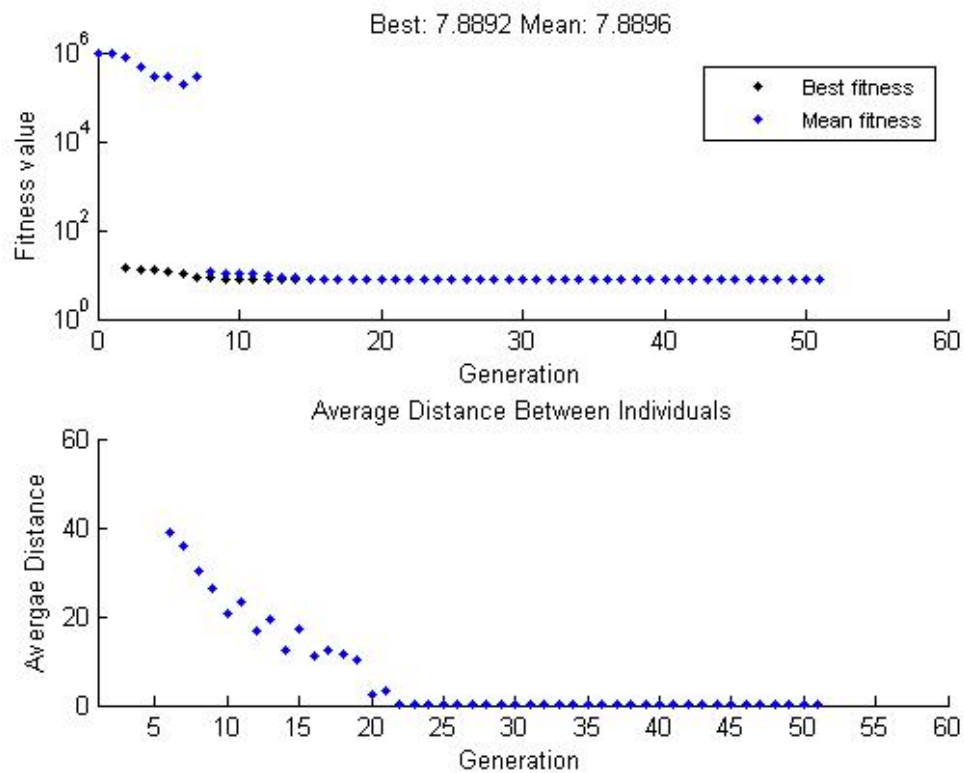


Figure 4.14: Genetic Algorithm optimization. Fitness function

in order to have a global search, while the distance is then decreased in order to refine the optimal solution.

The performance index is the same used in 5.10 in order to take into account limit in the drugs assumption. In fact we have described in the introduction on optimization algorithms that one of the GAs challenge is the inclusion of constraints. In order to avoid finding a solution completely infeasible it is therefore necessary to introduce the penalty function. Otherwise there is an indiscriminate growth of immune system cells.

This method introduces the so called soft constraints which cannot be satisfied, but the evolution of the population will tend to eliminate those individuals who show high levels of control and in this way tend to have a Dendritic cells concentration over the upper-bound.

The chromosome of the best individual of the last generation is used as a first solution of the direct transcription via multiple shooting. As described in the previous chapter this procedure is designed to prevent that the final solution is sensitive to an arbitrary initial solution that can lead to convergence on a local minimum. Furthermore, the gradient-based methods allow easy management of constraints. So with this hybrid algorithm we can exploit the advantages of both methods, converging to a global optimum that satisfies the constraints.

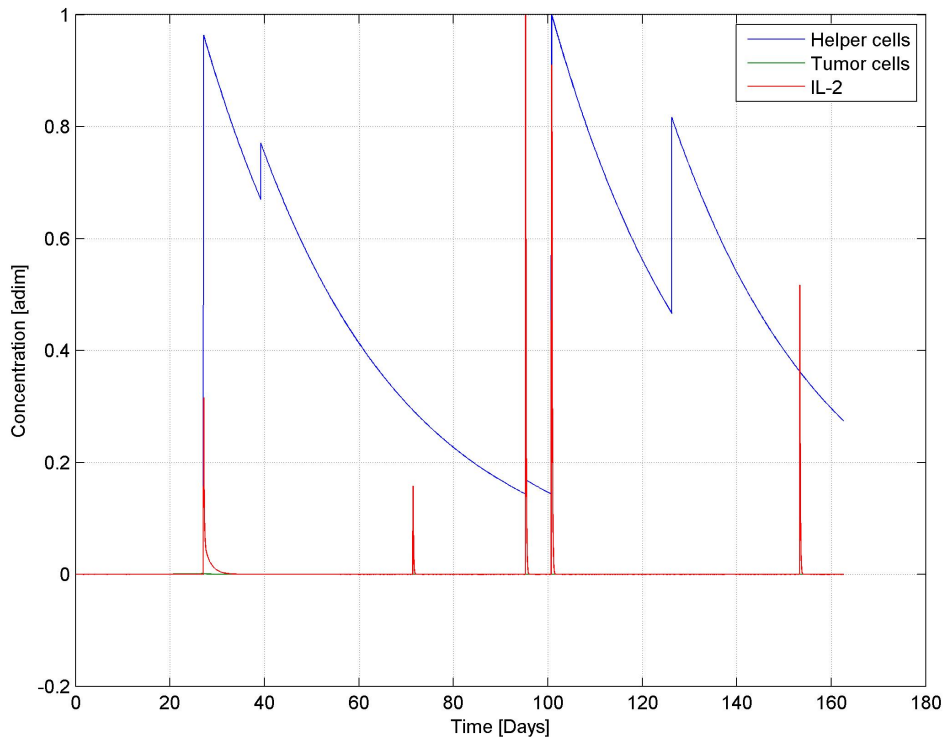


Figure 4.15: Controlled system dynamics

The first oscillation in the concentration of the population of tumor cells determines the time interval in which it is conducted the first control action. The injections act to prevent the tendency of the uncontrolled system to reach a value close to that of the carrying capacity of the tumor. It is possible to see from figure 4.15 that the population is kept under control during the entire protocol. With the discrete optimal control there is no evidence of the general trend of the continuous controlled system in which there is a central phase of treatment where the concentration reaches a local maximum or global.

The optimal solution determines a treatment that can be divided into two similar phases with time duration equal to half the entire time interval. In each of these two phases injections of adaptive cells have a structure in which the first injection has a high dose and the subsequent maintains the concentration of the helper cells. Injections of IL-2 instead present a maximum concentration in the middle of the treatment. We demanded that the injections of the two different drugs were made at the same time point. Although this, the solution presents time instants in which it is present only one kind of control. The optimization has led to zero the concentration of the other control. This is not a consequence of the fact that the two drugs are mutually exclusive.

The two controls could lead to a better solution if given at different time instants.

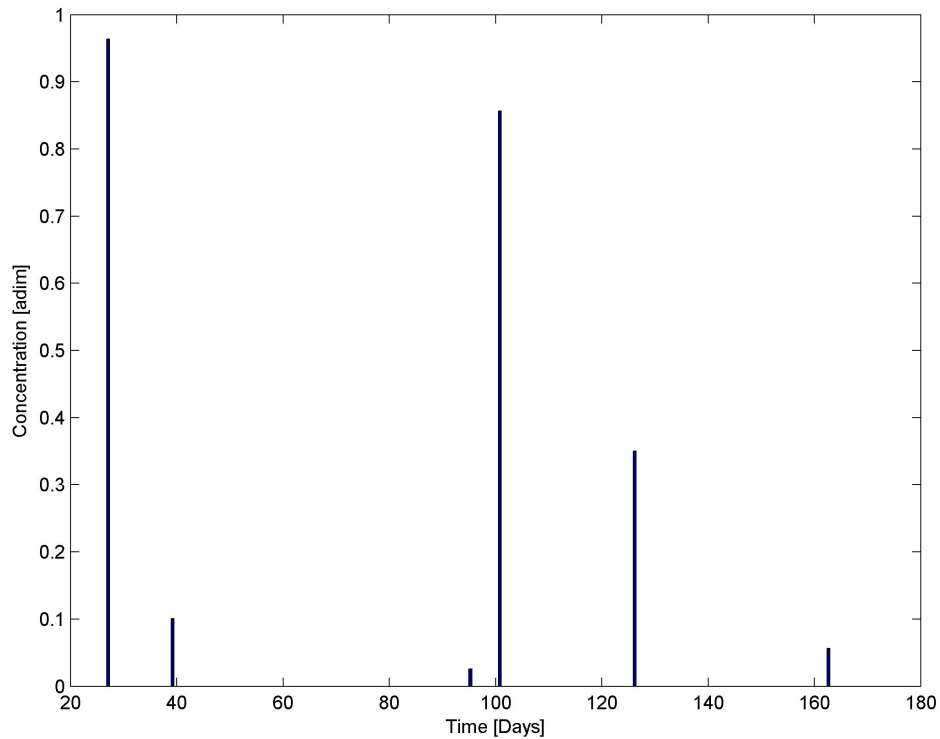


Figure 4.16: LAK or TIL cells administrations

In order to take into account this aspect the best solution is to consider the same algorithm structure that includes both injections of LAK cells and IL-2 in the same time instant. At the same time it is possible to increase their number so that the optimizer, if required, bring one or all the two concentrations levels to zero.

The solution does not show similarities with those assessed through continuous control. The genetic algorithm in fact analyzes the entire search space in stochastic manner without any sensitivity on the initial solution generated randomly. One way to go and assess a discrete solution that does not deviate from the solution of the continuous problem is to use this one to evaluate a first guess solution of the discrete problem. This procedure avoids considering the optimization with the genetic algorithm.

We will discuss in the next chapter on a more complex model that this techniques does not necessarily lead to a global optimum solution because of the sensitivity of algorithms based on the gradient to the initial solution.



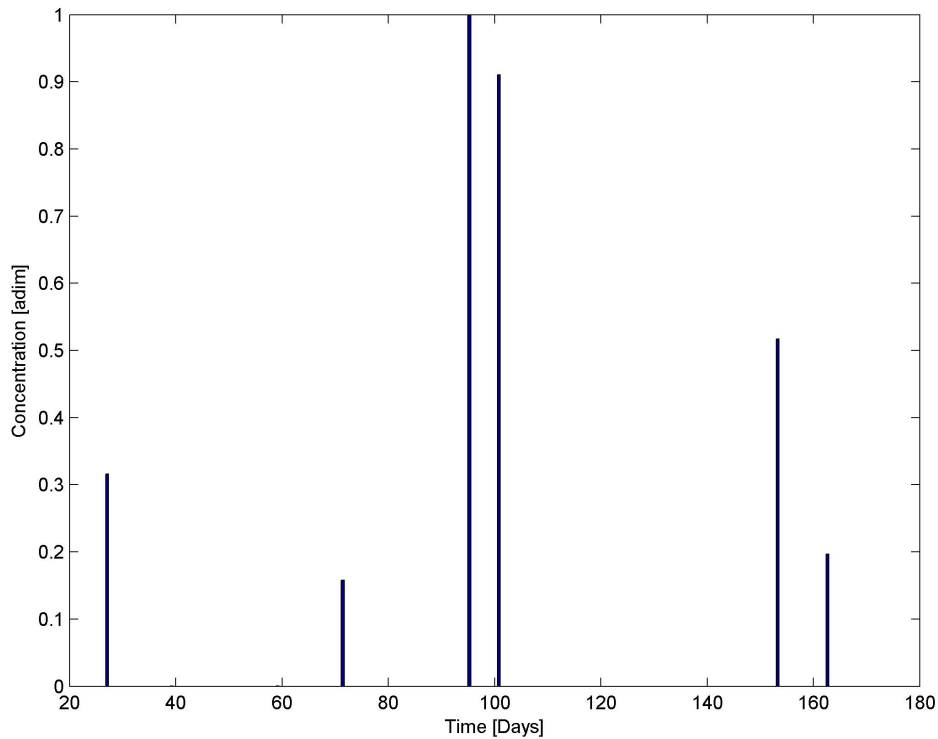


Figure 4.17: IL-2 injections

## 4.4 Conclusions

PK model describes the role of IL-2 in tumor dynamics, particularly, long-term tumor recurrence and short-term oscillation in a mathematical perspective. The aims of our analysis are only to describe the different phases involved in the resolution of an optimal control problem, because of the simplicity of the model. Despite this, the results obtained are in full agreement with [28] and all the subsequent work on the same dynamic system:

- If the IL-2 input is high, the tumor can be cleared but the immune system grows without bounds causing problems such as a capillary leak syndrome.
- With the combined treatment with ACI and IL-2 and in presence of low-antigenicity there is a region of tumor clearance.
- The results indicate that a treatment with ACI may be a better option either as a monotherapy or in conjunction with IL-2.

One of the fundamental aspects of the analysis of a nonlinear ODE system is the identification of all the equilibrium points and the evaluation of their stability.

The free dynamics showed that without any control the patient that presents a tumor with low antigenicity may tend to two areas of stable attraction: the first without the neoplasia while the second one is a tumor regime state. We can define the ultimately optimal solution the one that determines the final state of the system at the end of therapy in the first type of stable equilibrium so that the patient's response is stable and permanent.

Starting from these informations we have analyzed the problem of optimal control. The choice of continuous or discrete type of approach is essentially due to the next stage of clinical trials. In fact at numerical level both choices give rise to acceptable solutions.

The algorithm that we have developed has allowed us to obtain the same considerations that were made in [28]. This results served as a validation of these tools that will be used on a more complex model in the next chapter.

Obviously, given the origin of the mathematical model and particularly its aim for the study of oscillatory dynamics of the tumor mass in the interaction with the immune system rather than the study of control therapy the results obtained in terms of therapy protocol can only provide some general guidance.

# Chapter 5

## Castiglione-Piccoli model

Kirschner-Panetta model is one of the first models that describe the dynamics relationship between tumor and immune system. As we have seen in chapter 2 the immune system response is not unique. It is necessary to consider a model that takes into account the dynamics of different immune system cells, describing the dynamics of each different population.

The ODE model of the tumor-immune interaction proposed by Castiglione and Piccoli [16] is quite simple and is likely to be one of the few specialized for autologous dendritic cell transfection therapy. Dendritic cells that are the most efficient antigen representing cells in vertebrate immune systems, are used in this model as the source of tumor associated antigen TAA presentation. Dendritic cells are introduced externally and ignite the immune response against themselves and, as side effect, also against the tumor cells. The model proposed by Castiglione and Piccoli is the following:

$$\frac{dH}{dt} = a_0 + b_0DH \left(1 - \frac{H}{f_0}\right) - c_0H \quad (5.1)$$

$$\frac{dC}{dt} = a_1 + b_1I(M + D)C \left(1 - \frac{C}{f_1}\right) - c_1C \quad (5.2)$$

$$\frac{dM}{dt} = b_2M \left(1 - \frac{M}{f_2}\right) - d_2MC \quad (5.3)$$

$$\frac{dD}{dt} = -d_3DC + u \quad (5.4)$$

$$\frac{dI}{dt} = b_4DH - e_4IC - c_4I \quad (5.5)$$

The first equation models the concentration of the tumor-specific CD4 T cells. The first ( $a_0$ ) and last term ( $c_0H$ ) represent the birth and natural death of cells. Another term ( $b_0DH(1 - H/f_0)$ ) is the proliferation of cells induced by dendritic cells. This element can consider a phenomenon of saturation. The second equation represents the tumor-specific CD 8 T cells. The cytokine IL-2 stimulates

Parameter	Description	Value	Unit $c$ =cells
$a_0$	CD4 T birth rate	$10^{-4}$	$ch^{-1}mm^{-3}$
$b_0$	CD4 T proliferation rate	$10^{-1}$	$c^{-1}h^{-1}mm^{-3}$
$c_0$	CD4 T death rate	0.005	$h^{-1}$
$f_0$	Carrying capacity of CD4 T	1	$cm^{-3}$
$a_1$	CD8 T birth rate	$10^{-4}$	$ch^{-1}mm^{-3}$
$b_1$	CD8 T proliferation rate	$10^{-2}$	$c^{-1}h^{-1}mm^{-3}$
$c_1$	CD8 T death rate	0.005	$h^{-1}$
$f_1$	Carrying capacity of CD8 T	1	$cm^{-3}$
$b_2$	1/2 saturation const of tumor	0.02	$h^{-1}$
$d_2$	killing by CD8 of tumor	0.1	$c^{-1}h^{-1}mm^{-3}$
$f_2$	Carrying capacity of tumor	1	$cm^{-3}$
$d_3$	CD8 T killing of DC	0.1	$c^{-1}h^{-1}mm^{-3}$
$b_4$	IL-2 production by CD4 T	$10^{-2}$	$c^{-1}h^{-1}mm^{-3}$
$c_4$	IL-2 degradation rate	$10^{-2}$	$h^{-1}mm^{-3}$
$e_4$	IL-2 uptake by CD8 T	$10^{-7}$	$c^{-1}h^{-1}mm^{-3}$

Table 5.1: Parameters of Castiglione-Piccoli model

CD8 T cells recruitment and proliferation. In analogy to the helper cells there are terms ( $a_1, c_1C$ ) that describe the birth and natural death of these types of cells. The term ( $b_1I(M + D)C(1 - C/f_1)$ ) that describes the proliferation takes into account the complicated interaction with the tumor and dendritic cells, showing in this case a phenomenon of saturation. The population of tumor cells is described in the third equation. Similarly to the previous equations, there is a term ( $b_2M(1 - M/f_2)$ ) of proliferation and saturation. The law of growth of tumor cells is logistic type and is based on experimental data obtained from immunodeficient mice. A term ( $d_2MC$ ) that causes the regression of tumor mass is directly proportional to the presence of cytotoxic CD8 T cells. The fourth equation describes the population of dendritic cells. These cells act as an activator on cytotoxic CD8 T cells. This action characterizing their contribution to the response of the immune system and leads them to decay. In fact, after a certain number of activations these cells are destroyed by the immune system. The injection of cells  $u$  is the control variable. Dendritic cells specific for the tumor are prepared in vitro and then administered as a vaccine.

The last equation takes into account the dynamics of interleukin IL-2. The first term ( $b_4DH$ ) shows that an increase in concentration is due to dendritic cells and thus also to CD4 T cells. The production of IL-2 due to the cytotoxic CD8 T cells is neglected, because these cells produce small quantities compared to CD4 T cells. The other members describe the consumption of this cytokine due to natural death and decay that occurs when they have done their task to stimulate

the immune system response.

In practice, however, there are other mechanisms of immune evasion of cancer due to its ability to down regulate the immune recognition. Those mechanisms are not taken into account in the present model and we will stress on this point during the work.

The other aspect to consider is that the immune system is able to act before the cancer has reached the phase of carcinoma in situ simply because, after a solid tumor is formed, it is usually unable to get in contact and kill malignant cells that are in the inner part of the tumor mass.

Table 5.1 shown the parameter used in the model. The setting of these parameters starts from the set of values used in Kirschner and Panetta (1998) and by tuning the system to reproduce qualitatively the dynamics of the tumor-immune competition.

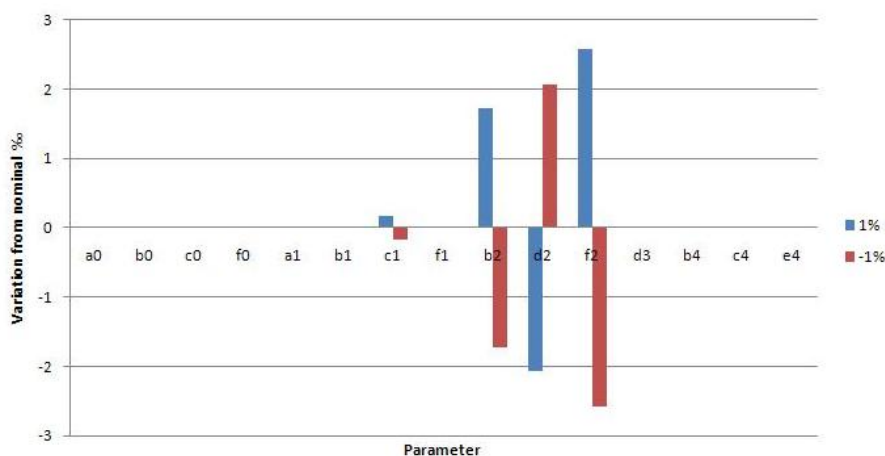
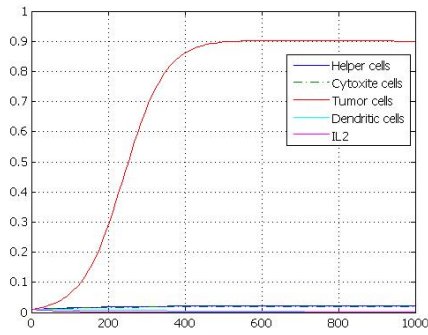
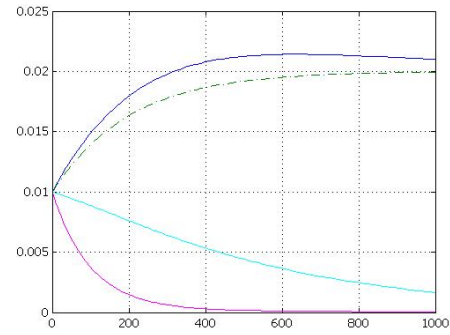


Figure 5.1: Parameter sensitivity analysis

In order to identify the sensitivity of the system to the parameter figure 5.1 shows the parameter sensitivity analysis of the system. This evaluation has been done considering a variation of  $\pm 1\%$  in the parameter and then integrating the system equation over 25 days. The results emphasize that the tumor growth is controlled with the parameter of the logistic growth law in particular the system presents an high sensitivity to the variation of the tumor carrying capacity. The tumor growth law is one of the most studied aspects in the tumor immune system modelisation. At the end of the chapter we will consider another growth law in order to evaluate the robustness of the solution obtained. The other parameter that strictly influences the dynamic behavior of the cancer population is the antigenicity. This aspect does not create any surprise, because we have stated before that the value of this parameter influences the interaction of the tumor-immune system. In the analysis only slightly different value has been considered, while we have seen in the Panetta-Kirschner model that considering very different values



5.2.1: System variables



5.2.2: Without tumor cells

Figure 5.2: System behavior without control

of the tumor antigenicity determines a radical change in the system trajectory. In fact KP model was created in order to analyze this particular aspect of the neoplasia. Figure 5.2 shows the dynamic behavior of the system without control. It is evident that the value of the antigenicity leads to a solution that we have identified previously as tumor regime state. In the Panetta Kirschner model this solution is obtained with patients that show low-antigenicity values. The final concentration of the cancer cells is near their carrying capacity.

The other variables that identify the immune system reach asymptotic value in half time interval considered. In particular the concentrations of the IL-2 and of the dendritic cells tend to decrease. This aspect is strictly related to the fact that in equation 5.4, that describe the population of dendritic cells, it survives only a term that it is necessarily negative over the whole integration time.

## 5.1 Equilibrium points

In this section, as in the analysis of PK model, a grid of initial values was used in order to identify all the stationary points of the system. As a matter of fact different initial conditions can lead to different points of attraction. In particular we are interested in the equilibrium points that show a low final tumor concentration. The solution of the nonlinear system of equation  $F(\hat{\mathbf{y}}) = 0$  is obtained via Trust-Region Dogleg Method implemented in the `fsolve` Matlab function.

A linearization of the CP model is required in order to make an eigenvalues

analysis. The Jacobian matrix is

$$\mathcal{J} = \begin{pmatrix} b_0 D \left(1 - \frac{2H}{f_0}\right) - c_0 & 0 & 0 & \dots \\ 0 & b_1 I (M + D) \left(1 - \frac{2C}{f_1}\right) - c_1 & b_1 I C \left(1 - \frac{C}{f_1}\right) & \dots \\ 0 & -d_2 M & b_2 \left(1 - \frac{2M}{f_2}\right) - d_2 C & \dots \\ 0 & -d_3 D & 0 & \dots \\ b_4 D & -e_4 I & 0 & \dots \\ \dots & b_0 H \left(1 - \frac{H}{f_0}\right) & 0 & \dots \\ \dots & b_1 I C \left(1 - \frac{C}{f_1}\right) & b_1 (M + D) C \left(1 - \frac{C}{f_1}\right) & \dots \\ \dots & 0 & 0 & \dots \\ \dots & -d_3 C & 0 & \dots \\ \dots & b_4 H & -e_4 C - c_4 & \dots \end{pmatrix}$$

From the eigenvalues analysis of the Jacobian it is possible to identify the stable and unstable region of the system. In particular if all the eigenvalues of  $J$  have negative real parts that the equilibrium point obtained is asymptotically stable.

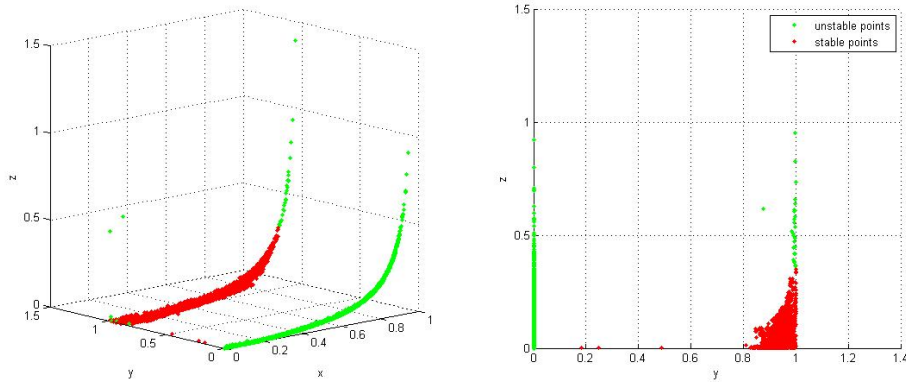


Figure 5.3: Equilibrium points with an initial grid of  $10^5$  points

Figure 5.3 shows the equilibrium points of the system focusing the attention on the variables that represent effector cell, tumor cell and IL-2.

Considering the results obtained with PK model we can make some comparison and assumptions. As in the previous model with a low value of the antigenicity the stable regions are strictly related with the extreme value of the tumor-regime state with low values of the interleukin concentration. Interesting results is the identification of stable points with medium concentration of tumor cells [0.2-0.5]. These points identify a state in which the tumor is dormant. The tumor is present but it not decreases or increases its mass. We have to note that there are no stable equilibrium points with a final cancer cells concentration equal to zero. This aspect leads to two main consequences:

- a final state in which the tumor concentration is less than 0.1 can be maintained only with a permanent protocol;
- if the final tumor concentration after the protocol is around 0.2 then the system tends naturally to be attracted to a stable equilibrium state with a low cancer concentration.

When we have identified the solution of the optimal control we have to compare the final concentration of the tumor cells to those of the stable equilibrium points in order to consider the future development of the solution and of the protocol.

## 5.2 Optimal control Problem

This section aims to present the problem of the optimization of the CP system of equations considering the implementation in the algorithm formalism. This process looks like a map between the physical phenomenon, the required performances and constraints and the algorithm structure. The structure of the variables that are the base of the algorithm will be presented in order to better understand the direct methods of optimization used.

### Boundary conditions

Boundary conditions are defined in terms of initial values of the state vector. Initial conditions can be different from one patient to another. As reported in [26] the different cells populations have the same magnitude, with a concentration almost twice than the other for the tumor cells. We consider a condition in which the tumor cells are over the 50% of its carrying capacity, and the other population shows values mediated from those presented in the reference [26]. The formalization of the initial boundary condition can be written as

$$\phi_i : \mathbf{y}(0) - \mathbf{y}_i = \mathbf{0} \quad (5.6)$$

where  $\mathbf{y}_i$  is a vector whose components are represented in table 5.2. The adimen-

Cell	Helper	Cytotoxic	Tumor	Dendritic	IL2
Concentration [adim]	0.1	0.1	0.6	0.1	0.1

Table 5.2: Initial patient condition

sionalization of the variable allows generalizing the problem also considering an initial situation in which a surgical treatment has been made to reduce tumor. In this case the number of cells can be considered reduced by an order of magnitude [31][26]. The role of this surgery pretreatment is not completely clear, but from



a clinical study [31] there was evidence of positive results. Surgical treatment before immunotherapy improves response and increases the chance of survival. This aspect is related to the fact that in addition to a decrease in tumor mass, there is a reduction of immunosuppressive factors. It is possible to proceed in a different way by considering a pre-treatment of chemotherapy to reduce the immunosuppressive factors. In this case it is necessary to have a dynamic model that describes the interactions with the tumor and the immune system. The initial conditions are not provided directly, but are the result of optimization. Knowing the initial state of the patient before the pretreatment  $\mathbf{y}_{pt}$ , the condition at the beginning of the immunotherapy are given by  $\mathbf{y}_i(t_0) = \varphi$

As in the previous model it is possible to identify a variables vector with the following structure:

$$\mathbf{x}^T = (h_1, c_1, m_1, d_1, i_1, u_1, \dots, h_N, c_N, m_N, d_N, i_N, u_N, t_f) \quad (5.7)$$

The limits of each variable are fixed to their maximum normalized value. In this model the lower and the upper bounds are fixed with vectors of zeros and ones. The other equality constraints are defined in order to respect the differential equations of the system. The Hermite-Simpsons method define  $N - 1$  defects equation that approximate each system equation. To sum up a total of  $n(N - 1)$  defect equations can be defined. It is worth observing that this integration scheme allows computing analytically the Jacobian of both the equality and inequality constraints, and the gradient and the Hessian of the objective function. These feature speeds-up the solution of the Karush-Kuhn-Tucker for the nonlinear programming and avoids the introduction of any numerical error.

The final time is added to the variables vector, in this way the optimization process will look for therapy time span. It is necessary to set a guess for the final time in order to start the iteration.

If the cost function does not directly depend from time variable, the result expected tends to an optimal solution with a final time slightly different from the first iteration value. The consequence is that the guess final time is a crucial parameter to set. In order to prevent the convergence to wrong solution the time constraint inequality  $t_f$  greater than the initial time  $t_i$  should be added as a row to the constraint vector. Another solution is to set a lower bound major than the initial time.

The initial time is fixed and set to zero because the problem is autonomous.

The first step of the optimization is to use Mayer form trying to minimize the final tumor concentration as in the previous model. This is the main task of the optimization. No other terms in the functional cost means no limit or soft constraints on the other state and control variables. The merit function is

$$F(\mathbf{x}) = \Phi(M(t_f)) \quad (5.8)$$

where  $\Phi(M(t_f))$  is equal to  $M(t_f) - \rho = 0$

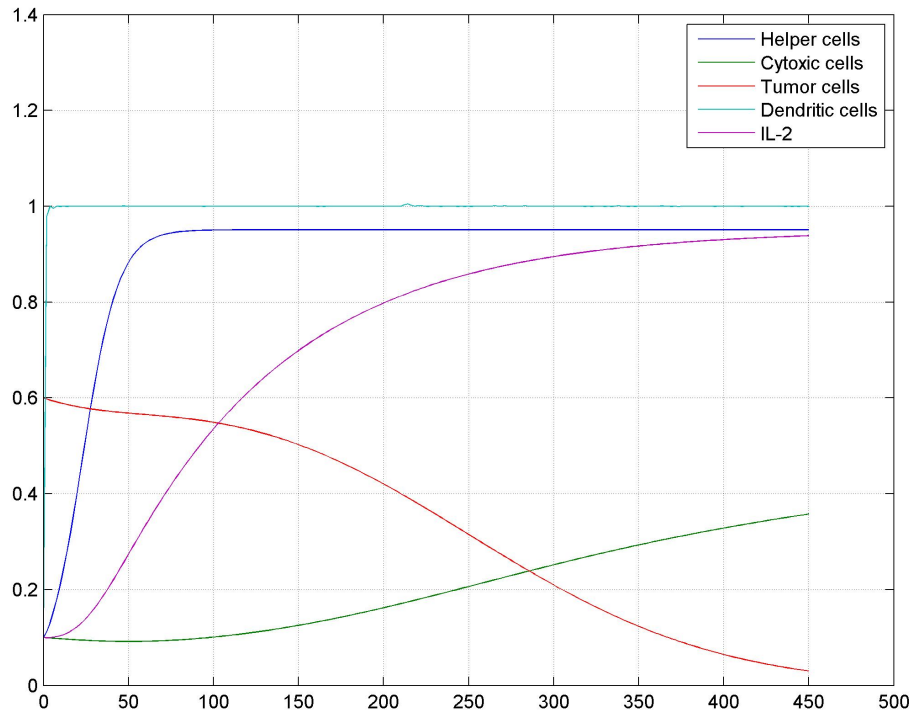


Figure 5.4: State variables

Figures 5.4 and 5.5 shows the optimization results with a uniform grid of 235 points. In order to minimize the amount of tumor cells an initial high dose of drug is injected in the patient. With this solution there is a rapid increase in concentration of the immune system cells. These ones in less than one hundred therapy days reach their maximum values over the malignant cells concentration. This aspect is in analogy with the PK model, where a high dose of drugs lead to a tumor-free state with side effects on the immune system.

The simulation results shows that with an adequate control the tumor cells concentration should be decreased. One of the main issues is that the concentration cannot be equal to zero. This aspect is related to the fact that we have limited the uncontrolled growth of the dendritic cells concentration. Simulation without these constraints has lead to a solution in which the neoplasia has been defeated, but the immune system grows unbounded. The optimization takes into account the physical limits of the normalized system variables setting the lower and the upper bound. This action prevents the possible side effects of a free boundary

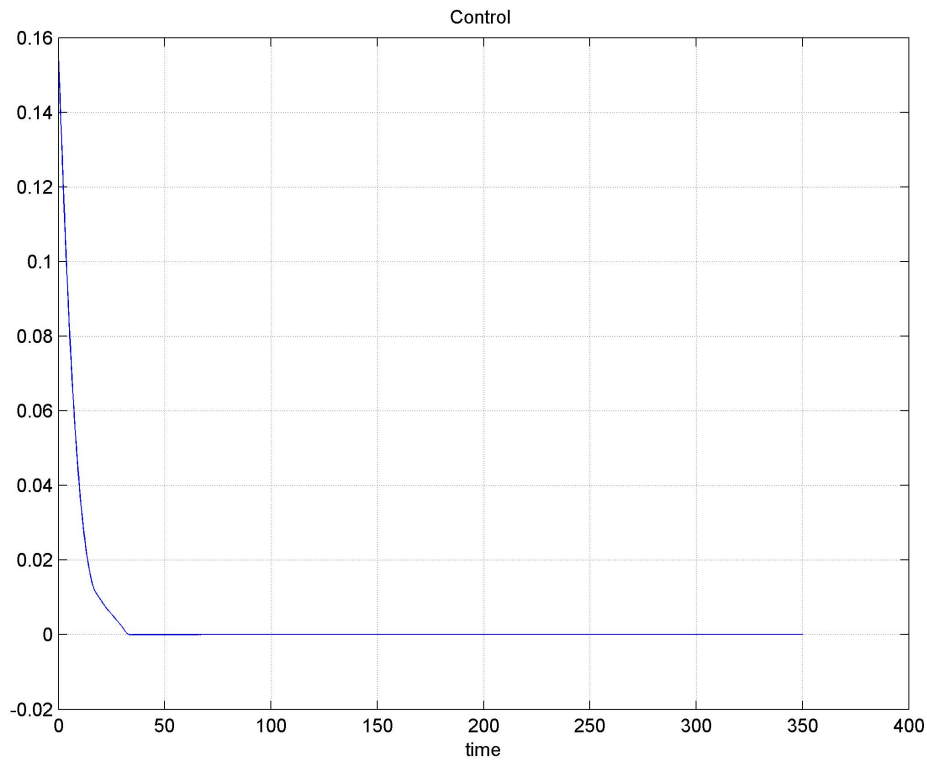


Figure 5.5: Control

problem as already seen in the previous chapter. The optimization in this way converges at a solution that limits the immune system growth.

We have limited this aspect with path constraints but in order to reduce the toxicity of the treatment during the application of the control, as in the PK optimization problem, we have to consider a penalty function on the total drug administered during the immunotherapy. The aims are to prevent a control that consists in a high initial impulse, and to optimal distribute the drugs administration during the whole interval of therapy. The modified functional that takes into account this goal is:

$$F(\mathbf{x}) = \Phi(m(t_f)) + w \int_{t_f}^{t_0} u^2(t) dt \quad (5.9)$$

where  $w$  is a weight selected in order to balance the two terms that are in contrast each other.

Figure 5.10 shows the behavior of the controlled system with a uniform mesh of 280 points. The functional, that we have selected acts in order to prevent the saturation of the dendritic cells at the beginning of the therapy. The optimized control consists in a diffused continuous administration during the entire protocol interval. When the concentration of dendritic cells reaches its maximum admissible value, the dosage of the injection decreases in order to satisfy the constraints,

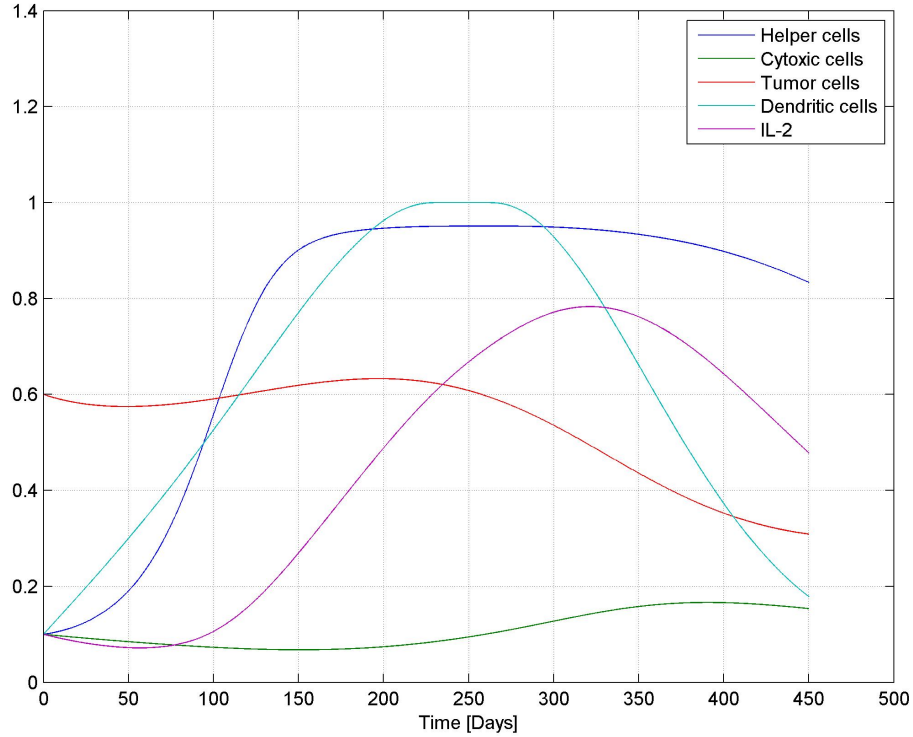


Figure 5.6: State variables

until the concentration level of IL-2 reaches its saturation level. At this point the control decreases and in the same way the concentration of the dendritic cells, while the task of IL-2 is to stimulate the production of cytokines and so contrast the tumor growth. These cells act directly on the tumor before they reach their saturation value. After this point no further decrease of the neoplasia is possible.

We have to notice that the final concentration of tumor cells is higher than the previous obtained with a functional cost that does not take into account a penalty on the total amount of drugs administered. A compromise between the two situations can be done with an appropriate tuning of the weight  $w$ .

In order to solve the continuous problem direct transcription approximate the problem with the Hermite-Simpson integration scheme. The resulting solution is verified by numerical integration adopting a 7th/8th order Runge-Kutta integration scheme with absolute and relative tolerances set to  $10^{-8}$ . The forward integration is carried out taking the optimal first grid point  $y_1$  as initial condition, and with a cubic spline of the controls  $u_j$ . This higher order method is useful to evaluate the accuracy of the solutions found, here obtained with a low-order method. Figure 5.8 shows that the maximum residuals on the tumor cells variables between the approximate and the real solution is  $O(10^{-5})$ . The state vector respects the following condition:

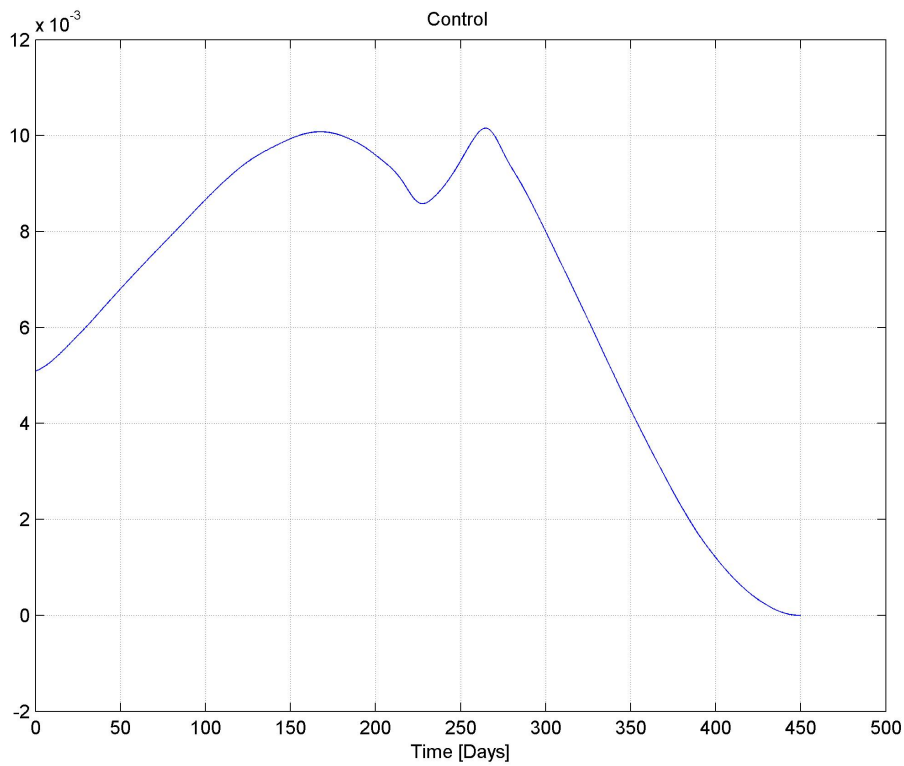


Figure 5.7: Control

$$\|\mathbf{y}(t_f) - \mathbf{y}_N\| \leq \epsilon \quad (5.10)$$

where  $\mathbf{y}(t_f)$  is obtained through the Runge-Kutta integration, while  $\mathbf{y}_N$  is obtained with the Hermite-Simpson integration. The tolerance is set to  $10^{-4}$ . In order to respect this condition a grid refinement has been done.

As we have previously stated the algorithm starts with a coarse mesh in order to speed up the convergence. The solution obtained is then interpolated on a refined mesh and the optimization repeated. This process must be iterated until condition 5.10 is respected.

### 5.2.1 Discrete control approach

We have analyzed a continuous control approach in which cells are continuously being implanted in patients in the interval of care. If computationally it has been possible to arrive at a feasible solution, the same cannot be said for the practical feasibility.

Discrete is defined in term of the control strategy, because also the continuous control problem is discrete, but only in term of the computational approximation. As mentioned earlier, in medical practice the administration are made for short

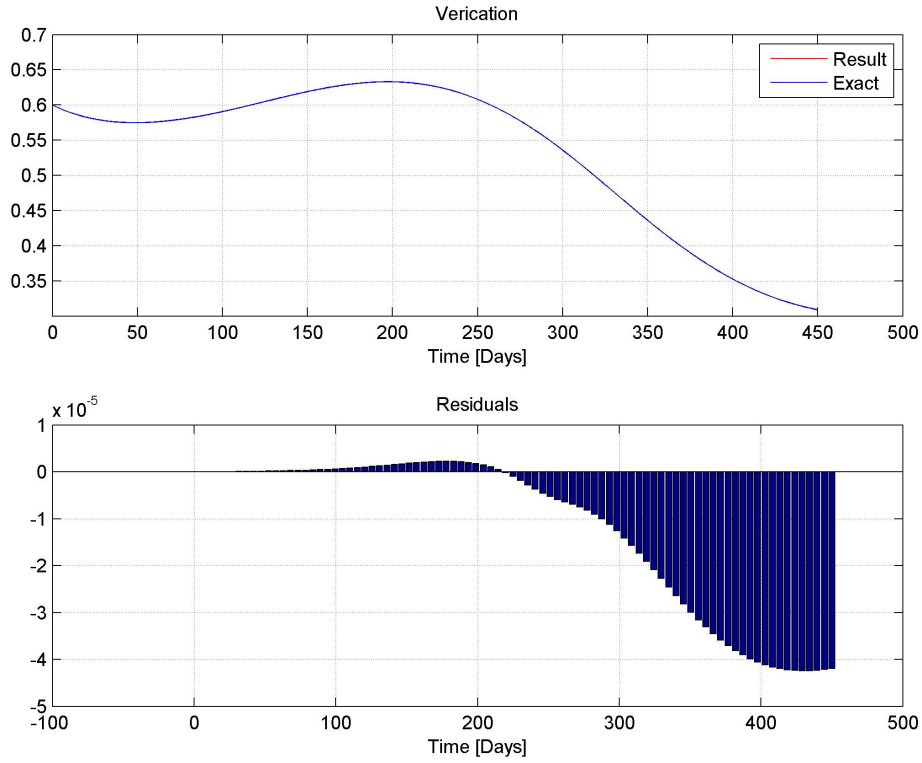


Figure 5.8: Tumor error verification

periods of time, separated by intervals of drugs holiday. We must therefore move from a continuous to a discrete formulation for the control. This basically determines the transition from the solution of the optimization problem by collocation to a solution with the multiple shooting approach.

The time domain is divided into  $m + 1$  interval, where  $m$  is the number of the injections. The variables vector to be optimized is defined as

$$\mathbf{x}^T = (u_1, \dots, u_m, \Delta t_1, \dots, \Delta t_{m+1}) \quad (5.11)$$

where  $u_i$  is the control at each  $i$ -period and  $\Delta t_i$  is the drugs holiday interval. Using the drugs interval instead of the time at which administer the drugs prevents the introduction of inequality constraints on the time variables.

The structure is different from the collocation method because the dynamics variable does not appear in this vector. In fact assuming the variables  $\mathbf{y}_j$ , for  $j = 1, \dots, m+1$ , as the initial value of the dynamics for each trajectory segment, such initial conditions are propagated forward under the flow of the differential Castiglione-Piccoli system in time interval  $\Delta t_j$ .

The dynamics is integrated and not approximated as in the previous method and do not appear in the variable to be optimized that is always smaller than the previous one. This aspect can be useful if we want to use an evolutionary

algorithm, as in the following section.

The first step is the identification of a first guess solution. The parameters required are the number of the injections, the interval between each of them and the dosage. The number of injections clearly is linked with the implementation of the multiple shooting algorithm and this value is fixed, while the drugs holiday is not an important parameter. The idea is to administer the same drug amount as in the optimized continuous problem, in order to use a feasible protocol.

$$\int_{t_i}^{t_f} u(t)dt = \sum_{i=0}^n u_i \quad (5.12)$$

where  $n$  is the total number of injections and  $u_i$  is the  $i$ -th dosage of the injection.

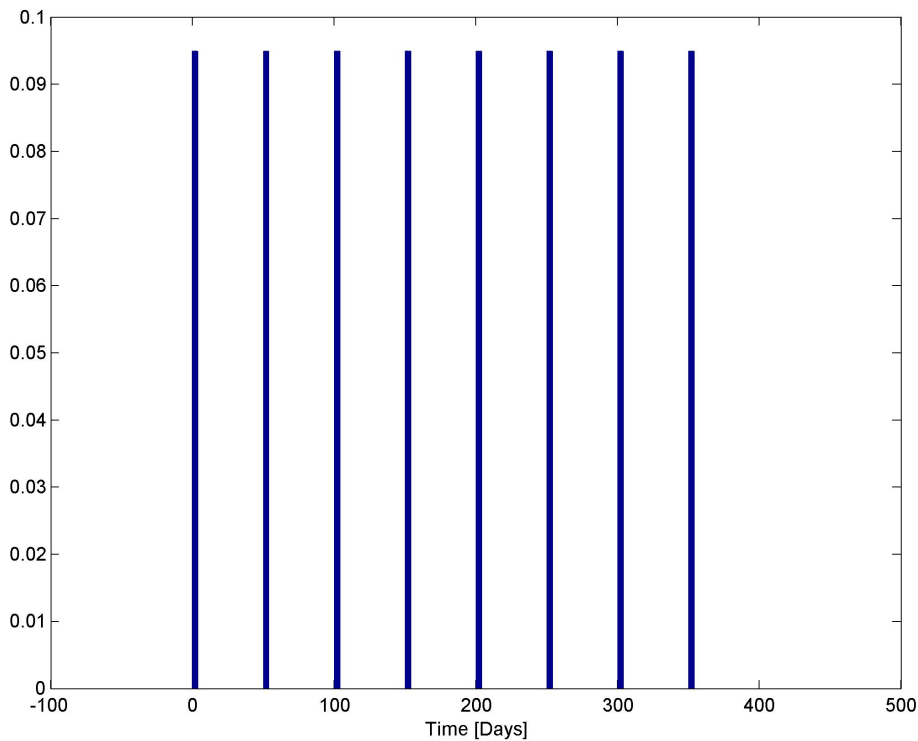


Figure 5.9: Control discretization

Each discrete injection is considered impulsive because the clinical time required to administer the drug is around 15 minutes, as we have seen in the standard approach, that in comparison with the interval of therapy is negligible. The number of the total injections is set a priori to the value of 8, and the drugs holiday between each administration is 50 days.

The guess solution for the control variable is shown in figure 5.9, while the integration of the system is reported in figure 5.10.

The solution is qualitatively similar to that presented for the continuous control except for the discontinuity in the immune system cells concentration due to

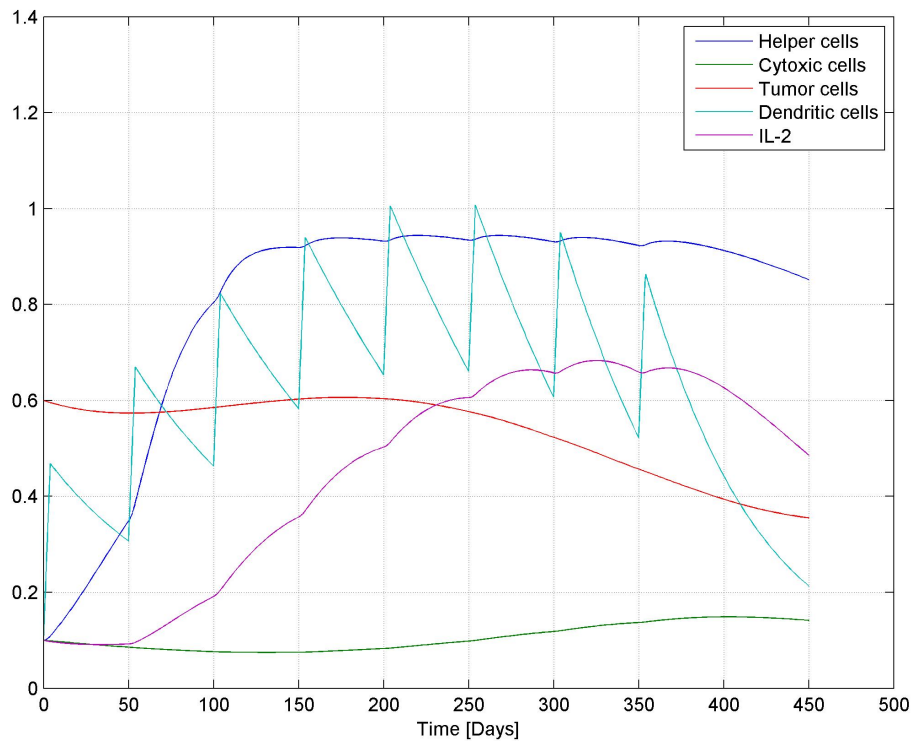


Figure 5.10: State variables with the initial control discretization

the discretization of the drug administrations. As in the continuous problem the variables that identify the immune system population reach their maximum value with complete respect of the path constraints. The value of the final tumor concentration and the dynamic behavior during the therapy is quite similar to the result obtained previously. The final concentration of tumor cells is less than 5% higher than the previous one.

The results obtained confirms that is an appropriate method use the continuous solution in order to define a discrete control therapy. We expect that using this solution as a first guess for an optimal discrete control problem will lead to a better result.

In figure 5.11 it is shown the optimized solution of the state variables with a minimization of the final concentration of tumor cells as in the functional 5.8. The administration maintains approximatively the same drugs holiday period and in this way the administration frequency is similar to that in the initial guess solution. This aspect is a consequence to the fact that in the functional we have not take into account any term directly dependent with the total duration of the therapy. The optimal strategy aims to bring the concentration of the dendritic cells at its maximum level and maintain it during the protocol. This aspect is related to the high dose of the first injection shown in figure 5.12, while the other



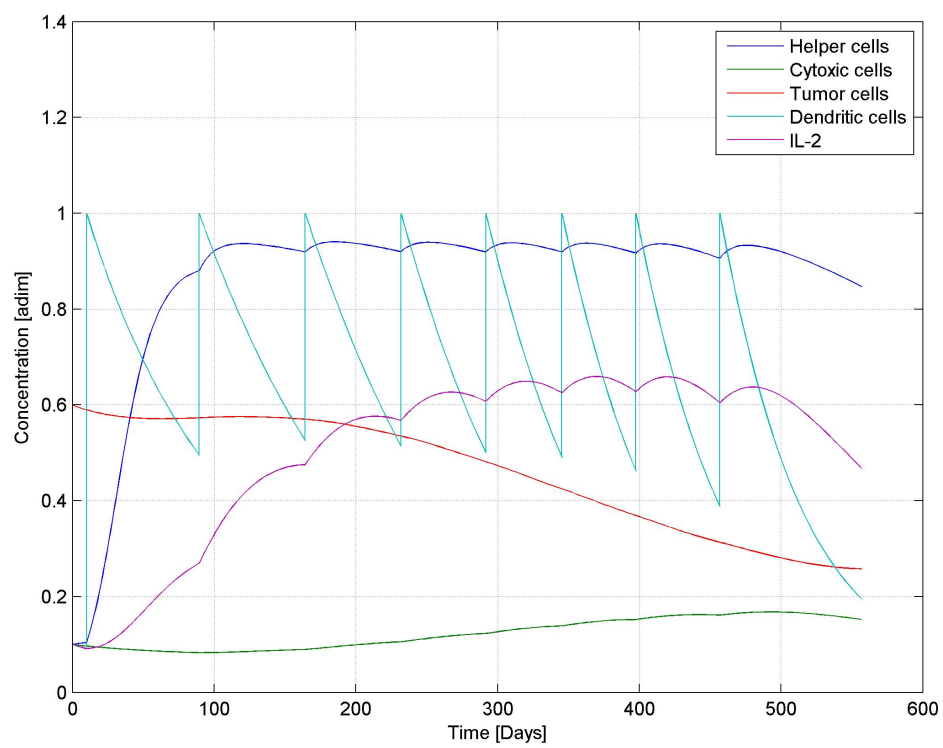


Figure 5.11: State variable impulsive control. Minimization of final tumor cells concentration.

are always less than the first one but they tend to increase as the concentration of cytotoxic cells increase.

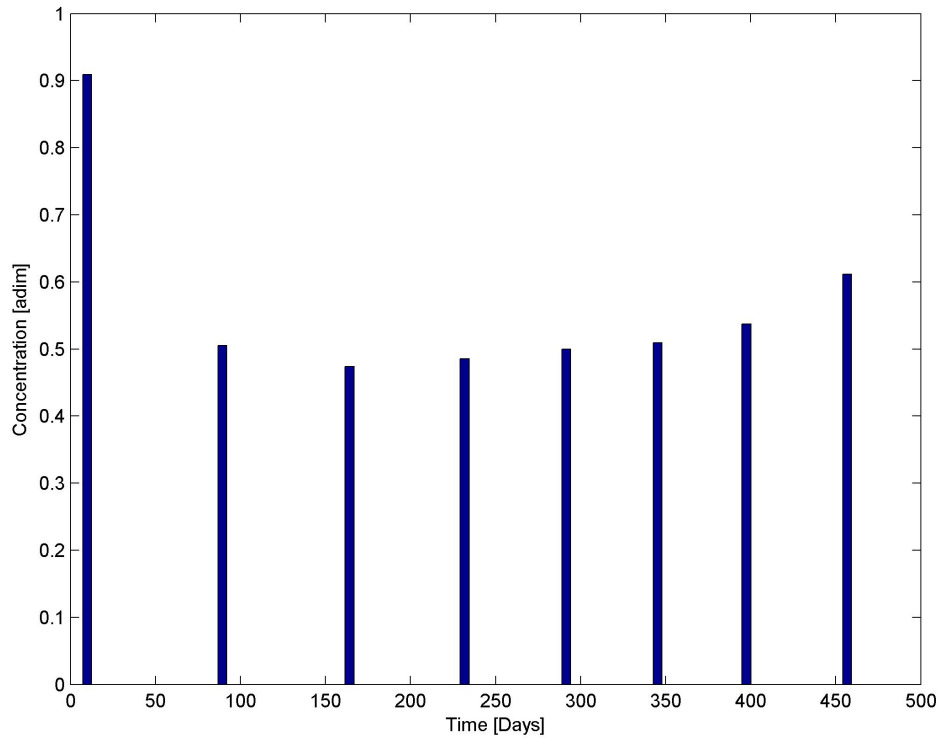


Figure 5.12: Injections schedule and dose, impulsive control. Minimization of final tumor cells concentration.

Period	Dosage [adim]	Holiday [days]	Period	Dosage [adim]	Holiday [days]
1	0.91	5	5	0.50	55
2	0.51	85	6	0.51	50
3	0.48	70	7	0.53	55
4	0.49	75	8	0.61	55

Table 5.3: Drugs holiday period and administration dosage. Minimization of final tumor concentration.

At this point following the same scheme introduced with the continuous problem we consider a problem with the functional 5.9, in which there is a penalty that tries to reduce the total drug administered. In the therapeutic practice we have stated before that this aspect is strictly related with the reduction of the side effects of the therapy. If the therapy defeats the initial problem, but introduces other ones is not efficient. In figure 5.13 the dynamic behavior of the optimal controlled system is shown. The final tumor concentration of the tumor cells is

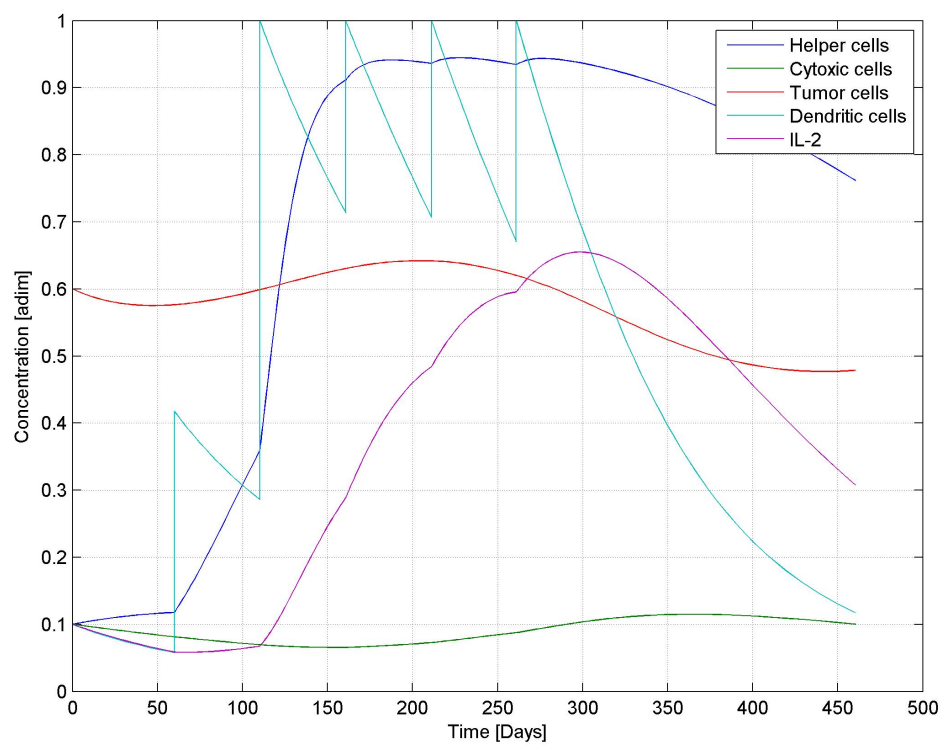


Figure 5.13: State variable impulsive control. Minimization of final tumor cells concentration and drugs administration penalty.

the 90% of the initial concentration and the trajectory shows an elongation the reach a maximum peak that is the global maximum. This aspect is related to the weight on the control that limits the level of the dosages. As we can see in figure 5.14 the initial and the final concentrations have a dosage equal to zero. The trajectory of the dendritic cells population is qualitative similar to that in the continuous problem, this because of the elimination of the initial and final injections.

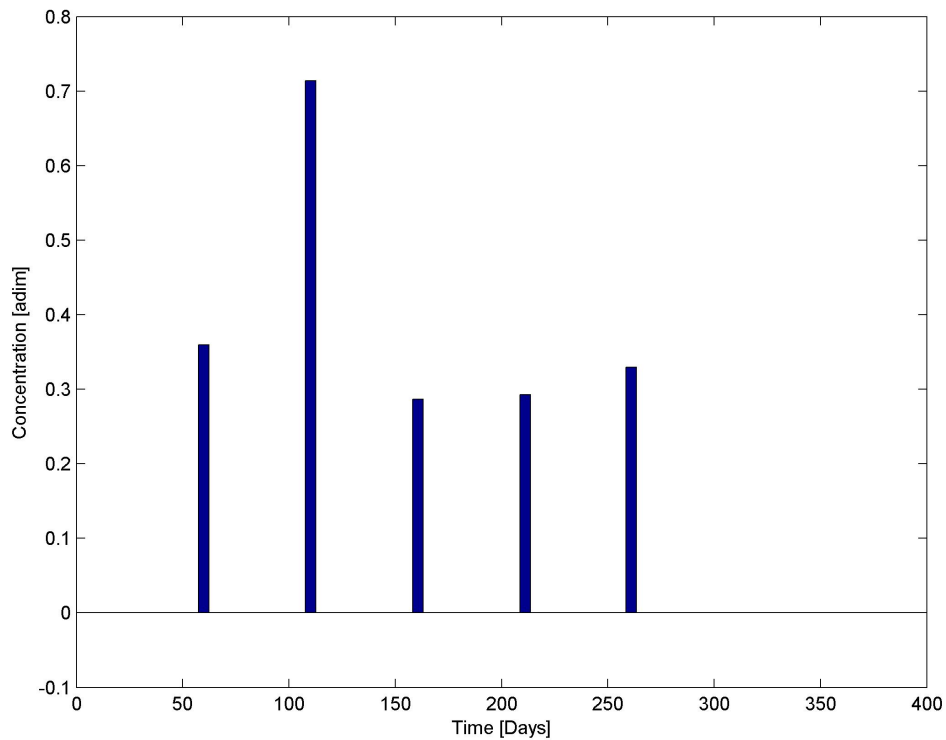


Figure 5.14: Injections schedule and dose, impulsive control. Minimization of final tumor cells concentration and drugs administration penalty.

Period	Dosage [adim]	Holiday [days]	Period	Dosage [adim]	Holiday [days]
1	0	-	5	0.30	51
2	0.37	55	6	0.34	52
3	0.72	52	7	0	-
4	0.29	51	8	0	-

Table 5.4: Drugs holiday period and administration dosage. Minimization of final tumor concentration and penalty on the control.

To sum up we have obtained an optimal discrete solution that respects the problem constraints. The main problem is the introduction of the penalty on the

maximum administered drugs that lead to not satisfactory solution.

This problem is a consequence to the fact that a gradient based method is very sensitive on the initial solution. The control strategy that we have identified depends on the initial guess solution. In order to prevent this aspect and find a better solution in the next section we use a robust algorithm that prevents this fact. The aim is to prevent the convergence to a local minimum solution, that it is acceptable but not efficient.

### 5.3 Hybrid algorithm optimization

Following the same procedural scheme that we have introduced in chapter 1 and used for the optimal control of the PK model, this section aims to use genetic algorithms in order to produce an initial solution for the direct method. Using an initial solution for the discrete problem that derives from the continuous problem in terms of total drugs administered do not lead to satisfactory results. This aspect is due to the therapy protocol strategy that is selected without any physical considerations. Running the optimization algorithm with these initial guess does not determine the convergence to a good solution in terms of final tumor cells concentration. Running the so-called hybrid algorithm can determine a final solution obtained joining together the advantages of the two methods that we have previously described.

The structure of the algorithm is influenced by the number of injections, and these parameters are one of the main factors that influence the final solution. A parametric analysis has been done in order to evaluate the best number of drug injections. This value cannot be added to the optimization variable vectors, because the structure of the discretization strictly depends on this parameter. In order to overcome this problem several genetic algorithm optimization and then direct transcription have been done. The results are shown in figure 5.15. It is evident that there is not any direct proportionality between the number of injections and the tumor cells concentration. The tumor concentration reaches its minimum between 15 and 20 injections. Further increase in the number of injections lead to an increase of the tumor concentration global maximum and an increase of the therapy time interval. These aspects are no related with a decrease of the final tumor cells population. This analysis shows that the best number of injections must in be in the range between 15-20 during the entire therapy protocol, in this way it is possible to reach a final concentration  $< 80\%$  of the initial concentration with low global maximum. This solution is also an optimal compromise in terms of the total therapy time horizon.

Using a fixed structure with 18 injections we have run the hybrid algorithm.

Figure 5.16 shows the value of the function cost minimized by the algorithm and

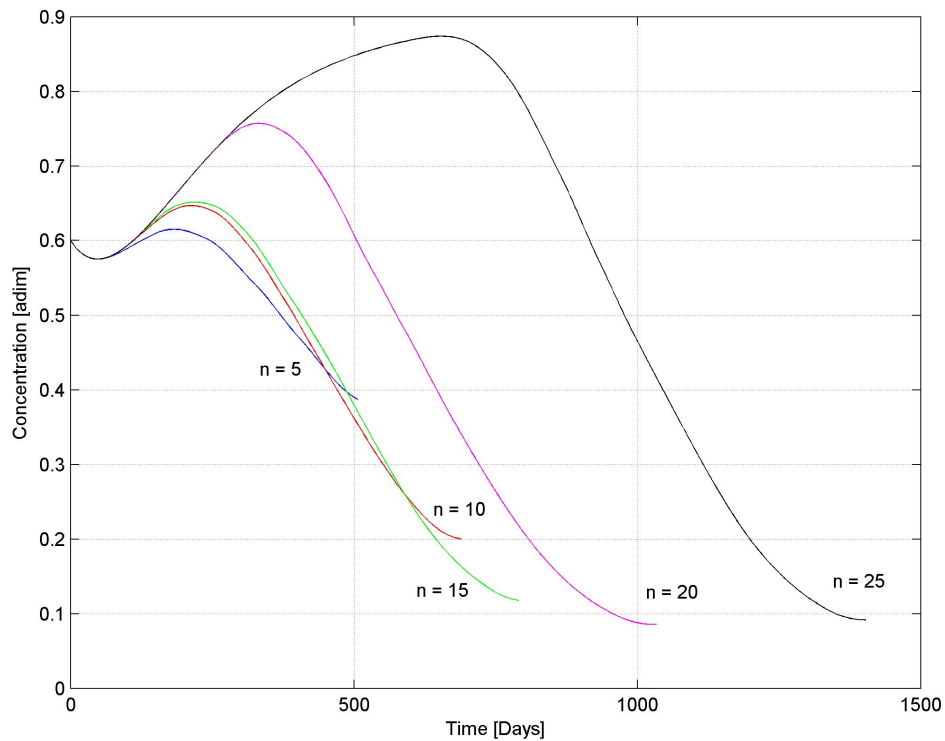


Figure 5.15: Tumor cells concentration as function of the number of injections

the average diversity of individuals from the previous generation. The distance between individuals is an important parameter that can determine the convergence of the optimization. Low distance should compromise the rate of convergence, otherwise high distance determines a rapid convergence but the best individuals are far from the optimal solutions. The solution shows a good compromise in terms of average distance that lead to a good diversity between individuals that enables the algorithm to search a large region of the space.

The population size at each generation has been selected in order to enlarge the search space of the algorithm and consequently obtain better results.

Figures 5.17 and 5.18 the result after the optimization using the hybrid algorithm. One of the relevant aspect of the results is the frequencies of the injections. In the first part of the protocol, the control aims to quickly bring the concentration of Helper cells to the value of maximum saturation. This value we call maximum saturation level for helper cells is closely related to the maximum concentration established for dendritic cells.

As we have seen previously, from this point without control the neoplasia tends to grow in order to reach the tumor regime state.

The control prevent this growth with a first injection, see figure 5.18, which is the one with the highest dosage. This aspect is strictly related to the strategy

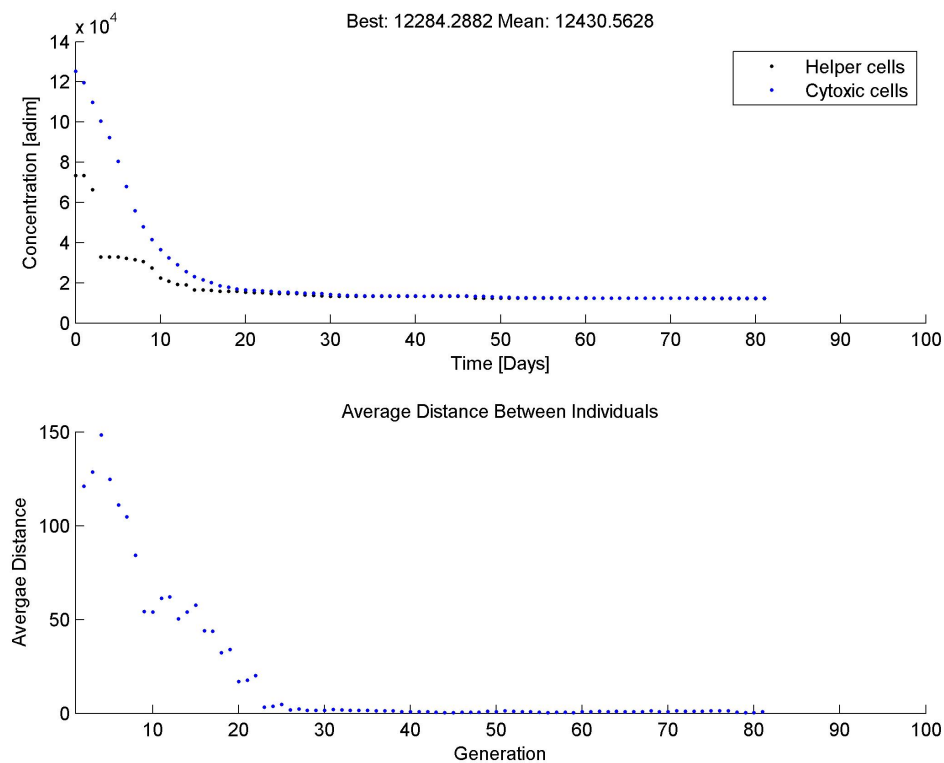


Figure 5.16: Genetic algorithm optimization

that aims to bring the concentration level of the dendritic cells at their maximum admissible value. In this way a new saturation level is fixed for the Helper cells concentration. As a matter of fact we have to emphasize that in the equation 5.1 the level of saturation defined with the second term is strictly dependent from the concentration of dendritic cells.

The first stage with duration of around 300 days consists in a low frequency - high dosage drugs administration. During this period the control gives the way of countering the growing of the tumor cells population and at the same time allows increasing the concentration of Interleukin. This dynamic behavior is in fact dependent on the term related to Dendritic and Helper cells that forced the growth of IL-2 population. As mentioned earlier, the main task of IL-2 is to create an environment that stimulates the growth of the immune system cells. The growth of the cytotoxic cells concentration is precisely due to the combination of phenomenon described.

It is here where the trends to increase and decrease, respectively, for the tumor and cytotoxic cells were reversed that the optimized control strategy enters a new phase. Starting from the fourth injection the frequency of the administration increases while the dosage decreases. In this way you can keep almost the same value of Helper cells concentration, and this stage is where most enforcement

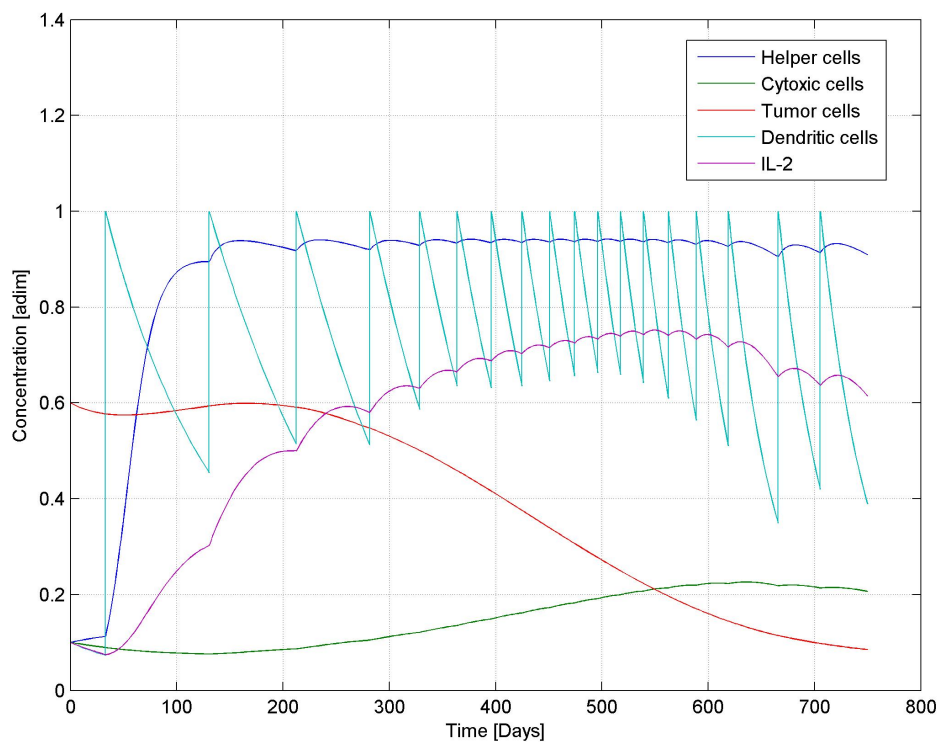


Figure 5.17: State variables optimized with direct transcription with initial conditions generated through GA

Period	Dosage [adim]	Holiday [days]	Period	Dosage [adim]	Holiday [days]
1	0.93	38	10	0.35	21
2	0.56	94	11	0.34	25
3	0.50	80	12	0.35	20
4	0.50	65	13	0.36	23
5	0.43	66	14	0.41	24
6	0.38	32	15	0.40	17
7	0.39	21	16	0.49	39
8	0.38	31	17	0.66	55
9	0.36	25	18	0.58	32

Table 5.5: Drugs holiday period and administration dosage. Minimization of final tumor concentration and penalty on the control with hybrid algorithm



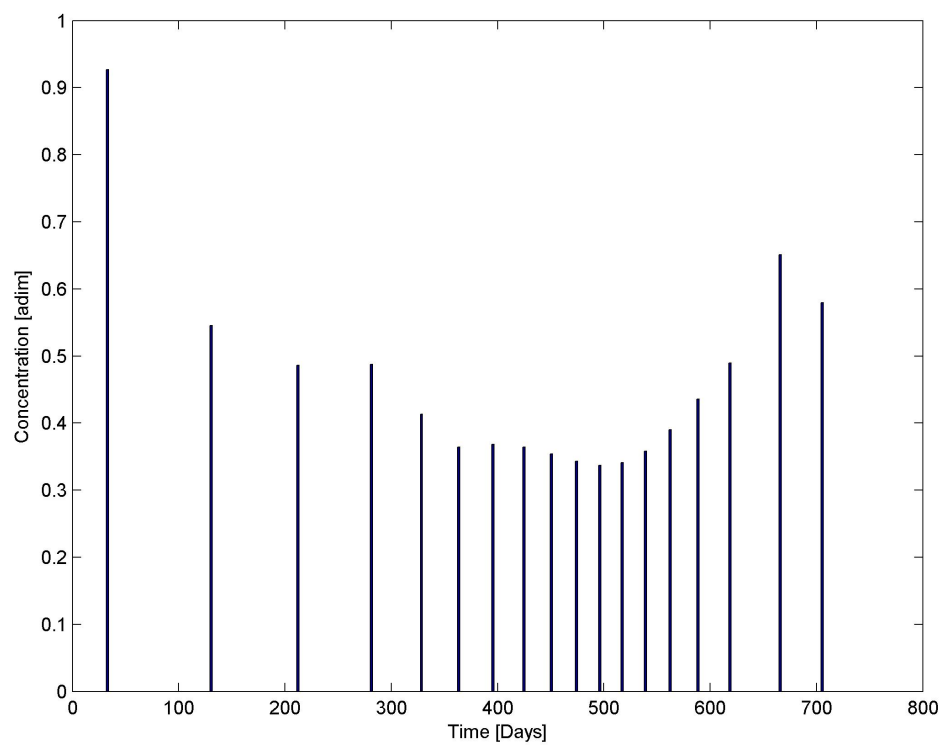


Figure 5.18: Control variables optimized with direct transcription with initial conditions generated through GA

efforts on the growth of tumor cells have been done. In a period of time similar to that of the first phase the tumor mass is reduced by over 60%, thanks to the growth of cytotoxic cells population.

The optimal care protocol consists in a further stage in which the frequency of administration is low. This stage that we can define conservation, serves to maintain the concentration of tumor cells at the levels achieved in the previous period.

It is possible to state in this this period of care that the consumption of dendritic cells is higher compared to the previous phases. This happens because the decrease is directly dependent on the value of cytotoxic cells that as a result of the previous phase is increased. This phenomenon leads to an increase in the injections dosage in this final interval of treatment.

## 5.4 Monte Carlo statistic analysis

In this section we want to analyze the robustness of the control and the sensitivity of the model to small changes in initial conditions. The initial patient conditions are generated through Monte Carlo method in order to explore the solution in a dense space. The first analysis implies a 10 % variation on the initial tumor cells concentration. The average of the initial tumor concentration  $\mu_{T_i}$  evaluated over 1000 samples and the standard deviation  $\sigma_{T_i}$  are reported in table 5.6. The statistic parameters related to the final cancer cells concentration are also shown.

Dynamics	$\mu_{T_i}$	$\sigma_{T_i}$	$\mu_{T_f}$	$\sigma_{T_f}$
Free	0,5982	0,0584	0,8853	4,5969e-5
Controlled	0,6004	0,0571	0,0854	1,2907e-5

Table 5.6: Statistic values. Monte Carlo generation of initial tumor concentration

The average of the initial tumor concentration generated are very close to the nominal value with a high  $\sigma_{T_i}$  in both free and controlled dynamics, while the results are completely different in the final condition. The control appears to be robust from disturbance in the initial condition, because the final tumor concentration is close to the nominal condition for all the samples considered. Figure 5.19 and 5.20 shows respectively the behavior of the tumor variable in the limit concentration cases and the tumor cells concentration for the free dynamics case. These graphs highlight the results given by statistical parameters. It is possible to see that the final condition of tumor regime is reached in the case of free dynamics, thus demonstrating the existence of a strong attractor. After a period of less than one year the solutions converge approximatively at the same value, in fact, the final standard deviation is  $O(10^{-4})$ .

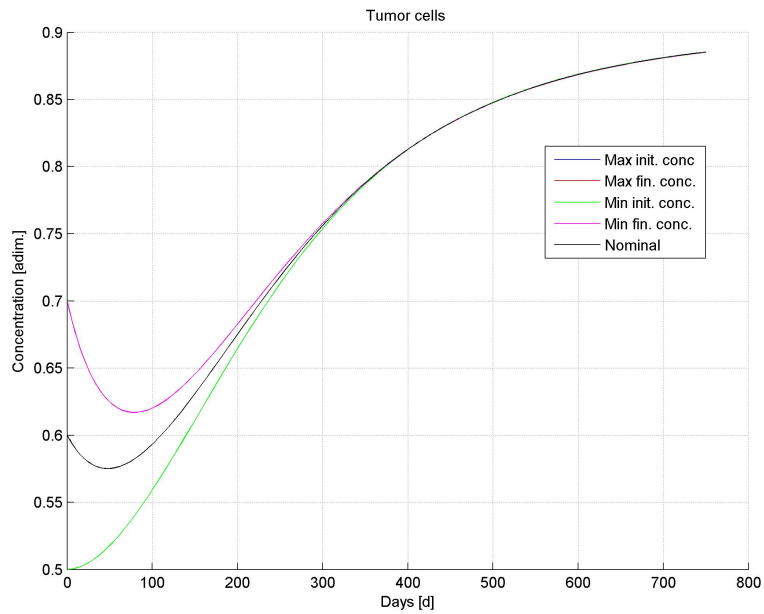


Figure 5.19: Tumor cells concentration versus time, with a Monte Carlo generation of initial tumor concentration. Free dynamic

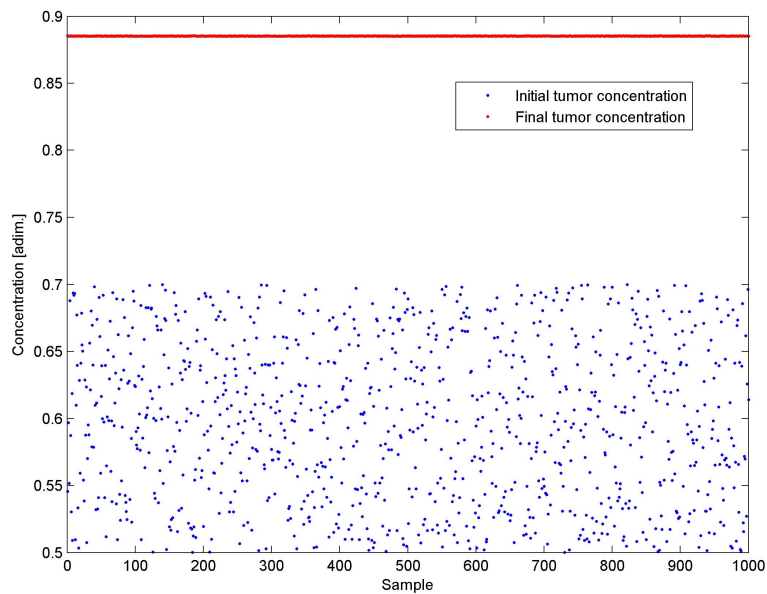


Figure 5.20: Initial and final concentration of tumor cells with a Monte Carlo generation of initial tumor concentration. Free dynamic

The same graphs for the controlled dynamics are reported in figure 5.22 and 5.21. The controlled solution is non sensitive on the variation of the initial tumor cells concentration. The final average tends to converge to the nominal value with a small standard deviation. This appear a great result, the optimal control strategy is robust and can be used with high uncertainty on the initial concentration obtaining positive final results.

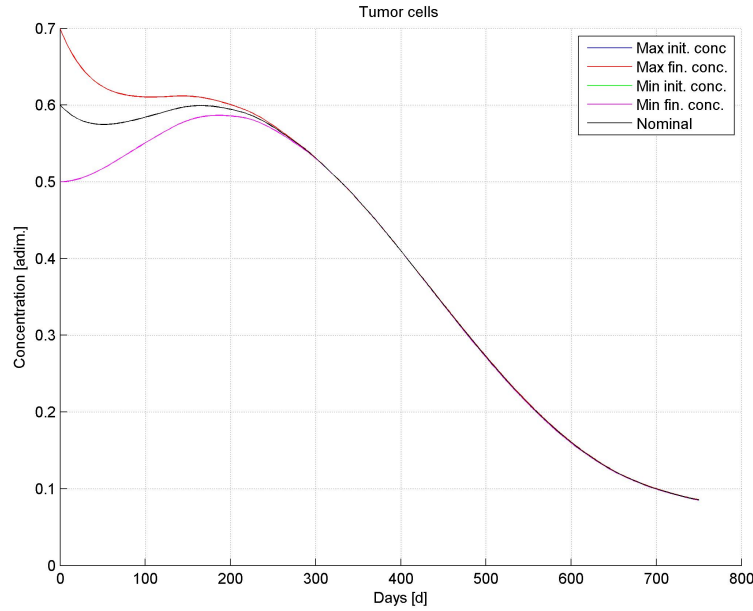


Figure 5.21: Tumor cells concentration versus time, with a Monte Carlo generation of initial tumor concentration.

The same procedural scheme was adopted for the evaluation of system sensitivity due to a variation on the initial state vector. This analysis can evaluate the influence of great disturbance on the dynamics of the free system, but also determines the possibility to use the same protocol therapy for different patients. This aspect is relevant for the clinical application of the treatment proposed.

Dynamics	$\mu_{T_i}$	$\sigma_{T_i}$	$\mu_{T_f}$	$\sigma_{T_i}$
Free	0,6011	0,0566	0,8852	0,0095
Controlled	0,6024	0,0573	0,0827	0,0044

Table 5.7: Statistic values. Monte Carlo generation of initial conditions

Table 5.7 confirms the previous results obtained with fewer disturbances. The final concentration average is quite similar to the previous.

The free dynamics shows and confirm the presence of a tumor regime state attraction that we have previously identified in the Monte Carlo generation of the initial tumor cells concentration.

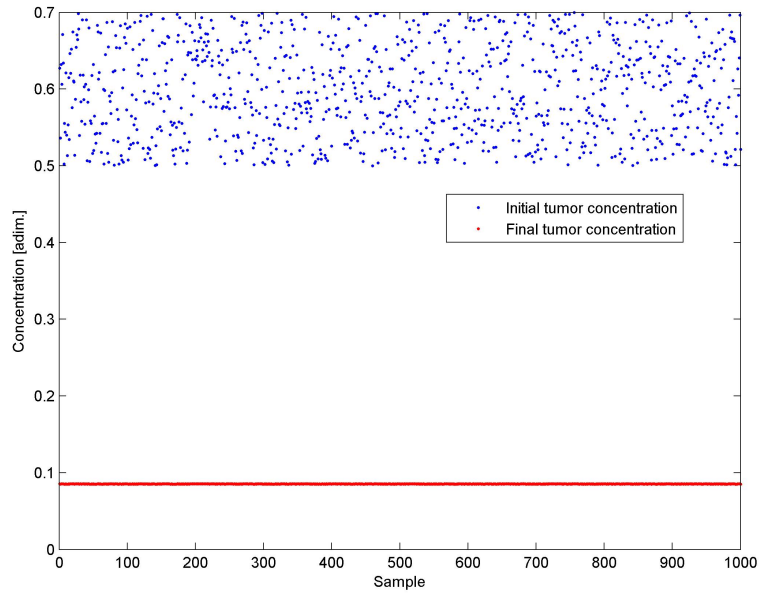


Figure 5.22: Initial and final concentration of tumor cells with a Monte Carlo generation of initial tumor concentration.

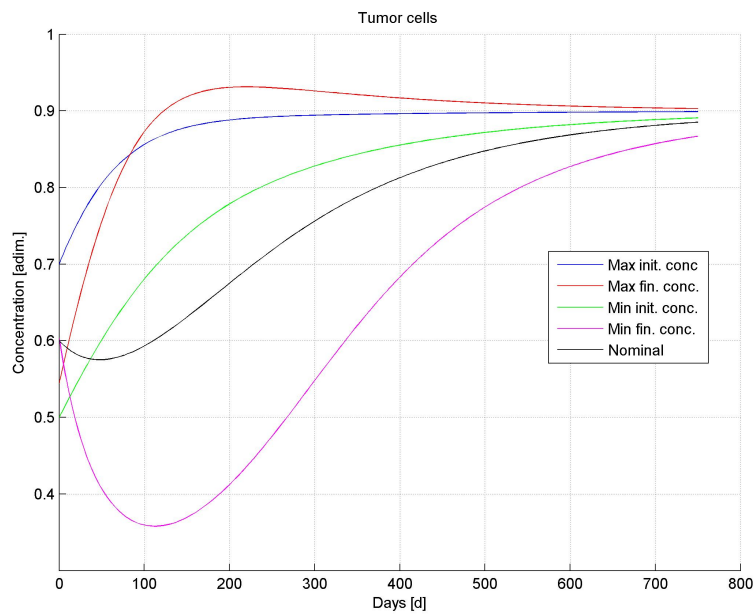


Figure 5.23: Tumor cells concentration versus time, with a Monte Carlo generation of initial conditions. Free dynamic

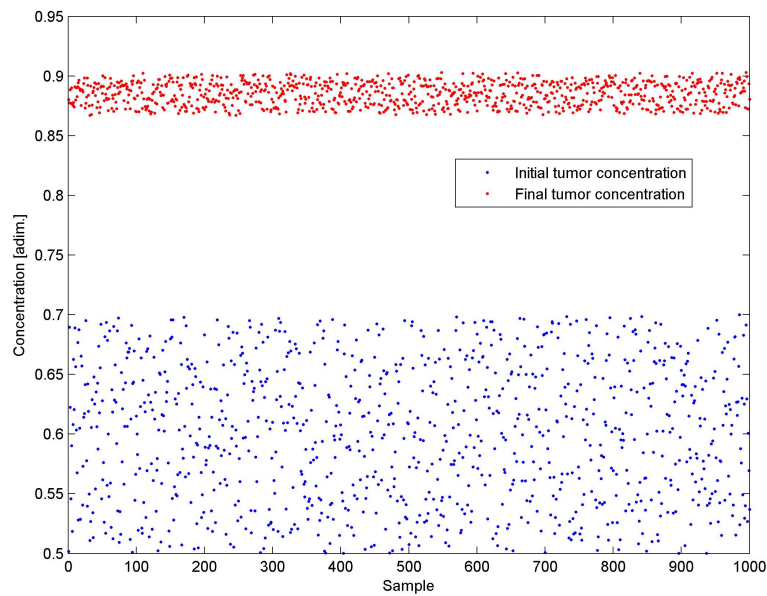


Figure 5.24: Initial and final concentration of tumor cells with a Monte Carlo generation of initial conditions. Free dynamic

The controlled system tends to converge at the nominal value of concentration. The final standard deviation for the controlled system is bigger than that evaluated previously, this aspect is confirmed in figure 5.25 and 5.26. This value is due to the fact that the initial conditions considered are very different, but do not influence the good results of the optimal solution. The tumor concentration at the end of the treatment is always below the initial condition. The standard deviation suggests that the best results are given considering individual therapeutic strategy.

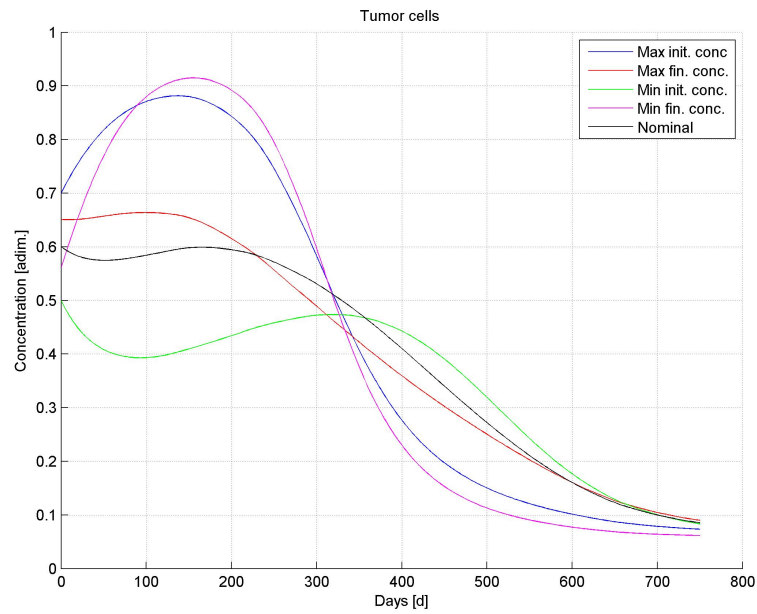


Figure 5.25: Tumor cells concentration versus time, with a Monte Carlo generation of initial conditions

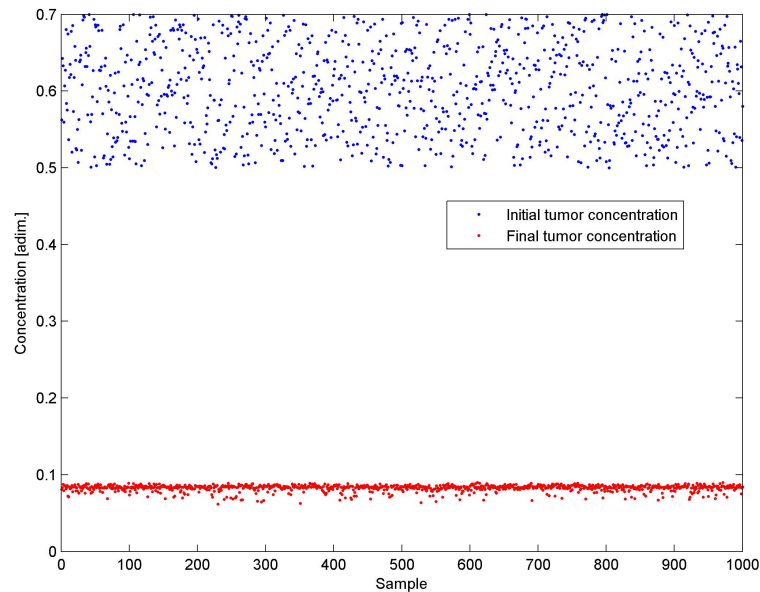


Figure 5.26: Initial and final concentration of tumor cells with a Monte Carlo generation of initial conditions

## 5.5 Gompertz tumor growth law

One of the most interesting aspects in cancer research and in the mathematical modelisation of the phenomenon is the study of the tumor carcinogenesis. This is the process that leads from the onset of a single cancer cell at the time in which the tumor becomes detectable. Crucial in this area is the development of models that are able to correctly describe from appropriate supposes the growth of tumor cells.

The correctness of the model determines the validity of the solution obtained through optimization. To further verify the robustness of solutions we are going to use a different tumor cells law of growth. In [25] different models that describe the dynamics of the tumor with both deterministic and stochastic laws are presented. In this work we have considered only deterministic models leaving to further development the analysis of models with random variables. Given the purely deterministic nature we focus our attention on the Gompertz model.

In the early seventies Falkman [25] assumed that most of the tumor growth develops in two stages: in the initial phase (avascular), the tumor providing nourishment and eliminates what does not serves through transportation only by diffusion. During this phase, tumor growth is limited (no more of few mm) and its shape is roughly spherical. This happens when the cancer consumes the nutrients with a rate proportional to its volume, while the supply of nutrients is achieved with a rate proportional to its surface area.

The second stage (clinically more relevant) is the so-called vascular phase, which can only take place in vivo. This phase involves the formation of new capillary vessels acquired from the surrounding tissues: the phenomenon is called angiogenesis.

Tumors begin the vascularization process secreting a large number of chemical compounds in the surrounding tissues. These compounds are known as angiogenic factors. These factors spread around the tumor and ensure adequate nutrition and adequate oxygenation to invoke surrounding tissues and metastasize also distant tissues.

The deterministic Gompertz model, introduced by Benjamin Gompertz in 1825, is a continuous time model particularly suitable for describing the dynamics of population growth. It is universally adopted to reproduce the growth of organisms, tissues and populations, and is now considered the principal model for describing the growth of tumors. What proposed is a modified exponential growth: it has a growth rate that decrease over time and mortality rate constant. Because of the deceleration in the rate of growth, the tumor size reaches an asymptotic value (carrying capacity).



The model is expressed by the following differential equation:

$$\frac{dM}{dt} = aM - bM \ln M - d_2MC \quad (5.13)$$

where  $a$  is the intrinsic growth rate of the tumor and it is a parameter related to the initial mitotic cell rate,  $b$  is the deceleration factor related with antiangiogenic processes. Unlike the classic model presented in [16], we introduce in the model the term already presented in the equation 5.3 that link the population of tumor cells to cytotoxic cells. In this way we can model the interaction between the immune system and cancer, and then control the system even after the change in the growth law. In order to set the parameter we integrate the first part of

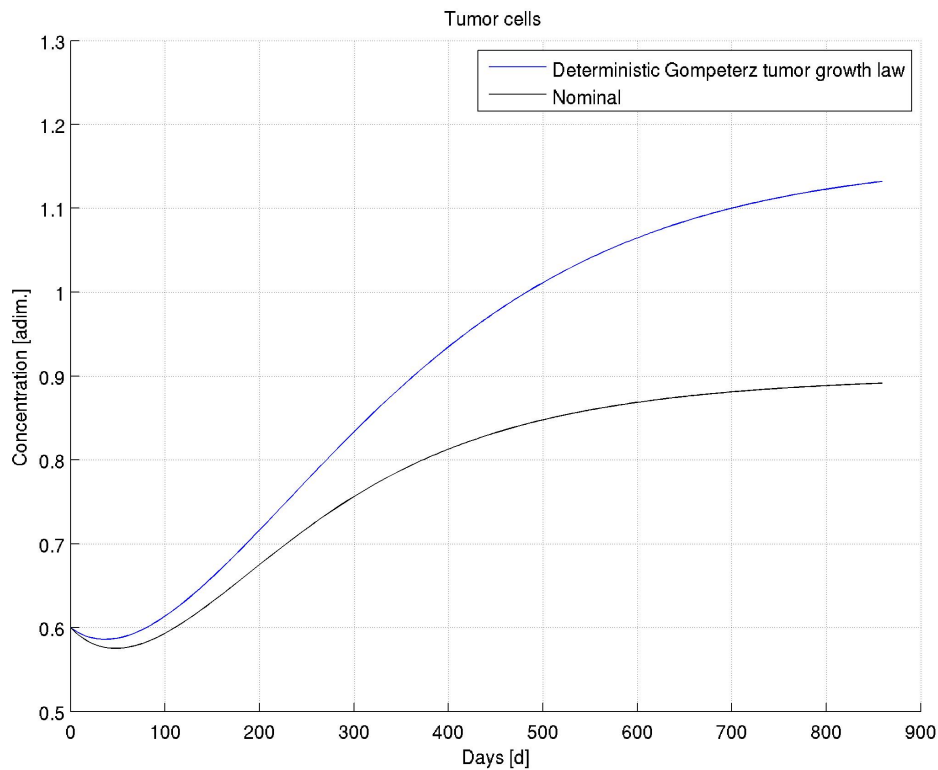


Figure 5.27: Dynamics of the uncontrolled system. Tumor cells concentration equation 5.13. The asymptotic value must be below the carrying capacity of the tumor.

$$\lim_{t \rightarrow \infty} x_0 e^{\frac{a}{b}} (1 - e^{-bt}) = x_0 e^{\frac{a}{b}} < 1 \quad (5.14)$$

The correct integration must consider that the initial concentration must be elevated to  $e^{-bt}$ , but many Gompertz model do not take into account this factor. The relationship obtained from 5.14 tells us that

$$\frac{a}{b} = \ln \frac{l}{x_0} \quad (5.15)$$

Where  $l \in (0, 1)$ . Setting  $l = 0.85$  is a good compromise considering the approximation in the integration and that we have neglect to take into account the term that show the relationship with the immune system cells. This term in fact plays its role in the definition of the asymptotic value of the concentration. A change in the single parameter  $a$  or  $b$  that respect the ratio, determines a change in the time required to the population to reach the regime value. The solution obtained with an appropriate tuning of these parameters compared to the solution obtained with the previous model is shown in figure 5.27. The difference between the two model increases in a monotonically direct proportionality with time.

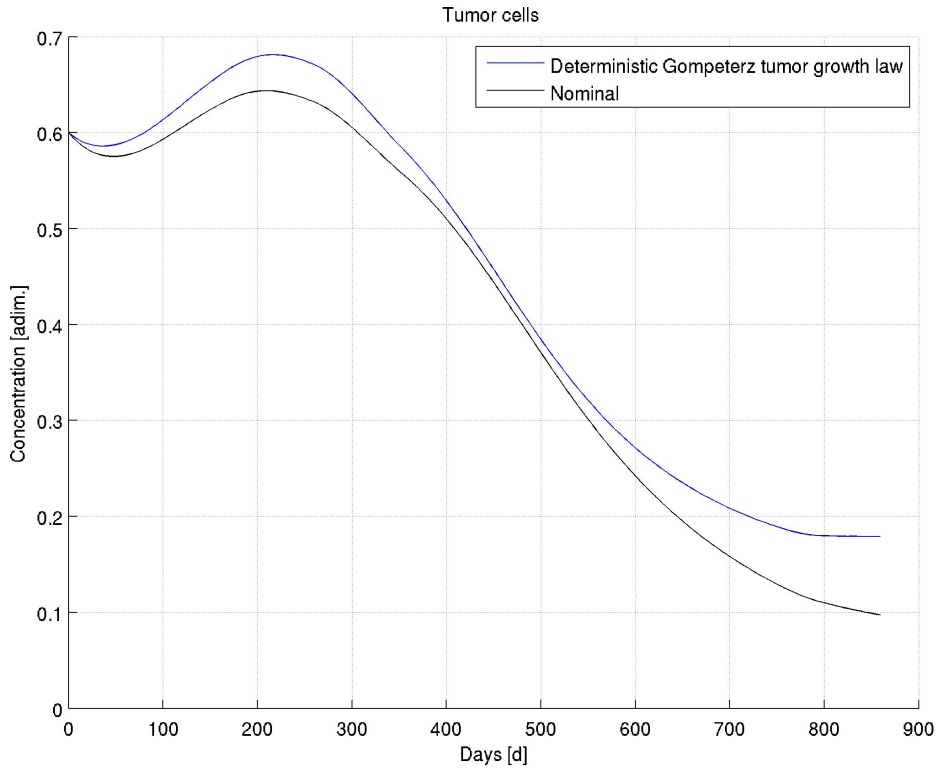


Figure 5.28: Dynamics of the controlled tumor cells population

We want to verify the robustness of the control strategy evaluated through the hybrid algorithm of the CP system modified with the equation 5.13 instead of the 5.3. The following integration scheme is used

$$\mathbf{y}(t) = \begin{cases} \varphi(u = 0, t, x_{i-1}) & t \neq t_i, (t_{i-1}, t_i) \\ \mathbf{y}(t) + \mathbf{p}(u_i) & t = t_i \end{cases} \quad (5.16)$$

where  $\varphi$  is the flow of the system CP modified with the Gompertz law and  $\mathbf{p}$  is a row vector that add the control to the appropriate equation. The solution is shown in figure 5.28 and demonstrate that the optimal control law evaluated with the classical CP model can be applied in order to diminish the cancer cells

concentration in this modified model. In particular it seems that with this tumor growth law the control acts efficiently when the frequency of the injections is high. As a matter of fact in the medium phase of the therapy, when the drugs holiday time is limited, the trajectory of the tumor concentration in the two models are really close each other.

The concentration at the end of the treatment is 15% higher than the one obtained with the classic tumor growth law, but the concentration is around the 30% of the initial concentration. This means that the optimal control identified is a robust strategy that can be applied also with uncertainties on the model.

These uncertainties mainly depends on the fact that obviously this mathematical modelisation of a physical phenomenon that are formalized with observation, experience and interpolation of the database.

## 5.6 Conclusions

Following the same procedure adopted in the discussion of the PK system, starting from the analysis of the free dynamics, we have proposed an optimal control strategy.

From the numerical results it can be seen that the best outcome in terms of final tumor cells concentration is achieved with a strategy not applicable at a clinical level. The best solution consists in a continuous strategy that does not take into account side effects which are not present in the dynamic model, but which characterize the physical phenomenon.

The analysis has evolved looking for solutions that take into account these aspects, but at the same time trying to get closer to the results obtained with the continuous-high dosage therapy. To ensure that the final solution is sensitive to the first guess solution sets a priori without any physical consideration, we have adopted a hybrid algorithm that allowed us to propose an optimal control protocol feasible at a clinical level. The cancer concentration is close to that obtained with the continuous strategy and the control avoids the rapid growth of the immune system cells. This result was achieved by increasing the time horizon of therapy. Furthermore, a complete conclusion of the treatment is possible only if the evolution of the uncontrolled system at the end of the therapy tends to the low tumor concentration stable equilibrium that we have identified in the dynamic analysis. This is not possible starting directly from the final conditions of the therapy. A post-treatment is necessary to bring the values of the immune system cells concentration to the equilibrium values.

The subsequent control robustness analysis respect to uncertainties on parameters, initial conditions and on the tumor dynamic shows that the controlled system despite the disruption can limit in each case the tumor growth.



# Chapter 6

## Analogies between astrodynamics and immunotherapy

This section aims to describe the analogies between the processing of a dynamic model and its control in the different fields of cancer immunotherapy and astrodynamics.

In the previous chapters is described in a specific way the dynamics and control models for immunotherapy against cancer. The models that are used for optimization of spacecraft trajectories are introduced here, and in particular with the problem of interplanetary transfer will be used as comparisons.

The aim is not to solve with the direct or indirect methods described above a complex problem of trajectories optimal control. The dynamic models and the control strategies adopted will be taken into analysis, and it will be given emphasis to the similarity in the resolution.

What we want to demonstrate is that despite the diversity of physical models analyzed in the two areas, the philosophy which leads to an optimal final solution is the same.

### 6.1 The n-body problem

In this section, as a difference from the cancer immunotherapy problem, the analysis of the astrodynamics problem starts with the most complex model. With a series of approximations and hypothesis we arrive to more simple models that are used in practice.

In astrodynamics the motion of a body like a spacecraft or a meteorite is studied under the gravitational influences of primary bodies (Sun, planets and moons e.g.). These entities are considered primaries because the spacecrafts or the meteorites can be approximated as massless in comparison to them.

The Newtonian inverse square distance law describes the motion of  $n \geq 2$  mass  $m_k$

$k = 1, \dots, n$  moving in the three dimensional space  $(x, y, z)$ :

$$m_k \ddot{\mathbf{r}}_k = \sum_{j=1}^n G \frac{m_j m_k}{r_{jk}^3} (\mathbf{r}_j - \mathbf{r}_k) \quad (6.1)$$

where  $\mathbf{r}_k$  is the position vector of the  $k$ -th body and  $r_{jk} = \sqrt{(x_j - x_k)^2 + (y_j - y_k)^2 + (z_j - z_k)^2}$  is the Euclidean distance between two different masses.

Equation 6.1 states that the motion of a single body is influenced by the vector field generated by the other masses. It describes the dynamics of all the  $n$  body and it shows that they influence each other through the gravitational acceleration. In astrodynamics the trajectories of the primaries are given as a function of the time and the problem is restricted to study the motion of the  $n$ -th infinitesimal mass. The hypothesis of the restricted  $n$ -body problem are:

- the primaries moves under their mutual influences;
- the  $n$ -th body does not influence the motion of the primaries, but it moves in the vector field generated by the  $n-1$  bodies.

The system of equation of the restricted  $n$ -body problem that describes the motion of the spacecraft is

$$\ddot{\mathbf{r}}_k = \sum_{i=1}^n G m_i \frac{\mathbf{r}_i - \mathbf{r}}{\|\mathbf{r}_i - \mathbf{r}\|^3} \quad (6.2)$$

## 6.2 Two-body problem

The basic approach to the problem is determining the motion of two bodies due solely to their own mutual gravitational attraction. Considering the Spacecraft and a planet, the effects of gravitational attraction on the planet due to the spacecraft is negligible. The dynamics derives from the system 6.2 for  $k=1:2$  can be written as

$$\begin{aligned} \ddot{\mathbf{R}}_1 &= -G m_2 \frac{\mathbf{R}_1 - \mathbf{R}_2}{R_{21}^3} \\ \ddot{\mathbf{R}}_2 &= -G m_1 \frac{\mathbf{R}_2 - \mathbf{R}_1}{R_{12}^3} \end{aligned} \quad (6.3)$$

where the subscripts refer respectively to the planet and to the spacecraft. With the assumption that the mass of the spacecraft is negligible with respect to the planet mass, the dynamics of the spacecraft obtained from the previous system is written as:

$$\ddot{\mathbf{r}} = -\mu \frac{\mathbf{r}}{r^3} \quad (6.4)$$

where  $\mathbf{r}$  is the relative position between the spacecraft and the planet and  $\mu$  is the gravitational constant of the planet considered.

In this case it is often useful to switch to polar coordinates  $(r, \theta)$ , since the motion is planar.

Equations 6.4 translated in polar coordinates are:

$$\left(\ddot{r} - r\dot{\theta}^2\right) \hat{r} + r\ddot{\theta} + 2\dot{r}\dot{\theta}\hat{\theta} = -\mu\frac{\hat{r}}{r^2} \quad (6.5)$$

Splitting equations 6.5 in the transverse and tangential component with  $u$  radial velocity and  $v = r\dot{\theta}$ , the 2BP can be written in a set of first order differential equations:

$$\begin{aligned} \dot{r} &= u \\ \dot{u} &= \frac{v^2}{r} - \frac{\mu}{r^2} \\ \dot{v} &= -\frac{uv}{r} \end{aligned} \quad (6.6)$$

### 6.3 Interplanetary transfer solved via direct transcription

In previous chapter all the ingredients of the direct transcription and genetic algorithm have been presented and we have applied these numeric algorithm in order to solve cancer immunotherapy problems In perfect analogy, the versatility of this approach can permits to solve an optimal control problem for an interplanetary transfer using the simple model presented in the previous section.

The equation for the controlled motion of the spacecraft obtained form 6.6 adding the term that takes into account the propulsive thrust are:

$$\begin{aligned} \dot{r} &= u \\ \dot{u} &= \frac{v^2}{r} - \frac{\mu}{r^2} + \frac{T}{m} \sin \Phi \\ \dot{v} &= -\frac{uv}{r} + \frac{T}{m} \cos \Phi \end{aligned} \quad (6.7)$$

where

$r$  = radial distance of spacecraft from the attracting center

$u$  = radial velocity

$v$  = transverse velocity

$T$  = propulsive thrust

$m$  = spacecraft mass

$\Phi$  = thrust angle

$\mu$  = gravitational constant

The problem goal is to maximize the radius of the final circular orbit in a given time  $t_f$ .

The spacecraft at the beginning is orbiting around a circular path. The initial

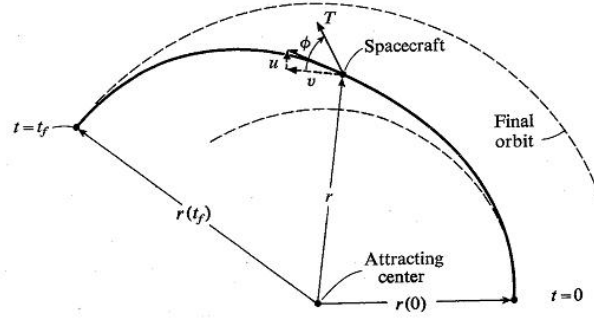


Figure 6.1: Earth-Mars transfer problem

boundary conditions are defined as:

$$r(t_i) = r_0 \quad (6.8)$$

$$u(t_i) = 0 \quad (6.9)$$

$$v(t_i) = \sqrt{\frac{\mu}{r_0}} \quad (6.10)$$

It is possible to formalize it as

$$\phi_i : \mathbf{y}(t_i) - \left\{ r_0, 0, \sqrt{\mu/r_0} \right\}^T \quad (6.11)$$

The final boundary conditions are selected in order to define a circular orbit:

$$u(t_f) = 0 \quad (6.12)$$

$$v(t_f) = \sqrt{\frac{\mu}{r(t_f)}} \quad (6.13)$$

In the transcription formalism these conditions are defined as

$$\phi_f : \mathbf{y}(t_f) - \left\{ u(t_f) - 0, v(t_f) - \sqrt{\mu/r(t_f)} \right\}^T \quad (6.14)$$

Considering fuel consumption it is possible to define the spacecraft mass as :

$$m(t) = m_0 - \dot{m}t \quad (6.15)$$

where  $m_0$  is the initial mass and  $\dot{m}$  is the propellant flow rate.

In order to solve numerically the problem it is necessary to adimensionalize the problem.

The adimensionalized equation are

$$\begin{aligned} \dot{x}_1 &= x_2 \\ \dot{x}_2 &= \left( x_3^2 - \frac{1}{x_1} \right) / x_1 + \gamma \sin(u) \\ \dot{x}_3 &= -\frac{x_2 x_3}{x_1} + \gamma \cos(u) \end{aligned} \quad (6.16)$$



where  $\gamma = \frac{\alpha}{1-\beta t}$  and the state vector is defined as  $\mathbf{y} = \{x_1, x_2, x_3\}$ . The dynamics is translated into  $3(N-1)$  defect equations  $\xi_k$ , with  $N$  equal to the number of grid points and  $k=1, \dots, N-1$ . These equations are equality constraints that represent the Hermite-Simpson numerical integration over the sub-interval  $[t_j, t_{j+1}]$ ,  $j=1, \dots, N-1$ . In this way it is possible to determine an equality constraint vector as

$$\mathbf{c}(\mathbf{x}) = \{\phi_i, \xi_1, \dots, \xi_{N-1}, \phi_f\} \quad (6.17)$$

The performance to be maximized is the final radius and can be stated in the NLP formalism as

$$F(\mathbf{x}) = -r_N \quad (6.18)$$

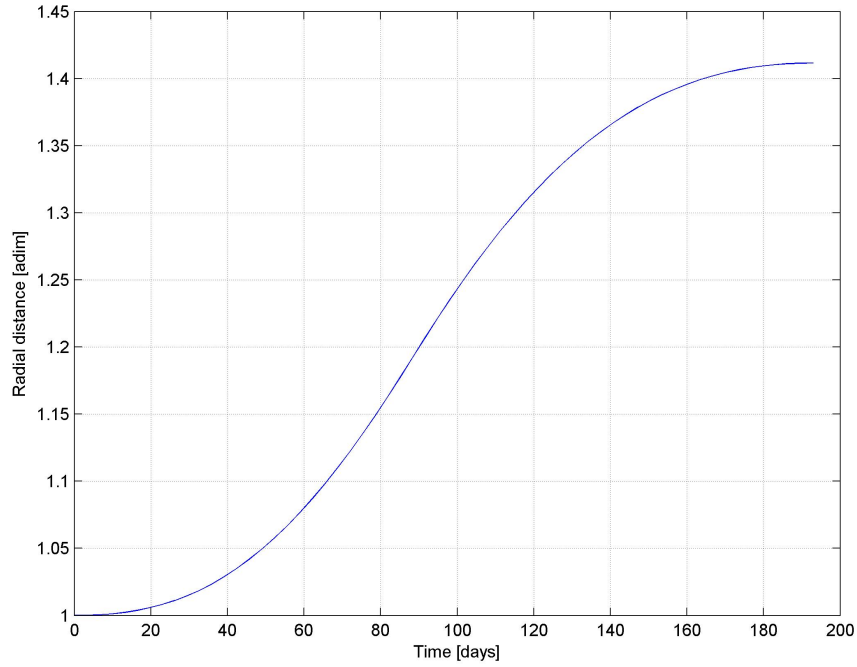


Figure 6.2: Radial distance

The solution for the control is shown in figure 6.5. The thrust angle determines a thrust direction outward in the first half of the trajectory and inward in the second half, obtaining a final radius that is close with Mars orbit.

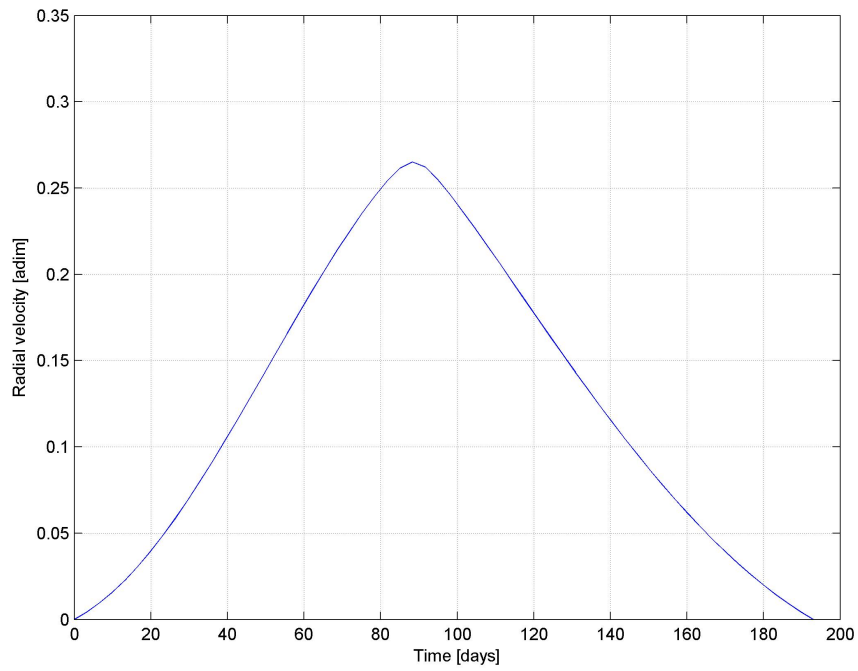


Figure 6.3: Radial velocity

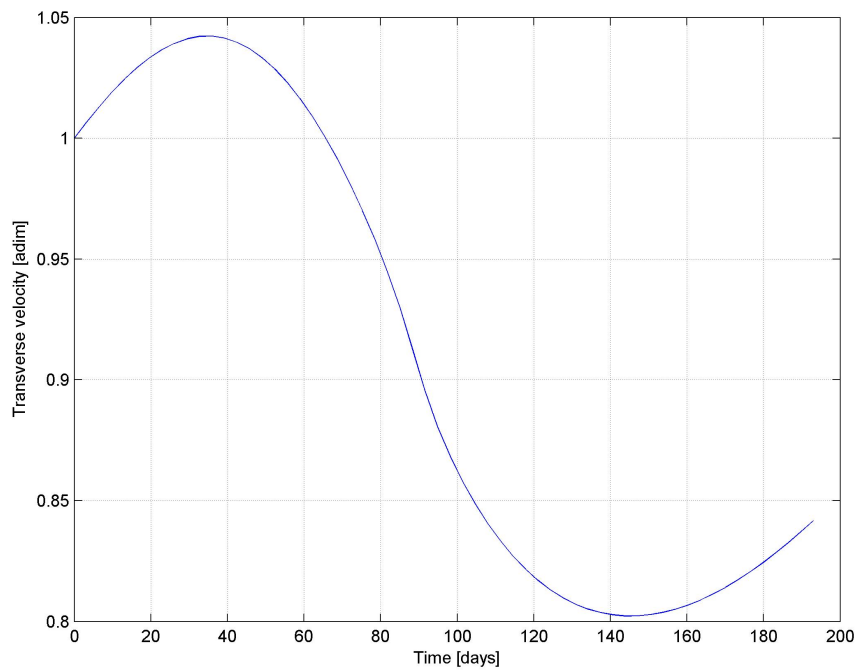


Figure 6.4: Transverse velocity

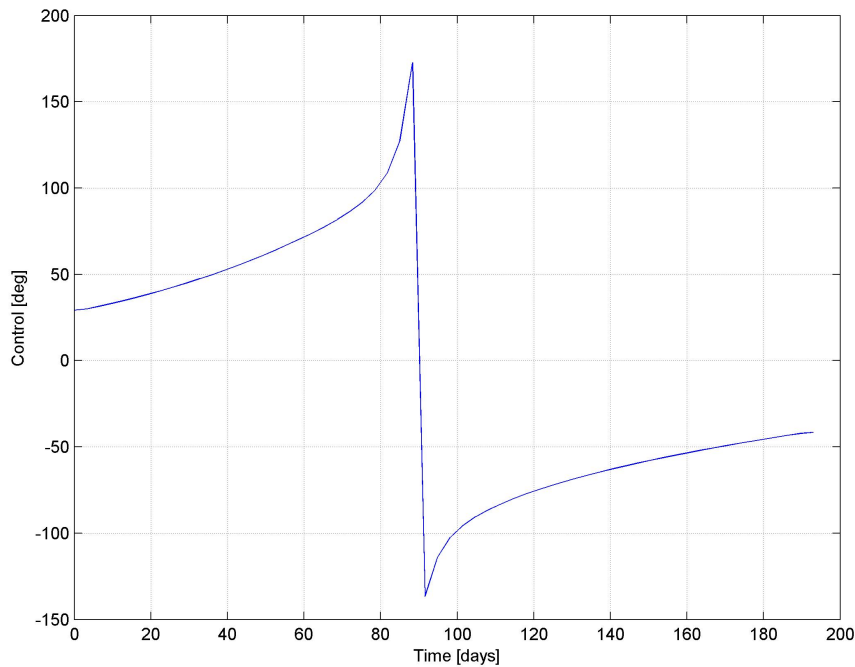


Figure 6.5: Thrust angle

## 6.4 Interplanetary transfer solved via genetic algorithm

GAs are attractive when the number of variables is limited such as in impulsive control problems that will be considered later. In this section an interplanetary low-thrust transfer solved via genetic algorithm will be presented in order to proceed in analogy with the immunotherapy optimization problem. The problem is similar to that analyzed with direct transcription and it is formulated in [13]. The goal is determine the control profile that minimizes propellant consumption while satisfying specified boundary conditions. The planar dynamic in the polar coordinates  $(r, \theta)$  is rewritten as a first order ODE system:

$$\begin{aligned}
 \dot{r} &= u \\
 \dot{\theta} &= \frac{v}{r} \\
 \dot{u} &= \frac{r}{v^2} - \frac{\mu}{r^2} + \frac{T \sin(\Phi)}{m_0 - \dot{m}t} \\
 \dot{v} &= \frac{uv}{r} + \frac{T \cos(\Phi)}{m_0 - \dot{m}t}
 \end{aligned} \tag{6.19}$$

As a difference from the previous problem in this case the control variables are the thrust magnitude  $T$  and the thrust direction  $\Phi$  that resides between 0 and 360 deg. The thrust can range between 0 and 3.787N, the maximum provided by the electric motor. The transfer time is fixed in 200 days. In addition circular orbits

for both Earth and Mars are assumed. The boundary initial and final conditions represent respectively Earth and Mars orbit:

$$\begin{aligned} x_0 &= [1, 0, 1, 0] \\ x_f &= [1.524, 0, 0.81, free] \end{aligned} \quad (6.20)$$

where the dimension used are distance unit and time unit.

Solve a low-thrust problem with this optimization procedure is strictly linked with a loss of accuracy.

The genetic algorithms are used for unconstrained problem, because they do not take into account any constraints directly. It is possible to overcome this aspect introducing a penalty function in the cost functional that maximize its value if the constraints are not respected. The direct consequence is that the individuals that do not respect the constraints will be discarded by the optimization because of the survival of the fittest. This modification is called Augmented Lagrangian Genetic Algorithm [50].

Representing the 3-dimensional vector of the constraints by

$$\mathbf{g} = [r_f - x_f(1), u_f - x_f(2), v_f - x_f(3)] \quad (6.21)$$

The functional cost  $J$  is equal to the mass consumption defined as:

$$\dot{m}(t) = -\frac{T(t)}{v_e} \quad (6.22)$$

where  $v_e$  is the gas exhaust velocity.

The fitness function can be written as

$$\hat{J} = J + w\mathbf{g}\mathbf{g}^T \quad (6.23)$$

where  $J$  is the cost functional and  $w$  is the weight of the penalty function.

Figure 6.6 shows the trend of the fitness function 6.23 at each generation and figure 6.7 shows the creation of a new population using the genetic mechanisms. The red lines indicate children obtained after mutations, blue lines indicate crossover children while black lines indicate elite individuals.

Solve a low-thrust problem with this optimization procedure is strictly linked with a loss of accuracy, but the solution obtained can results useful as an initial guess for a direct transcription algorithm. In fact the final conditions on the state are not completely satisfied figure (6.9) and (6.8).

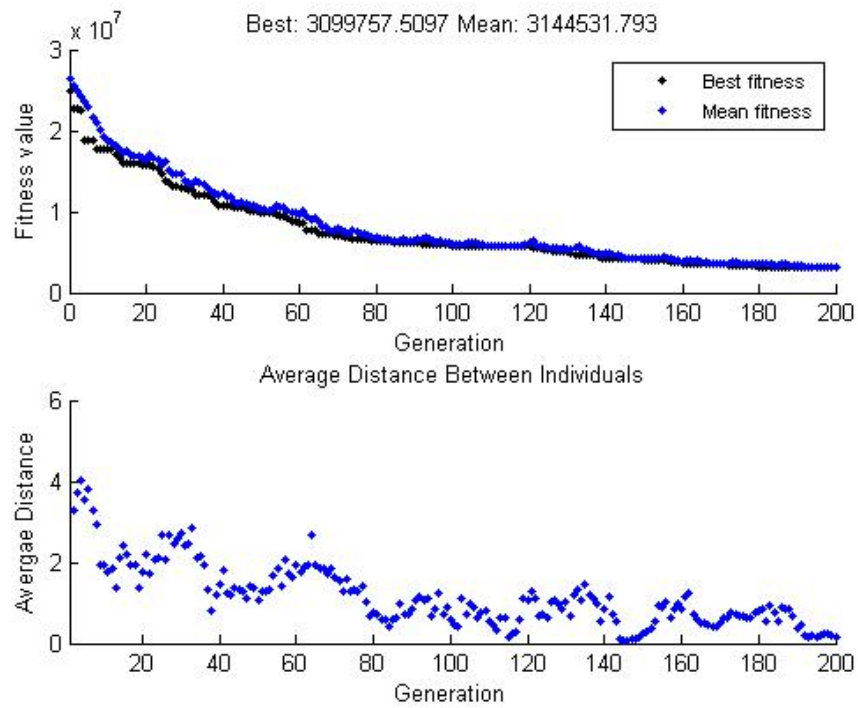


Figure 6.6: Genetic algorithm fitness value

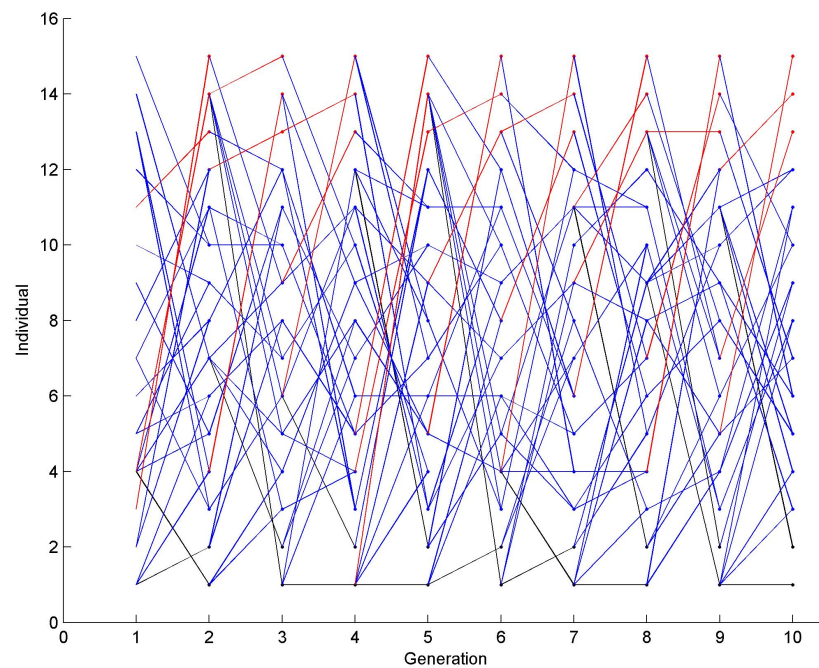


Figure 6.7: Algorithm genealogy over 10 generations

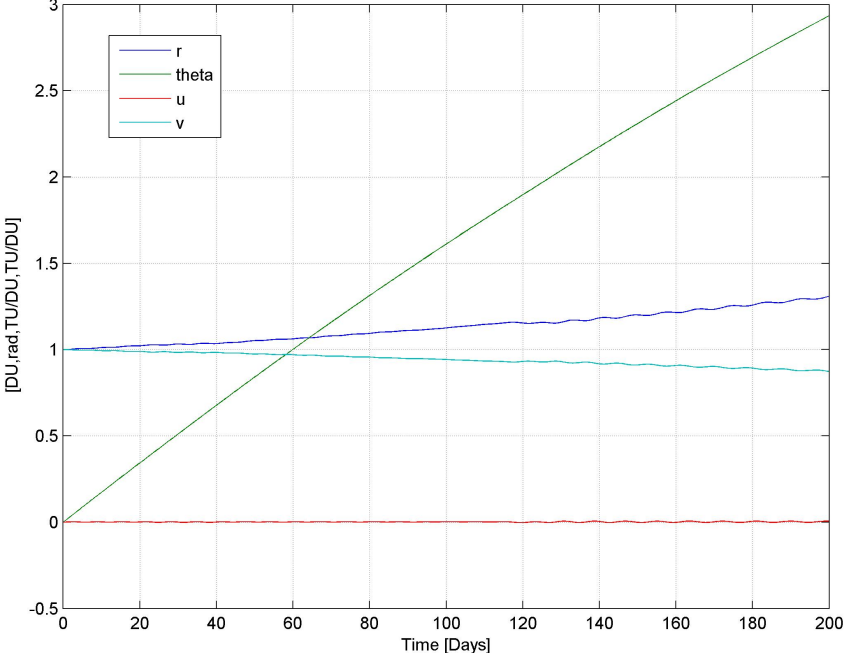


Figure 6.8: State variables

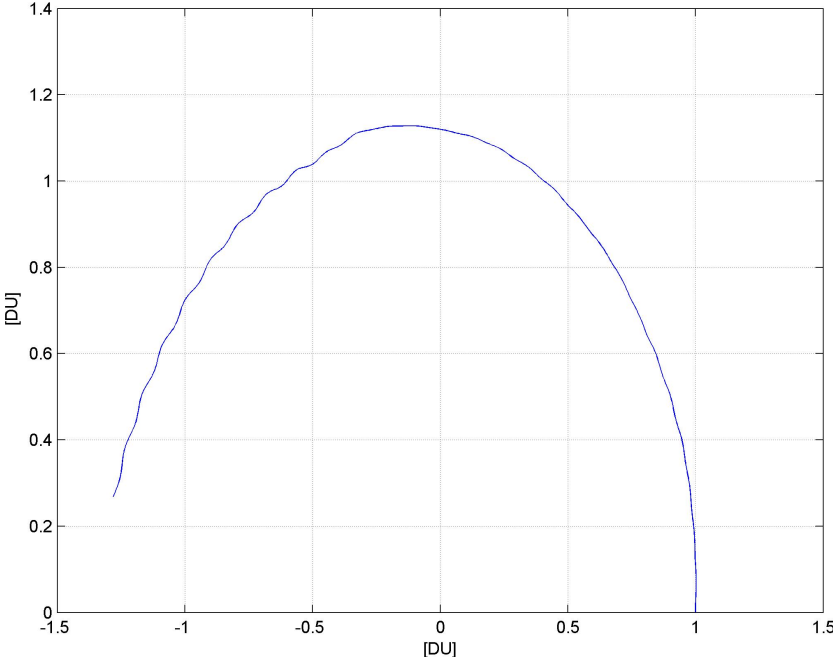


Figure 6.9: Spacecraft trajectory

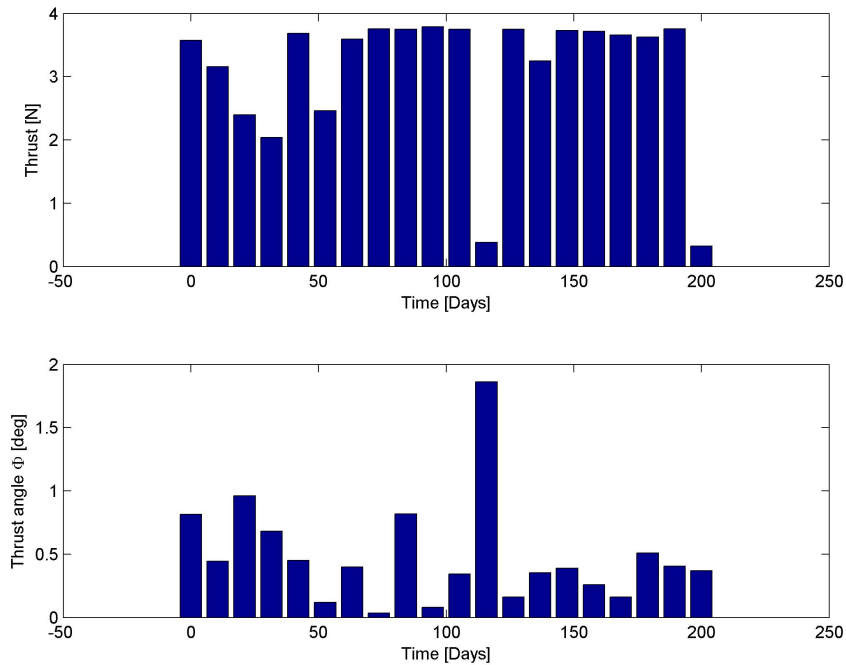


Figure 6.10: Control variables

## 6.5 The restricted three-body problem

The two-body problem is a simple model but do not satisfy accuracy requirements in the final solution. In this section and in the following we want to upgrade the model such as in the immunotherapy problem and optimize the trajectory design using direct transcription. Euler's three-body problem describe the motion of a mass under the influence of two centers that attract the particle with central forces that decrease with distance as an inverse-square law, such as Newtonian gravity. The equations of motion of the restricted three body problem derives from the system 6.2 for  $k=1:3$

$$\begin{aligned}
 \ddot{\mathbf{R}}_1 &= -Gm_2 \frac{\mathbf{R}_1 - \mathbf{R}_2}{R_{21}^3} - Gm_3 \frac{\mathbf{R}_1 - \mathbf{R}_3}{R_{31}^3} \\
 \ddot{\mathbf{R}}_2 &= -Gm_1 \frac{\mathbf{R}_2 - \mathbf{R}_1}{R_{12}^3} - Gm_3 \frac{\mathbf{R}_2 - \mathbf{R}_3}{R_{32}^3} \\
 \ddot{\mathbf{R}}_3 &= -Gm_1 \frac{\mathbf{R}_3 - \mathbf{R}_1}{R_{13}^3} - Gm_2 \frac{\mathbf{R}_3 - \mathbf{R}_2}{R_{32}^3}
 \end{aligned} \tag{6.24}$$

where  $\mathbf{R}$  are the position vectors described in an inertial frame (figure 6.11). The first two equations describe the motion of the primaries, while the last one represent the spacecraft dynamics.

Introducing the hypthothesis that the spacecraft gravitational attraction on the primaries is negligible, the restricted three body problem becomes

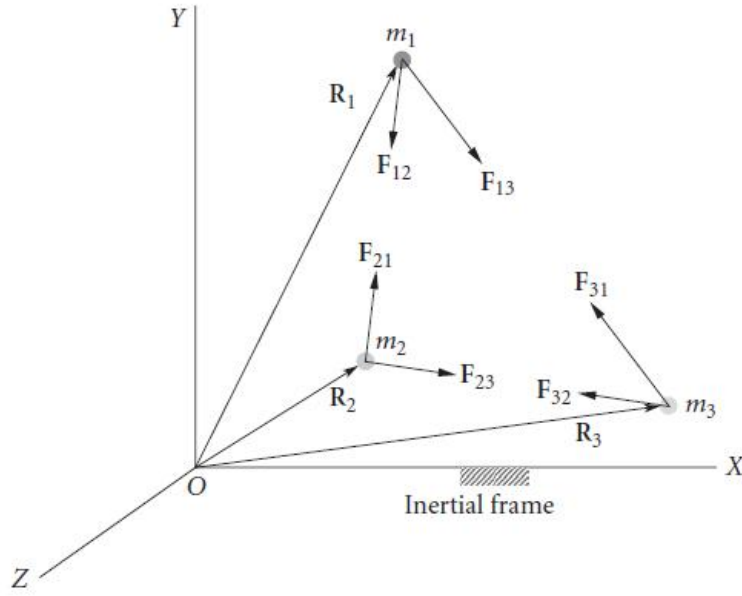


Figure 6.11: Three body problem

$$\begin{aligned}
 \ddot{\mathbf{R}}_1 &= -Gm_2 \frac{\mathbf{R}_1 - \mathbf{R}_2}{R_{21}^3} \\
 \ddot{\mathbf{R}}_2 &= -Gm_1 \frac{\mathbf{R}_2 - \mathbf{R}_1}{R_{12}^3} \\
 \ddot{\mathbf{R}}_3 &= -Gm_1 \frac{\mathbf{R}_3 - \mathbf{R}_1}{R_{13}^3} - Gm_2 \frac{\mathbf{R}_3 - \mathbf{R}_2}{R_{32}^3}
 \end{aligned} \tag{6.25}$$

The system states that the primaries interact each other through the Kepler problem. The primaries are assumed to move in circular orbits around their common center of mass. This assumption defines the circular restricted three body problem - RTBP from now on for brevity. The last system of equations study the influence of the primaries on the motion of the spacecraft. These three second order differential equations can be rewritten in an inertial frame centered at the baricenter of the primaries

$$\ddot{\mathbf{R}}_3 = -Gm_1 \frac{\mathbf{R} - \mathbf{R}_1}{R_1^3} - Gm_2 \frac{\mathbf{R} - \mathbf{R}_2}{R_2^3} \tag{6.26}$$

where  $\mathbf{R}$ ,  $\mathbf{R}_1$ ,  $\mathbf{R}_2$  are the spacecraft position and its distances to the primaries respectively.

System 6.26 is time dependent, because the vectors are defined as function of the time. In order to get the equations autonomous we rewrite the equations in the synodic system. This frame is centered at the baricenter of the primaries and rotate uniformly with them. The plane of motion of the primaries is the y-axis and they are fixed in the x-axis.

The spacecraft position in the synodic system  $\mathbf{r}$  is related to the position  $\mathbf{R}$  in the sidereal system through the rotation matrix  $T(t)$  defined by the uniform angular



velocity  $\omega = \{0, 0, n\}^T$ .

$$\mathbf{R}(t) = T(t)\mathbf{r} \quad (6.27)$$

Applying this system transformation, the equations of the RTBP can be rewritten

$$\frac{d^2\mathbf{r}}{dt^2} + 2\omega \times \frac{d\mathbf{r}}{dt} + \omega \times (\omega \times \mathbf{r}) = -Gm_1 \frac{\mathbf{R} - \mathbf{R}_1}{R_1^3} - Gm_2 \frac{\mathbf{R} - \mathbf{R}_2}{R_2^3} \quad (6.28)$$

The rotation of the reference frame introduce the centrifugal and Coriolis terms. Considering  $r = \{x, y, z\}^T$  the coordinates of the spacecraft and  $\{0, 0, x_1\}^T$   $\{0, 0, x_2\}^T$  the fixed positions of the primaries, the equations 6.28 can be rewritten explicitly

$$\begin{aligned} \ddot{x} - 2n\dot{y} - n^2x &= -Gm_1 \frac{x-x_1}{r_1^3} - Gm_2 \frac{x-x_2}{r_2^3} \\ \ddot{y} - 2n\dot{x} - n^2y &= -Gm_1 \frac{y}{r_1^3} - Gm_2 \frac{y}{r_2^3} \\ \ddot{z} &= -Gm_1 \frac{z}{r_1^3} - Gm_2 \frac{z}{r_2^3} \end{aligned} \quad (6.29)$$

The next step is to introduce a dimensionless set of equations where the distance between the two primaries, their angular velocity and the sum of the masses  $m_1$  and  $m_2$  are set to one. The dimensionless equations of the RTBP are

$$\begin{aligned} \ddot{x} - 2\dot{y} &= \Omega_x \\ \ddot{y} - 2\dot{x} &= \Omega_y \\ \ddot{z} &= \Omega_z \end{aligned} \quad (6.30)$$

where the subscripts denote the partial derivatives of the auxiliary function

$$\Omega(x, y, z) = \frac{1}{2}(x^2 + y^2) + \frac{1-\mu}{r_1} + \frac{\mu}{r_2} + \frac{1}{2}\mu(1-\mu) \quad (6.31)$$

where  $\mu$  is the mass parameter

$$\mu = \frac{m_2}{m_1 + m_2} \quad (6.32)$$

with this choice  $G=1$  and the position of the primaries are set to  $r_1 = \{-\mu, 0, 0\}^T$  and  $r_2 = \{1-\mu, 0, 0\}^T$ , while  $r_1$  and  $r_2$  are the euclidean distances between the spacecraft and the primaries.

## 6.6 Low thrust transfer

We have introduced the free dynamics of the spacecraft. In this section we want to introduce the optimal control theory, in particular the design of an optimal low thrust arc. The equations of the controlled RTBP states as follows

$$\begin{aligned} \ddot{x} - 2\dot{y} &= \Omega_x + u \\ \ddot{y} - 2\dot{x} &= \Omega_y + v \\ \ddot{z} &= \Omega_z + w \end{aligned} \quad (6.33)$$

In the case of low thrust trajectory the control  $\mathbf{u} = \{u, v, w\}^T$  is the force per unit mass

### 6.6.1 The optimal trajectory design problem

The equations of the controlled RTBP must be written in the first order form  $\dot{\mathbf{y}} = \mathbf{f}(\mathbf{y}(t), \mathbf{u}(t), t)$  in order to design the optimal control. The problem states :

$$\begin{aligned} \dot{x} &= v_x \\ \dot{y} &= v_y \\ \dot{z} &= v_z \\ \dot{v}_x &= 2v_y + \Omega_x + u_x \\ \dot{v}_y &= -2v_x + \Omega_y + u_y \\ \dot{v}_z &= \Omega_z + u_z \end{aligned} \tag{6.34}$$

The objective is to design the optimal low thrust transfers to the Earth-Moon Halo orbit that minimizes the following scalar performance index

$$J = \frac{1}{2} \int_{t_i}^{t_f} \mathbf{u}^T \mathbf{u} dt \tag{6.35}$$

while satisfying certain mission constraints.

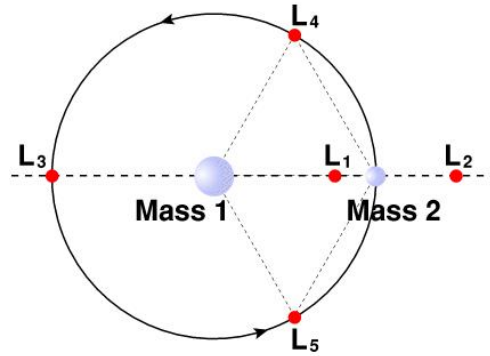


Figure 6.12: Lagrangian points

Halo orbits are strictly linked with the identification of the five equilibrium of the R3BP, called Lagrangian points (figure 6.12). All of these points lie in the primaries plane and two of them  $L_4$  and  $L_5$  form equilateral triangles with the primaries, while the other lies on the joining line of the primaries and are called collinear libration points ( $L_1, L_2$  and  $L_3$ ). Halo orbits are three-dimensional periodic orbits around the collinear points. The motion on these orbits is not constrained to lie on the primaries plane, but it can present an out-of-plane component. Their interesting characteristic is the constant relative position of the orbit with respect to the primaries.

### 6.6.2 Boundary and saturation conditions

The problem consists in a two point boundary value problem. In order to define the correct initial condition the mission strategy has been selected. The spacecraft is propelled tangentially in order to raise its semimajor axis in the minimum time and then the optimal control problem is solved between the tangential spire and the stable manifold. Hence the initial state of the optimal control problem  $\mathbf{y}(t_i)$  correspond to the end point of the tangential arc thrust starting from the perigee  $\mathbf{y}_0$  of the initial GTO. The initial condition  $\mathbf{y}(t_i)$ , considering this strategy, depends on two scalar:

- $\omega$ , the perigee anomaly of the initial GTO respect to the x-axis of the synodic frame.  $[0, 2\pi]$
- $\tau_l$ , time necessary to elevate the spacecraft starting from the GTO perigee and then duration of the tangential arc thrust.

The end point of the tangential arc thrust can be written as

$$\mathbf{y}_l(\omega, \tau_l) = \varphi_{\mathbf{u}(0)}(\mathbf{y}_0(\omega), t_0 = 0, \tau_l) \quad (6.36)$$

where  $\varphi_{\mathbf{u}(\tau)}(\mathbf{y}_0(\omega), t_0, t)$  is the flow at time  $t$  of system 6.34 starting from the initial condition  $\mathbf{y}$ , with the control law  $\mathbf{u}=\mathbf{u}(\tau)$ ,  $[t_0, t]$ .  $\mathbf{u}(0)$  is equal to  $\bar{u}\mathbf{v}/\|\mathbf{y}\|$ , where  $\mathbf{v} = \{v_x, v_y, v_z\}^T$ ,  $\tau \in [0, \tau_l]$  and  $\bar{u}$  is the maximum thrust level.

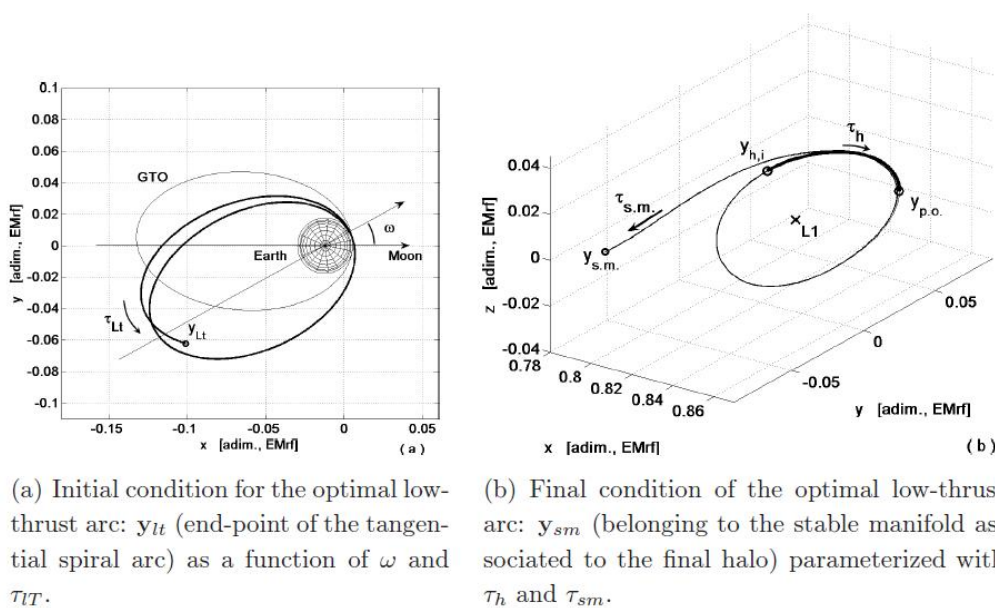


Figure 6.13: Initial and final boundary conditions for the optimal low-thrust leg [45]

It possible to formalize the first point of the optimization represented in figure 6.13 as

$$\phi_i : \mathbf{y}(t_i) - \mathbf{y}_l(\omega, \tau_l) = \mathbf{0} \quad (6.37)$$

The final point of the low thrust arc must lie on the stable manifold associated to the nominal halo orbit chosen for the mission. A generic point on the halo orbit depends from  $\tau_h$ , that is the time variable taken along the orbit, starting from the nominal initial conditions  $\mathbf{y}_{h,i}$  necessary to generate the orbit. If  $T$  is the period of the halo orbit  $\tau_h \in [0, T]$ . A point  $\in$  at the halo orbit can be written as  $\mathbf{y}_p(\tau_h) = \varphi_{\mathbf{u}(0)}(\mathbf{y}_{h,i}(\omega), t_0 = 0, \tau_h)$

In order to identify a point on the stable manifold it is necessary to introduce another parameter. If  $\tau_{sm}$  is a time parameter along the stable manifold, the generic point  $\mathbf{y}_{sm}$  can be computed by backward integration from  $\mathbf{y}_p(\tau_h)$  (figure 6.13).

The final boundary condition is

$$\phi_f : \mathbf{y}(t_f) - \mathbf{y}_{sm}(\tau_h, \tau_{sm}) = \mathbf{0} \quad (6.38)$$

Before starting the transcription of the problem it is necessary to introduce a path constraint due to saturation of the electric ion propulsion system. This system provides a maximum level of thrust  $\bar{T}$ . In order to translate this constraint into a consistent value for the optimization the instantaneous thrust  $T(t)/m(t)$  is equal to the acceleration magnitude  $\|\mathbf{u}(t)\|$  acting on the spacecraft. The nonlinear constraints can be introduced in the optimization as

$$\|\mathbf{u}(t)\| \leq \bar{u} \quad (6.39)$$

where the maximum acceleration is evaluated from the maximum thrust  $\bar{T}$  and the initial mass of the spacecraft.

### 6.6.3 Direct transcription and collocation formulation

Following the same scheme used in the immunotherapy optimization problem the method used to design the low thrust trajectory involves discretizing the states and the controls of the continuous problem. The time domain is discretized into  $N-1$  intervals, where  $N$  is the uniform mesh points. The variables of the nonlinear programming problem are the state and the control variable at each grid point. It is possible to define the variable optimization vector as

$$\mathbf{x} = \{\mathbf{y}_1, \mathbf{u}_1, \dots, \mathbf{y}_N, \mathbf{u}_N, \mathbf{p}, t_i, t_f\} \quad (6.40)$$

This  $9N+6$  dimensional vector contains 6 state and 3 controls for each grid point and it is augmented in order to take into account the parameter  $\mathbf{p} =$

$\{\omega, \tau_l, \tau_h, \tau_{sm}\}$  which are described in the previous section, and also the initial and final time of the optimal control in order to have a variable formulation of the optimal control problem.

In the immunotherapy optimization there are no parameter, but it is possible to extend the model considering parameters that influence the initial condition such as variable related to the lymphodepletion treatment. In this way it is possible also to generalize the problem considering the initial time as an optimization variable. This modification of the problem needs an adequate knowledge on the dynamics describing the pre-treatment.

Considering the low-thrust problem, the ODE model described by system 6.34 is transcribed into a set of  $6(N-1)$  defects  $\varsigma_i = 0$ . Each of this defect is an equality constraint that represent a numerical integration over the sub-interval  $[t_j, t_{j+1}]$ ,  $j=1, \dots, N-1$ .

The equality constraints vector is then completed including the 12 two-point boundary conditions 6.37 and 6.38:

$$\mathbf{c}(\mathbf{x}) = \{\Phi_i, \varsigma_1, \dots, \varsigma_{N-1}, \Phi_f\} \quad (6.41)$$

In the same way the saturation condition 6.39 is written for each  $N$  grid point. The objective function 6.35 is translated in the algorithm formalism using the same numerical integration scheme of the defects.

The optimal control problem translated into a NLP states as follow: Find the  $9N+6$  variables that solve the problem

$$\min_{\mathbf{x}} F(\mathbf{x}) \quad (6.42)$$

subject to  $\mathbf{c}(\mathbf{x}) = 0$  and  $\mathbf{g}(\mathbf{x}) \leq 0$ .

The formulation is the same for every optimal control problem considered and demonstrates the extreme versatility and power of this algorithm. Indeed once created an efficient algorithm is possible to apply it to solve various optimization problems.

In order to complete the problem defined using the RTBP, the results presented in [45] are reported. In particular figure 6.14 shows the trajectory optimization for a mission Earth to Halo transfer. The design strategy consider the begin of the transfer at the perigee of an initial GTO. The low-thrust arc connect this point to the stable manifold associated to the final Halo. The optimal solution lead to increase the energy in the minimum time, after this first stage the spacecraft is the stable manifold associated to the final Halo. In this way it is the dynamical behaviour of the system that bring the spacecraft to the desired orbit. It is possible to see from the figure reported here that all the boundary and saturation condition that have been translated into the algorithm formalism are respected.

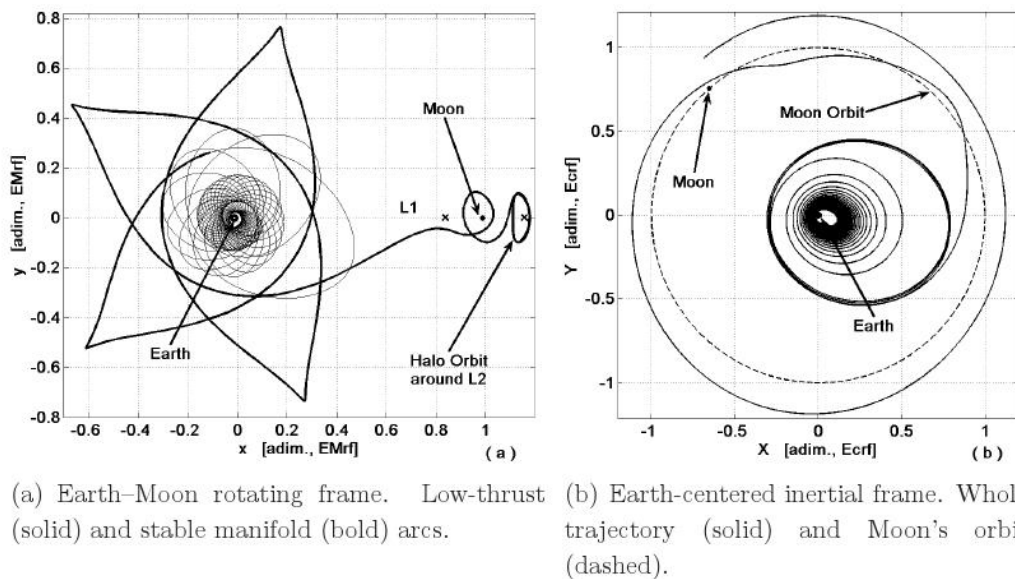


Figure 6.14: Transfer trajectory from the Earth to a  $L_2$  halo orbit [45]

#### 6.6.4 The Sun-Perturbed Earth Moon Bicircular Model

In immunotherapy Panetta-Kirschner model takes into account the dynamics of CD8 T cells neglecting the dynamics of CD4 cells. CD4 are necessary to activate and sustain the survival of CD8 cells and it is an important class of lymphocytes that have to be considered in an accurate model. Castiglione-Piccoli upgrade the PK model considering these cells, but also dendritic cells. These kind of cells described in chapter 2 are part of the innate immune response strategy. Their action is less specific than the adaptive response, but it is more rapid and it is the first stage of defense. Not consider this variable can influence negatively the simulation of the interaction between tumor and immune system.

In analogy we have studied in the previous section the dynamics of a low thrust Earth-Moon transfer using a RTBP. Nevertheless, the same model becomes not so accurate when the spacecraft moves in regions far from both the Earth and the Moon, or when it remains for long times about the EarthMoon equilibrium points, especially in the region around  $L_2$ . In these cases, the perturbation due to the Sun must be taken into account, in order to be consistent with the real dynamics [32].

In this case the dynamics is described with a Four-body problem in which the primaries are Sun, Earth and Moon. With the hypothesis of planar dynamics the equations derived from 6.2 with  $n=4$  are:

$$\begin{aligned}
\ddot{\mathbf{R}}_1 &= -Gm_2 \frac{\mathbf{R}_2 - \mathbf{R}_1}{R_{21}^3} - Gm_3 \frac{\mathbf{R}_3 - \mathbf{R}_1}{R_{31}^3} \\
\ddot{\mathbf{R}}_2 &= -Gm_1 \frac{\mathbf{R}_1 - \mathbf{R}_2}{R_{12}^3} - Gm_3 \frac{\mathbf{R}_3 - \mathbf{R}_2}{R_{32}^3} \\
\ddot{\mathbf{R}}_3 &= -Gm_1 \frac{\mathbf{R}_1 - \mathbf{R}_3}{R_{13}^3} - Gm_2 \frac{\mathbf{R}_2 - \mathbf{R}_3}{R_{23}^3} \\
\ddot{\mathbf{R}}_4 &= -Gm_1 \frac{\mathbf{R}_1 - \mathbf{R}_4}{R_{14}^3} - Gm_2 \frac{\mathbf{R}_2 - \mathbf{R}_4}{R_{24}^3} - Gm_3 \frac{\mathbf{R}_3 - \mathbf{R}_4}{R_{34}^3}
\end{aligned} \tag{6.43}$$

At this point it is possible to consider the R4BP and operate with this dynamics model or taking into account some useful approximation that leads to the more simple Bicircular problem BCP [3]. In the continuation of this work both BCP is considered and applied at the Earth-Moon trajectories optimization using respectively direct transcription. In this way it is possible to have a complete analogy with the resolution strategy applied to immunotherapy. In fact the simple models are improved considering other variables that influence the dynamic behaviour of the system, while the optimization tools available shows their versatility to move from one model to another and from one research field to another. A good command of these optimization techniques can eliminate barriers and limitations on their scope. Like all the algorithms of solution you may not be limited to use it unconscious as black box, it is necessary to have a broad knowledge of the dynamics in order to rational translate the problem in the algorithm language and then evaluate the results, taking into account the limits of the computational procedures.

In the Bicircular R4BP (BR4BP) considered, the primaries are the Earth, the Moon and the Sun with their respective mass denoted with  $m_1, m_2, m_3$ . As a difference from a classical RTBP the system is non autonomous since the Sun does not have a fixed position in the synodic frame. Some assumptions are taken into account [32]:

- the Earth and the Moon are revolving in circular orbits around their center of mass;
- the Earth-Moon barycenter is moving in a circular orbit around the center of mass of the Sun-Earth-Moon system;
- orbits of the primaries show low eccentricity values and the Moon inclination with respect to the ecliptic is little.

These hypotheses lead to a perturbation of the RTBP due to the presence of the Sun, that it is assumed to orbit around the barycenter of the other two primaries. The equations of the three-dimensional BR4BP are similar to those presented in RTBP, but include another equation that describe the angular acceleration of the Sun:

$$\begin{aligned}
\ddot{x} - 2\dot{y} &= \Omega_{4x} \\
\ddot{y} - 2\dot{x} &= \Omega_{4y} \\
\ddot{z} &= \Omega_{4z} \\
\dot{\theta} &= \omega_s
\end{aligned} \tag{6.44}$$

where  $\omega_s$  is the absolute angular velocity of the Sun. The auxiliary function is defined adding at the classic RTBP auxiliary function another term that describes the perturbation due to the Sun gravitation. The auxiliary function reads

$$\Omega_4(x, y, z, \theta) = \Omega(x, y, z, \theta) + \frac{m_s}{r_s} - \frac{m_s}{\rho_s^2} (x \cos \theta + y \sin \theta) \tag{6.45}$$

where  $m_s$  and  $\rho_s$  are the dimensionless mass and the dimensionless distance from the origin of the reference frame. The rotating location of the Sun is defined as  $r_3 = \{\rho_s \cos \theta, \rho_s \sin \theta, 0\}$ , such that the Sunspacecraft distance reads:

$$r_s^2 = (x - \rho_s \cos \theta)^2 + (y - \rho_s \sin \theta)^2 + z^2 \tag{6.46}$$

With this improvement of the model the problem presented in 6.34 can be rewritten as in [32] considering the perturbation of all the bodies involved in the interplanetary transfer (i.e. the Sun, the Earth and the Moon)

$$\begin{aligned}
\dot{x} &= v_x \\
\dot{y} &= v_y \\
\dot{v}_x &= 2v_y + \Omega_{4x} + T_x/m \\
\dot{v}_y &= -2v_x + \Omega_{4y} + T_y/m \\
\dot{\theta} &= \omega_s \\
\dot{m} &= -T/I_{SP}g_0
\end{aligned} \tag{6.47}$$

Considering a state vector defined as  $\mathbf{y} = \{x, y, v_x, v_y, \theta, m\}^T$  and a thrust vector defined as  $\mathbf{T} = \{T_x, T_y\}^T$  equations 6.47 can be rewritten in a compact form as

$$\dot{\mathbf{y}} = \mathbf{f}(\mathbf{y}(t), \mathbf{T}(t), t) \tag{6.48}$$

### 6.6.5 Moon Low-thrust transfer with Sun perturbation

The results of the problem considered and analyzed in [32] will be presented in order to complete the analogy with the immunotherapy problem in which we have improved the first model in order to consider other interactions.

The translation of the problem defined by the equations 6.48 into a discrete finite form lead to the definition of a NLP vector defined as

$$\mathbf{x} = \{(\mathbf{y}, \mathbf{T})_1, \dots, (\mathbf{y}, \mathbf{T})_N, t_1, t_N\}^T \tag{6.49}$$



The performance index is slightly different from the previous one because before the low-thrust phase there is an initial impulsive translunar manouver in which a launcher furnish a  $\Delta v$  and read as follow

$$J = \Delta v \frac{1}{2} \int_{t_1}^{t_f} \mathbf{u}^T \mathbf{u} dt \quad (6.50)$$

Considering initial boundary condition of a LEO and a final boundary condition of LMO and saturation on the thrust magnitude it is possible to arrive at a formulation that looks like the other NLP problems that we have considered:

$$\begin{aligned} \min_{\mathbf{x}} \quad & J \quad \text{subject to} \quad \mathbf{c}(\mathbf{x}) = 0 \\ & \mathbf{g}(\mathbf{x}) \leq 0 \end{aligned} \quad (6.51)$$

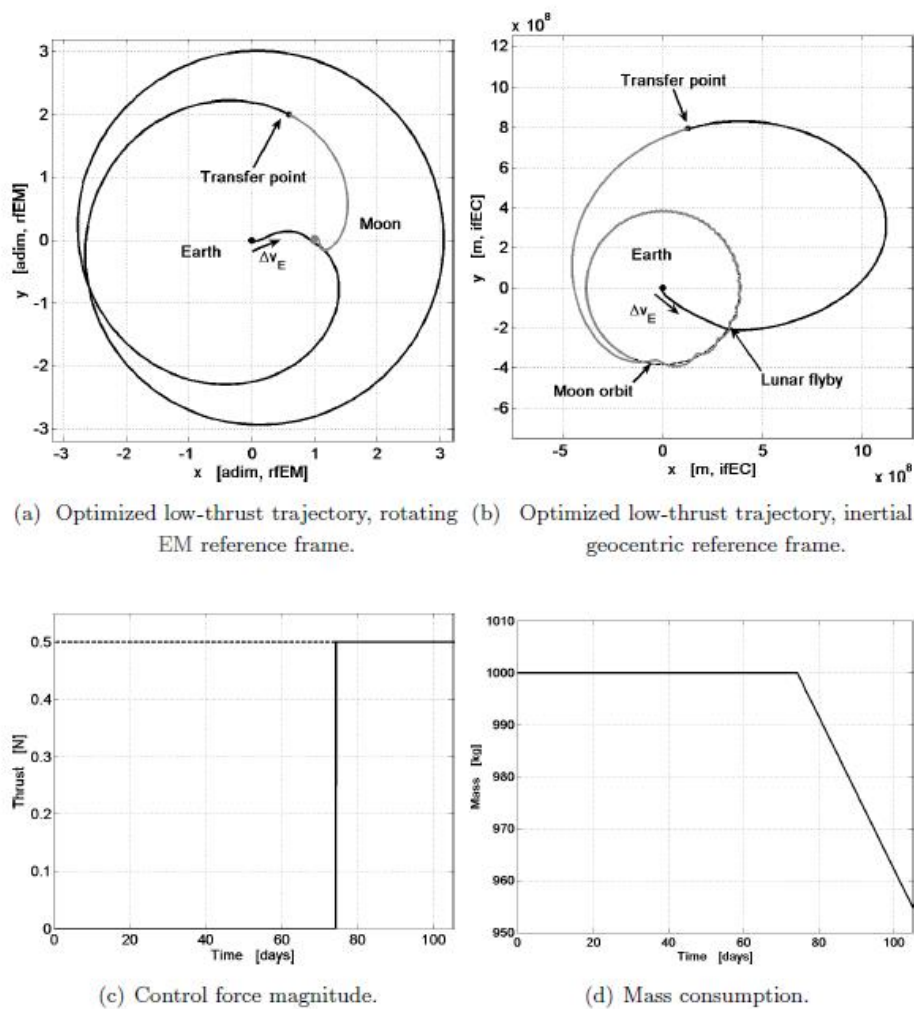


Figure 6.15: Optimized low-thrust transfer to a LLO [32]



# Chapter 7

## Conclusions

In this thesis we addressed two issues of current investigation in engineering and in general in the scientific area: the mathematical modeling of phenomena and the solution of optimal control problems.

The generality and breadth of this topic could fill pages and pages of pure theoretical discussion, this without the emergence of the salient aspects, the main problems and the necessary steps to be followed in practical application. For this reason, the ambitions of this work are numerous and essentially arising at two levels: one general and one local, specific and applied to real problems. These parts are not independent but closely allied as a single-stage process that starts from the observation of a phenomenon and has as its goal finding a way to control it.

We have seen that the mathematical modeling of a physical phenomenon can facilitate full understanding of it, using a synthetic representation of the relations between the different parameters of the system. Such modeling has as its ultimate goal the prediction of the system state in a finite time and if necessary the implementation of a control to arrive at a final state set. One of the limitations of this work is the impossibility of achieving a model starting from the observation of the phenomenon, but this is a matter of those who play the role of scientists that they must have the ability to know the problem but they also have the ability to use the mathematical tools to build a model.

The problem from an engineering standpoint assumes essentially a different perspective. Key point appears the choice of model to use. In the analysis of problems in immunotherapy and in astrodynamics we followed the principle of Occam's razor *entia non sunt multiplicanda praeter necessitatem*<sup>1</sup>, that leads to the conclusion that the simplest solution is the correct one.

In our analysis we start from simple models certainly correct, that take into consideration few variables and then move on to the analysis of more accurate models follow as a guideline for evaluating the new results those obtained previously.

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<sup>1</sup>entities must not be multiplied beyond necessity

Obviously there are always same limits on the modelization of phenomenon that are the consequence of the limited accuracy of the results. This aspect is particular evident in the analysis of the cancer immunotherapy problem. We must stress that the numerical results presented are highly dependent on the values of parameters used, and the dataset should be completely different for other tumors and other drugs, so that any generalisation of these results to clinical conclusions would at this stage be completely hazardous.

Despite this the results show that an approach through the theory of optimal control is efficient and effective in order to solve problems of immunotherapy, and the versatility and robustness of the algorithms minimize the problems of uncertainty in models and parameters.

Using an hybrid algorithm, we eliminate the gradient-based optimization tendency to converge to a local optimum if the solution does not lie close to the global optimum.

We also exploit the gradient-based algorithm to introduce the constraints that can not be introduced directly into the GA. Finally, we have shown how the approach and resolution of a problem of optimal control in cancer immunotherapy and in astrodynamics are in perfect analogy. To demonstrate that the algorithms used to solve an OCP immunotherapy have been used to solve optimization problems of low-thrust trajectory in astrodynamics.

Our procedure overcomes the problems highlighted in [16], avoiding the use of hybrid controls that approximate the problem and providing a valuable tool for immunotherapy cancer analysis.

The study of an optimal control problem related to immunotherapy against cancer has led to confront with a phenomenon modeled by non-linear equations. Academic studies have generally presented the modeling of systems to be solved through simplifications that lead to problems of linear type. If for some control problems e.g. active damping of vibrations of structures, LQR, LQG this technique provides a valid approximation, the linearization approach applied to immunotherapy models determines relevant change in the dynamics behaviour. The study has broadened my knowledge about issues of control starting from the knowledge on the calculus of variations to arrive at the numerical techniques that are used today for solving complex problems.

The fundamental limitation of this work is the validity of the results obtained in practice. While at the numerical level the solution has been validated in different scenarios, the key step is the translation into practice. Obviously this is a problem similar to the creation of a mathematical model albeit in the opposite direction. The comparison with experts in the medical field has given rise to this difference in language that are born into a problem that need to be multidisciplinary also in the solution strategy.

## 7.1 Future developments

We have tested the quality of the solution and the robustness and versatility of the algorithm in models relatively simple and well established. The developments aim to consider as for the astrodynamics problems more sophisticated model that takes into account with increased accuracy the tumor-immune system mechanisms. In the chapter related to the analysis of Castiglione Piccoli model we have modified the tumor cells growth law. Laws of type exponential, logistic and Gompertz are macroscopic and the simplest one. An extension would be to consider a Gompertz model modified with the dynamics of two tumor cell compartments, proliferating and quiescent. Kozusko-Bajzer in [29] were the first to describe this with an ODE model. The tumor growth law is described as

$$N(t) = N_0 \exp \left[ \frac{k_+}{k_-} (1 - \exp(-k_- t)) \right] \quad (7.1)$$

where  $N_0$  is the initial population and  $k_+, k_-$  represents respectively the growth rate constant and the retardation of growth. A two compartment model describes the evolution of the two compartments of a tumor. This model consists of proliferating  $P$  and quiescent  $Q$  cell compartments.

The two evolution of each of these compartments can be expressed by the following ordinary differential equations

$$\begin{aligned} \frac{dP}{Dt} &= [\beta - \mu - r_0(N)]P + r_1(N)Q \\ \frac{dQ}{Dt} &= r_0(N)P - [\mu + r_1(N)]Q \end{aligned} \quad (7.2)$$

where  $N = P + Q$  and  $r_0, r_1$  represent the rate of inactivation of proliferant cells and the rate of recruitment from quiescence to proliferation.

One of the main step to improve the models considered is the extension of the ODE model to a PDE model in order to include the spatial variables of cells and drugs distribution. In this way it is possible to consider local mechanisms of down regulation of the immune system response due to the inhibitory presence of IL10 or TGF [41]. In addition this aspect is strictly related with the pretreatment of lymphodepletion that permits us to eliminate the lymphocytes that compete with the transferred cells. This kind of model permits to evaluate local therapeutic strategies, in fact recent studies focus their attention on the administration of high dosage IL-2 only at a local level in order to avoid any side effects.

The evolution of the system with a PDE and 2 cell compartments lead to a tumor growth law described with

$$\begin{aligned} \frac{\partial P(t, x)}{\partial t} + \frac{\partial P(t, x)}{\partial x} + [K(x) + \gamma(t)]P(t, x) &= 0 \\ \frac{\partial Q(t, x)}{\partial t} + \frac{\partial Q(t, x)}{\partial x} + [\beta(t) + \delta(t)]Q(t, x) &= 0 \end{aligned} \quad (7.3)$$

with  $K$ =term describing cells leaving proliferation to quiescence, due to mitosis;  $\beta$ = term describing recruitment from quiescence to proliferation.

With the initial conditions defined as

$$\begin{aligned}
 Q(0, x) &= Q^0(x) \\
 P(0, x) &= P^0(x) \\
 P(t, 0) &= \beta(x) \int_0^\infty Q(t, \xi) d\xi \\
 Q(t, 0) &= 2 \int_0^\infty K(\xi) P(t, \xi) d\xi
 \end{aligned}
 \tag{7.4}$$

Clinical evidence has shown that other cytokines act as immune response stimulator, eradicating or substantially attenuating tumor mass. Nowadays these proteins increase the expectative of scientists because their limited side effects in contrast with IL2 treatment. Interleukin 21 [15] stimulates Dendritic cells, lymphocytes and natural killer cells and seems to be a promising weapon against tumor growth. The model presented in the research must be validated with scientific datas in order to consider IL-21 instead of IL-2. In [15] a model that considers the interaction between this cytokine and immunotherapy is presented, but several aspects are neglected such as the factors that influence CD8, the dynamics of CD4 cells and the inflammation related consequences of the therapy. The Castiglione-Piccoli model must be improved in order to consider the use of other cytokines in the immunotherapeutic treatment. This add-on can be useful for these new clinical researches. Optimal therapy evaluated with the model can be then tested in laboratory. At this moment the role of IL-2 in combination with other biological agents, such as IL-6, IL-10, IL-12 and probably many others, remains to be further elucidated by carefully designed protocols with a proven record of safety and tolerability, and appropriate correlative laboratory studies. Considering the dynamics of IL-2 clinical trial shows that there are immune stimulation effects from treatment with IL-2 (Keilholz et al., 1994; Gause et al., 1996; Hara et al., 1996; Kaempfer et al., 1996; Curti et al., 1996), and there is a time lag between the production of interleukin-2 by activated T-cells and the effector cell stimulation from treatment with IL-2. Hence, it is possible to modify the models considering a discrete time delay.

These different improvements can be combined together and determine a macroscopic model that takes into account this advance in the cancer research modelling. The optimal control theory and the algorithm that we developed, after some modification if the set of equations are PDE instead of ODE, can be applied to new models thanks to the robustness of the method.

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