FINITE AND INFINITE SINGULAR ARC IN CHEMOTHERAPY SCHEDULLING USING OPTIMAL CONTROL THEORY

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ABSTRACT

Keywords: optimal control theory, switching function, Hamiltonian function.

Cancer is one of the leading causes of death globally and chemotherapy being an effective approach for treatment has to be closely monitored and scheduled. In this work optimal control theory is used to schedule the administration of Temozolomide as a chemo drug. After obtaining the Hamiltonian function the cases of singular arcs are discussed. It is shown that the control of this treatment consists of both finite order and infinite order singular arcs. Finite order singular arcs in this work are of the third order and can be derived after deriving the switching function ($\frac{dH}{du}$) *for six times. In certain parts of this control, infinite order singular arcs appear. The previous numerical solutions for such cases are studied and a new approach, based on this particular case of infinite order singular arc is suggested. Combining all cases of bang-bang control, finite order singular arcs and infinite order singular arcs the results are simulated.*

ABSTRAK

Kanser adalah salah satu punca utama kematian di dunia dan kemoterapi menjadi pendekatan yang berkesan untuk rawatan yang perlu dipantau dan dijadualkan. Dalam teori ini, teori kawalan optimum digunakan untuk menjadualkan pentadbiran temozolomide sebagai ubat kemoterapi. Selepas memperoleh fungsi Hamiltonian, kes-kes arka tunggal dibincangkan. Ia menunjukkan bahawa kawalan rawatan ini terdiri daripada kedua-dua perintah terhingga dan arus tunggal yang tidak terhingga. Kemasukan lengkung tunggal dalam kerja ini adalah tertib ketiga dan boleh diperolehi selepas memperoleh fungsi pensuisan (dH / du) selama enam kali. Di bahagian tertentu kawalan ini, arus tunggal yang tidak terhingga muncul. Penyelesaian berangka terdahulu untuk kes sedemikian dikaji dan penyelesaian berangka yang baru, berdasarkan kes tertentu arka lengkung tunggal yang tidak terhingga ini dicadangkan. Menggabungkan semua kes-kes kawalan bang-bang, arka tunggal dan lengkung tunggal yang tidak terhad. Hasilnya disimulasikan. Selepas memperoleh fungsi Hamiltonian, kes-kes arka tunggal dibincangkan. Ia menunjukkan bahawa kawalan rawatan ini terdiri daripada kedua-dua perintah terhingga dan arus tunggal yang tidak terhingga. Kemasukan lengkung tunggal dalam kerja ini adalah tertib ketiga dan boleh diperolehi selepas memperoleh fungsi pensuisan (dH / du) selama enam kali. Di bahagian tertentu kawalan ini, arus tunggal yang tidak terhingga muncul. Penyelesaian berangka terdahulu untuk kes sedemikian dikaji dan penyelesaian berangka yang baru, berdasarkan kes tertentu arka lengkung tunggal yang tidak terhingga ini dicadangkan. Menggabungkan semua kes-kes kawalan bang-bang, perintah lengkung tunggal dan arbit singular tanpa had hasilnya disimulasikan.

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ODE	:	Ordinary Differential Equation
OCT	:	Optimal control theory
CV	:	Calculus of Variations

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CHAPTER 1: INTRODUCTION

1.1 Introduction:

According to WHO cancer is the second leading cause of death worldwide and was responsible for the deaths of 8.8 million people in 2015 and is expected to rise further over the next two decades by about 70%. The financial impact of cancer is also significant and growing. An approximation of treatment costs for cancer was estimated to be US$1.6 in 2011. an effective treatment is the most important course of action. The first goal is to cure cancer and to prolong life, but the quality of life is just as important[1]. Chemotherapy is one of the treatment approaches that can be used against many types of cancers, for some, chemotherapy might be the only kind of treatment they need[2]. Temozolomide is an anti-cancer chemotherapy drug. It can be used during radiotherapy or as a treatment on its own[3]. Temozolomide while being a worldwide used chemotherapy substance is believed to have less side effects and can provide better life quality in comparison with other similar chemotherapy drugs [4]. In 2013 Faivre et al [5] proposed a mathematical model for temozolomide administration. The model is based on 4 hypotheses: 1-without treatment the model follows a classic Gompertz model, 2- temozolomide is less effective on cancer cells than endothelial cells, 3- the anti-angiogenic effect on tumour, 4- endothelial cells are less likely to improve a resistance for temozolomide.

For an effective treatment both the dosage and the schedule of chemotherapy is considered to be of the utmost importance [6]. The mathematical model suggested in [5] consists of 7 ODEs. Which can be implemented as an OCT problem to obtain the optimal chemotherapy schedule. Doing so it is further showen that this problem contains many singular sub arcs. These sub arcs are of both finite (third order) and infinite order.

Singular arcs happen when the control variable shows up linearly in the Hamiltonian function [7]. Singular trajectories seem to appear in various cases of optimizing chemotherapy using OCP too. Applying OCT on the model proposed in[5] infinite order singular arc appears in addition to finite order singular arcs. Infinite order singular arc happens when the control variable does not show up in the switching function differentiation process. A singular solution is obtained by differentiating the switching function until the control variable appears in the derivative. if this is acquired after $2m$ differentiations, the order of the singular arc is m. If the control variable never appears explicitly in the differentiation process, then the optimal control problem is called an infinite-order singular problem [8]. Studies done on infinite-order singular arcs are fairly scarce. In this work first we discuss the mathematical model and the OCT problem, discuss the finite order singular arcs and the necessary and sufficient conditions for the trajectories are investigated. Further, the infinite order and the numerical solution for the singular part of the problem is calculated and simulated.

1.2 Problem Statement:

Finite order singular arc:

In the case of singular control, control variable does not appear in the switching function directly and it is obtained after differentiating the switching function for as many as times as it takes for the control variable to show up. After obtaining the singular solution the conditions for optimality needs to be checked. Ledzewicz [9] has concluded that only bang-bang control is optimal when treating a chemotherapy problem with OCT. he has shown that in his study singular trajectories does not provide optimal solution. In other future works he has reached the same conclusion of the singular arcs not being optimal [10-12]. In [13] and also [14] singular trajectories are found to violate generalized Legendre-Clebsch condition. This work studies singular control in another type of chemotherapy and the conditions of the optimality is studied.

Infinite order singular arc:

If the control variable does not appear in the derivations of switching function after differentiating for countless number of times(infinite) this control is classified as infinite order singular arc. in [15] when this type of control problem appears and the authors use arbitrary values as the solution for the singular arc. In this work another approach is taken when the output becomes independent of the control variable and infinite order singular arc happens.

1.3 objective:

the goal of this work is to find the optimal chemotherapy schedule which minimizes the cancer cells. By setting the cost function as minimization of the cancer cells and the chemo as the control variable, the problem becomes divided to 3 parts:

Bang-bang control

According to Pontryagin's Maximum Principle the control variable can be determined if the switching function which is the partial differential of the Hamiltonian function against the control variable, has either a positive or a negative value. If the switching function is zero over a period of time, either of the cases of finite or infinite order singular arc will happen.

Finite order singular arc

If the switching function is zero over a period of time, the derivates of the switching function will determine the value of the control variable. Note that this value is not necessarily a bang-bang (zero or one) value. The derivation of the switching function must go on until the control variable appears in the derivates. If the derivates does not contain the control variable regardless of the number of the times the switching function is being derivated then the next case will happen.

Infinite order singular arcs

When the output becomes independent of the control variable, it means that we are dealing with infinite order singular arc. In this work, this state is avoided by keeping the variables in a certain range, right before going into infinite order singular arc, so that we maintain the dependency of the output on the control variable.

Objectives of this research are based on the abovementioned problems in the problem statement section. All problems are addressed in the objective of the work and are the motivation for this research.

1.4 Methodology:

Details of the methodology for this research are as follow:

1- Conduct literature survey: this part involves the study of the previous work and investigating the details of implementing the optimal control theory. This includes the literature review on optimal control theory and its origins and looking into the reasons why singular control has become an important part of OCT.

The literature review on singular arcs investigates why and when this particular type of control has appeared and what approaches are used to handle singular control. Singular arcs are inseparable from the conditions they require for optimality. The necessary and sufficient conditions for singular arcs are investigated.

Another matter is the matter of infinite order singular arc. The sources on this topic are scares but this work covers most of the previous works conducted on this topic.

And in the end the cases of applying OCT in cancer treatment in recent years is studied briefly.

2- General assumptions and definitions of the research: this part includes studying the 7 ODEs proposed in [5] and their initial conditions. The cost function is then defined as the minimum of the cancer cells. The Hamiltonian function is developed based on the ODEs and the cost function. In the next step the derivates of the costates are calculated. The costates are devided into 3 groups based on the different conditions proposed in [5].
3- Bang-Bang Control: straight forward case in the control of the 7 ODEs. When the switching function has a negative or positive value the control variable is easily determined.
4- Finite order singular arc control: if the switching function equals to zero over a period of time the Hamiltonian function needs to be derivated in order to get the answer for the control variable. This part consists of 2 different cases based on the value of pharmacokinetic effect of the chemo**.** The switching function is derivated 6 times and the control variable is calculated. Optimality conditions are checked for singular trajectories.
5- Infinite order singular arc: this part is resolved by avoiding going into infinite order singular arc.

1.5 Research report outline

The remaining of this report project is organized as follows:

Chapter2 presents a comprehensive literature review on optimal control theory and how it is being applied on different problems. A survey on singular arc control is then conducted. proposed optimality conditions are studied. Infinite order singular arc is further studied. The methods of dealing with infinite order singular arc are studied.

In chapter3 the methodology is explained in detail. The mathematical model of administrating Temozolomide is discussed and OCT is applied on 7 ODEs. According to Pontryagin's maximum theory the bang-bang control is developed. Cases of finite order and infinite order singular arc are studied. Optimality condition for each singular case is developed.

In chapter 4 the results of the simulation in MATLAB is shown. The first step is changing the maximum dosage. After monitoring the effect of changing the maximum dosage the range of singular control is changed and its effect on singular control and bang-bang control is then studied. In the end of this chapter the optimality conditions for the finite order singular arc is studied.

Chapter 5 is dedicated to conclusion and a summary of the present work. This chapter also includes suggestions for further development of this work.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction:

Optimal control theory has roots in calculus of variations(CV) [16]. It involves finding the control function or the control feedback that minimizes a cost function based on differential equations and their constraints. Herman H. Goldstine has written a comprehensive scholarly history on CV[17]. Goldstine suggests that CV started with Pierre de Fermat (1601-1665) with his principle about light travel time. Isaac Newton (1642-1727) invented CV. Leonard Euler (1707-1783) pioneered many theorems amongst which the Euler-Lagrange equation is well-known in CV. In 1836 Jacob Jacobi (1804-1851) discovered Conjugate points in extremal fields. At nearly the same time William Rowan Hamilton (1805-1865) published his discoveries on least action. Jacobi's criticize of Hamilton's work resulted in the Hamilton-Jacobi equation which "dynamic programming" is based on.

At almost the same time William Rowan Hamilton (1805-1865) published his work on least action in mechanical systems which involved two partial differential equations. Jacobi criticized Hamilton's work in 1838, showing that only one partial differential equation was required. The result is the Hamilton-Jacobi equation, which is the basis of "dynamic programming" developed by Bellman over 100 years later. Karl Wilhelm Theodor Weierstrass (1815-1897) discovered the condition which is the predecessor of Maximum Principle. Alfred Clebsch (1833-1872) developed the Legendre condition further and shaped the Legendre-Clebsch condition. The maximum principle was developed by Pontryagin [18]. It states that a minimizing trajectory must satisfy Euler-Lagrange equation where the control variable maximizes the Hamiltonian within the region at each point along the path.

The following sections shows a classic OCT problem then the singular control literature is studied.

2.2 Optimal control theory

Optimal control theory has many applications including: economics[19-21], mechanics[22-26], electronics [27-30], medicine[31-34]. A fundamental optimal control theory problem can be demonstrated as follows.

x is an n dimensional state vector: $x = (x_1, x_2, \dots, x_n)^T$ and u is the m dimensional control vector: $u = (u_1, u_2, \dots, u_m)^T$ over an interval of time $t_0 < t < t_f$, the ordinary differential equations are:

$$\dot{x} = f(x, u, t) \qquad (2.1)$$

The boundary conditions are:

$$\begin{cases} x(t_0) = x_0 \\ \Psi = \left(x(t_f), t_f\right) = 0 \end{cases} \qquad (2.2)$$

Ψ is an s-dimensional constraint function. u needs to satisfy the condition below:

$$u(t) \in U \quad t \in \left[t_0, t_f\right] \qquad (2.3)$$

Where the U set is defined as:

$$U = \{u(t)\colon a_i < u_i(t) < b_i \quad i = 1,2, \dots, m\} \qquad (2.4)$$

a_i and b_i can either be constraints or defined functions of time. The optimal problem is to find the control function that satisfies (1.1) -(1.3) and minimized the cost function:

$$V(x_0\,, t_0) = F\big(x(t_f), t_f\big) + \int_{t_0}^{t_f} L(x,u,t)dt \quad (2.5)$$

The Hamiltonian function is defined as:

$$H(x,u,\lambda,t) = L(x,u,t) + \lambda^T f(x,u,t) \qquad (2.6)$$

$\lambda(.)$ is the costate matrix of Lagrange functions. Pontryagin's principle states that the condition below must hold thorough the whole optimal trajectories:

$$-\dot{\lambda} = H_x(\overline{x},\overline{u},\lambda,t) \quad (2.7)$$

If the control vector appears linearly in the Hamiltonian function, then extremal is singular. If $2p$ is the number of the time that the control variable shows up with a nonzero coefficient in derivative of $\frac{dH}{du}$ then that singular is of order p. This control vector is called singular control.

2.3 Singular control

Singular problems first appeared in aerospace problems [35]. Lwaden and Leitmann's study on possible use of CV in optimizing the aerospace paths in early 1950s and early 1960s introduced singular control to OCT problems [36]. Miele introduced the first approaches to solve singular problems [37]. But it could only solve two-dimensional linear problems. At that time, under the right assumptions, many flight mechanic problems fell into linear type of the problem that Miele's approach could solve.

At this time a number of researchers became interested in studying singular control problems and developing the necessary optimality condition. The classical Legendre-Clebsch condition:

$$\frac{\partial}{\partial u} H_u \geq 0 \quad (2.8)$$

is satisfied along a singular trajectory and the second variation of the cost function is used to infer further sufficient and necessary optimality conditions. In 1964 Kelly used a special control variable to create a new condition based on the second variation[38].

this condition then resulted in Generalized Legendre-Clebsch condition[39-41],.

Robbins and Goh developed the generalized Legendre-Clebsch condition for vector control[42]. The new condition is as follows:

$$\frac{\delta}{\delta u}\left[\frac{d^q}{dt^q} H_u\right] = 0 \quad \forall t \in [t_0\,, t_f] \quad q: odd$$

$$(-1)^p \frac{\delta}{\delta u}\left[\frac{d^{2p}}{dt^{2p}} H_u\right] \geq 0 \quad \forall t \in [t_0\,, t_f]$$

In the equation above p is the order of the singular arc. This new condition was used by Kopp and Moyer in 1965 to check the optimality of the singular trajectories in Lawden's singular spiral. They found out that the condition was not satisfied, therefore the singular extremal was found to be not optimal.

A different approach to singular extremals and their optimality conditions was introduced by the means of transformation in state and control variables. In this transformation the dimension of the states is reduced and the singular problem becomes a new nonsingular problem in which the generalized Legendre-Clebsch can be applied [43].

After establishment of the generalized Legendre-Clebsch condition the singular extremals investigation became possible. Around the same time a number of Russian mathematicians investigated the same matter [44-49].

In 1969 Jacobson derived a new necessary optimality condition based on differential dynamic programming [50]. This new condition is as follows:

$$H_{ux}f_u + {f_u}^T Q f_u \geq 0$$

Where:

$$-\dot{Q} = H_{xx} + {f_x}^T Q + Q f_x$$

$$Q(t_f) = F_{xx}(\bar{x}(t_f), t_f)$$

And the partial derivatives f_u, H_{ux} are calculated along the singular trajectories$(\bar{x}\ (.), \bar{u}(.))$.

In 1970 Jacobson presented sufficient conditions for the second variation which is the non-negative in both singular and non-singular control problems[51]. Conditions are shown to be applicable on both totally and partially singular functions.Since the first problems in flight control introducing singular control many cases of singular arc have been studied[15, 52-63].

2.4 Infinite order singular arc

In [8] Pwers studied the order of singular arcs and gives a definition of infinite order singular arcs. Optimal control is obtained by differentiating the switching function until the control variable appears. In certain problems the control variable never appears. This class of control problems are called infinite order singular arcs. in [64] Bortins et al. show that this class of problem can be useful in better understanding of optimal control theory. They characterized infinite and finite order singular arc for linear quadratic controllable problems. Necessary and sufficient conditions are developed for infinite order singular arc. They state that this class of singular arc problems has useful properties with respect to the theory of optimal controls. In particular, it is shown that for the time-invariant, singular, linear quadratic problems: 1-the singular order is infinity or less than or equal to the state dimensions, 2-infinite order problems can arise only from exact differential type cost functions, 3-the range of the second-variation operator (Hessian) is finite dimensional. They characterized the infinite order SLQP using a general Moyer problem. They showed that the fixed final time Moyer optimal problem, where the differential is linear time invariant and controllable, is infinite order singular. In a recent work Forouzanzade used a hybrid direct–Indirect approach for solving the singular optimal control problems of infinite order. they combine the direct Euler method with a modified indirect shooting method [65].

2.5 OCT in treating cancer

Approaching chemotherapy with OCT has been done in 3 different main models: first is based on cell cycle models the next involves miscellaneous growth kinetic models, and the third group is the rest of models[66]. The first model considers different phases in the cell life. Chemotherapy can be effective in some of these phases. The second model considers that all cancer cells act and live the same as each other.

Since the development of these models OCT has been implemented in chemotherapy in various ways. in [31] the mathematical model of breast cancer with two constraints is studied. The cost function is to minimize the electrode current. Which is used to detect early stages of cancer. In a recent work OCT is used to optimize chemotherapy in prostate patients. The cost function in the work is to minimize the testosterone levels using a quadratic function. it is proven that using their optimization model 63.9% of the patients have had a better reaction to chemotherapy [67] . Amongst different approcahes of optimizing chemotherapy model based approcahes which are based on anti-angiogenic therapy, can combine treatment with different personalized features and variables in treating cancer patients. [68] uses such model and concludes that old models of chemotherapy can not be sufficinet and using OCT for such nonlinear problems provide more convincing results. All the models mentioned earlier discount the delay factor. The delay factor is included in the mathematical model in[69]. They use a nonlinear constrained model and the effeciency of the model is studied.

2.6 Summary

In this chapter the appearance of OCT is studied and the structure of a basic Oct problem is introduced. The next part of this chapter discusses how singular control became an important part of OCT and why so much work has been dedicated to this particular class of control problems. The optimality conditions of the singular control is then studied and a brief history of the important works has been discussed. Since this work also includes infinite order singular arc a study of the most important works on infinite order singular arc is also conducted. The last part of this chapter is dedicated to studying the most recent work done on OCT in the treatment of cancer.

CHAPTER 3: METHODOLOGY

This work is based on the mathematical modeling of administrating Temozolomide provided in [5]. This models implements 7 ODEs explained further in order to define the mathematical model. This model is chosen as the base of this work because it takes both anti-angiogenic[1] effect of the temozolomide as well as the cytotoxic effect on the cancer cells into consideration.

We start by the 7 ODEs that define the mathematical model of administrating Temozolomide:

$$\dot{y_1} = -k_a y_1 + u(t) \tag{3.1}$$

$$\dot{y_2} = -k_e y_2 + \frac{k_a}{V} y_1 \tag{3.2}$$

$$\dot{y_3} = -a_1 \exp(-b_1 y_3)\, y_3 + (y_2 - c_1) H(y_2 - c_1) \tag{3.3}$$

$$\dot{y_4} = -a_2 \exp(-b_2 y_4)\, y_4 + (y_2 - c_2) H(y_2 - c_2) \tag{3.4}$$

$$\dot{y_5} = \lambda y_6 \log\left(\frac{K}{y_5}\right) y_5 - N_1 y_5 \tag{3.5}$$

$$\dot{y_6} = R - (R + N_2) y_6 \tag{3.6}$$

$$\dot{y_7} = (y_2 - c_1) H(y_2 - c_1) \tag{3.7}$$

Where : $N_1 = \exp(-res.\, y_7) u_1 y_3$ and $N_2 = u_2 y_4$. Anthe other parameters are as follows:

---

[1] Angiogenesis means the growth of new blood vessels. Anti angiogenic drugs are treatments that stop tumors from growing their own blood vessels

$$V = 14\,L\,, K_a = 2.4/h\ , K_e = 0.39/h\,,$$

$$a_1 = 0.7\,,\ b_1 = 0.31\,, c_1 = 3.7\,,$$

$$a_2 = 0.27\,, b_2 = 0.31\,, c_2 = 0.3\,,$$

$$res = 0.07\,, u_1 = 0.15\,, u_2 = 0.6\,,$$

$$K = 1000\,, R = 1\,, Lambda = 0.01$$

y_1 and y_2 are the pharmacokinetic modelling of temozolomide

y_3 the effect of temozolomide on cancer cells

y_4 the effect of chemo on endothelial cells

y_5 tumor growth (for $y_5 < 1$ the cancer is considered cured)

y_6 anti-angiogenic effect of temozolomide

y_7 area under the curve of plasmatic concentration y2 with a threshold (AUC)

The control variable needs to satisfy the condition:

$$u(t) \in U \qquad t \in [t_0, t_f] \tag{3.8}$$

Where the U set is defined as:

$$U = \{u(t): u_{min} < u_i(t) < u_{max} \quad i = 1,2, \ldots, m\} \tag{3.9}$$

The initial conditions are:

$$\begin{cases} y_1(t_0) = 0 \\ y_2(t_0) = 0 \\ y_3(t_0) = 0 \\ y_4(t_0) = 0 \\ y_5(t_0) = 30 \\ y_6(t_0) = 1 \\ y_7(t_0) = 0 \end{cases} \tag{3.10}$$

The control variable needs to be satisfy (1-10) and minimize the cost function. The cost function is defined as:

$$\int_{t_0}^{t_f} y_5(t)dt \qquad (3.11)$$

the Hamiltonian functions is:

$$H(x,u,\lambda,t) = L(x,u,t) + \lambda^T f(x,u,t) \qquad (3.12)$$

Where:

$$L(x,u,t) = y_5(t) \qquad (3.13)$$

And $\lambda(.)$ Is the costate matrix of the Lagrange functions. The Hamiltonian then will be as follows:

$$H = \lambda_1\big(-k_a y_1 + u(t)\big) + \lambda_2\left(-k_e y_2 + \frac{k_a}{V} y_1\right) + \lambda_3\big(-a_1 \exp(-b_1 y_3)\, y_3 +$$

$$(y_2 - c_1)H(y_2 - c_1)\big) + \lambda_4\big(-a_2 \exp(-b_2 y_4)\, y_4 + (y_2 - c_2)H(y_2 - c_2)\big) +$$

$$\lambda_5\left(\lambda y_6 \log\left(\frac{K}{y_5}\right) y_5 - N_1 y_5\right) + \lambda_6\big(R - (R + N_2)y_6\big) + \lambda_7\big((y_2 - c_1)H(y_2 - c_1)\big) + y_5$$

(3.14)

According to Pntryagin's maximum the condition below must hold through the optimal trajectories:

$$\dot{\lambda}_j = -\frac{dH(x,\lambda,u,t)}{dy_j} \qquad j = 1,2,..,7 \qquad (3.15)$$

Costates are then as follow:

$$\dot{\lambda}_1 = k_a \lambda_1 - \lambda_2 \frac{k_a}{V} \qquad (3.16)$$

For $y_2 < c_2$:

$$\dot{\lambda_2} = \lambda_2 k_e \qquad (3.17)$$

For $c_2 < y_2 < c_1$:

$$\dot{\lambda_2} = \lambda_2 k_e - \lambda_4 \qquad (3.18)$$

For $c_1 < y_2$:

$$\dot{\lambda_2} = \lambda_2 k_e - \lambda_4 - \lambda_3 - \lambda_7 \qquad (3.19)$$

Then $\dot{\lambda_2}$ is rewritten as:

$$\dot{\lambda_2} = \lambda_2 k_e - \lambda_3 H(y_2 - c_1) - \lambda_4 H(y_2 - c_2) - \lambda_7 H(y_2 - c_1) \quad (3.20)$$

The rest of costates are:

$$\dot{\lambda_3} = -\lambda_3 y_3 a_1 b_1 \exp(-b_1 y_3) + \lambda_5 y_5 u_1 \exp(-res.\, y_7) + \lambda_3 a_1 \exp(-b_1 y_3) \quad (3.21)$$

$$\dot{\lambda_4} = -\lambda_4 y_4 a_2 b_2 \exp(-b_2 y_4) + \lambda_6 y_6 u_2 + \lambda_4 a_2 \exp(-b_2 y_4) \quad (3.22)$$

$$\dot{\lambda_5} = -1 - \lambda_5 \lambda y_6 \log\left(\frac{K}{y_5}\right) + \lambda_5 \lambda y_6 + \lambda_5 u_1 y_3 \exp(-res.\, y_7) \quad (3.23)$$

$$\dot{\lambda_6} = \lambda_6 R - \lambda_5 \lambda \log\left(\frac{K}{y_5}\right) + \lambda_6 y_4 u_2 \qquad (3.24)$$

$$\dot{\lambda_7} = \lambda_5 y_5 u_1 y_3 (-res) \exp(-res.\, y_7) \qquad (3.25)$$

this is a finite time problem and according to transversility condition :

$$\lambda_j(t_f) = 0 \qquad j = 1,2,\dots,7$$

According to Pontryagin's Maximum Principle : $\begin{cases} u = 1 \;\; when \; \frac{dH}{du} < 0 \\ u = 0 \;\; when \; \frac{dH}{du} > 0 \\ singular \; arc \; when \; \frac{dH}{du} = 0 \end{cases}$

From the Hamiltonian equation switching function is : $\frac{dH}{du} = \lambda_1$

To get the singular arc solution we derivate λ_1 until u appears in the equations.

$$\dot{\lambda_1} = k_a\lambda_1 - \frac{k_a}{V}\lambda_2 \tag{3.26}$$

$$\ddot{\lambda_1} = k_a\dot{\lambda_1} - \dot{\lambda_2}\frac{k_a}{V} \rightarrow \; \ddot{\lambda_1} = k_a\left(k_a\lambda_1 - \frac{k_a}{V}\lambda_2\right) - \dot{\lambda_2}\frac{k_a}{V} \tag{3.27}$$

$$\dddot{\lambda_1} = {k_a}^2\left(k_a\lambda_1 - \frac{k_a}{V}\lambda_2\right) - \frac{{k_a}^2}{V}\dot{\lambda_2} - \ddot{\lambda_2}\frac{k_a}{V} \tag{3.28}$$

$$\frac{d^4\lambda_1}{dt^4} = {k_a}^3\left(k_a\lambda_1 - \frac{k_a}{V}\lambda_2\right) - \frac{{k_a}^3}{V}\dot{\lambda_2} - \frac{{k_a}^2}{V}\ddot{\lambda_2} - \frac{k_a}{V}\dddot{\lambda_2} \tag{3.29}$$

$$\frac{d^5\lambda_1}{dt^5} = {k_a}^4\left(k_a\lambda_1 - \frac{k_a}{V}\lambda_2\right) - \frac{{k_a}^4}{V}\dot{\lambda_2} - \frac{{k_a}^3}{V}\ddot{\lambda_2} - \frac{{k_a}^2}{V}\dddot{\lambda_2} - \frac{k_a}{V}\frac{d^4\lambda_2}{dt^4} \tag{3.30}$$

$$\frac{d^6\lambda_1}{dt^6} = {k_a}^5\left(k_a\lambda_1 - \frac{k_a}{V}\lambda_2\right) - \frac{{k_a}^5}{V}\dot{\lambda_2} - \frac{{k_a}^4}{V}\ddot{\lambda_2} - \frac{{k_a}^3}{V}\dddot{\lambda_2} - \frac{{k_a}^2}{V}\frac{d^4\lambda_2}{dt^4} - \frac{k_a}{V}\frac{d^5\lambda_2}{dt^5} \tag{3.31}$$

So in order to have the sixth derivative of λ_1 we need all the derivates of λ_2 from $\frac{d\lambda_2}{dt}$ to $\frac{d^5\lambda_2}{dt^5}$.

3.1 Case 1

For $c_1 < y_2$:

Let us consider that $\quad A = \lambda_4 + \lambda_3 + \lambda_7 \qquad (3.31)$

Then : $\quad \dot{\lambda_2} = \lambda_2 k_e - A \qquad (3.32)$

$$\frac{d^2\lambda_2}{dt^2} = k_e(\lambda_2 k_e - A) - \dot{A} \qquad (3.33)$$

$$\frac{d^3\lambda_2}{dt^3} = {k_e}^2(\lambda_2 k_e - A) - k_e\dot{A} - \ddot{A} \qquad (3.34)$$

$$\frac{d^4\lambda_2}{dt^4} = {k_e}^3(\lambda_2 k_e - A) - {k_e}^3\dot{A} - k_e\ddot{A} - \dddot{A} \qquad (3.35)$$

$$\frac{d^5\lambda_2}{dt^5} = {k_e}^4(\lambda_2 k_e - A) - {k_e}^4\dot{A} - {k_e}^3\ddot{A} - k_e\dddot{A} - \frac{d^4A}{dt^4} \qquad (3.36)$$

So now in order to get the derivates of λ_2 we need derivates of A.

A consists of $\lambda_3, \lambda_4, \lambda_7$. For each of these costates we need to calculate up until the fourth derivate.

$$\dot{\lambda_3} = -\lambda_3 y_3 a_1 b_1 \exp(-b_1 y_3) + \lambda_5 y_5 u_1 \exp(-res.\, y_7) + \lambda_3 a_1 \exp(-b_1 y_3)$$

(3.37)

$$\ddot{\lambda_3} = -\dot{\lambda_3} y_3 a_1 b_1 \exp(-b_1 y_3) + -\lambda_3 \dot{y_3} a_1 b_1 \exp(-b_1 y_3) +$$
$$-\lambda_3 y_3 \dot{y_3} a_1 {b_1}^2 \exp(-b_1 y_3) + \dot{\lambda_5} y_5 u_1 \exp(-res.\, y_7) + \lambda_5 \dot{y_5} u_1 \exp(-res.\, y_7) -$$
$$\lambda_5 y_5 \dot{y_7} u_1 res \exp(-res.\, y_7) + \dot{\lambda_3} a_1 \exp(-b_1 y_3) - \lambda_3 a_1 b_1 \dot{y_3} \exp(-b_1 y_3) \qquad (3.38)$$

$$
\begin{aligned}
\ddot{\lambda}_3 = &-\ddot{\lambda}_3 y_3 a_1 b_1 \exp(-b_1 y_3) - \dot{\lambda}_3 \dot{y}_3 a_1 b_1 \exp(-b_1 y_3) + \dot{\lambda}_3 y_3 \dot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
&- \dot{\lambda}_3 \dot{y}_3 a_1 b_1 \exp(-b_1 y_3) - \lambda_3 \ddot{y}_3 a_1 b_1 \exp(-b_1 y_3) \\
&+ \lambda_3 {\dot{y}_3}^2 a_1 {b_1}^2 \exp(-b_1 y_3) - \dot{\lambda}_3 y_3 \dot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
&+ \lambda_3 {\dot{y}_3}^2 a_1 {b_1}^2 \exp(-b_1 y_3) + \lambda_3 y_3 \ddot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
&- \lambda_3 y_3 {\dot{y}_3}^2 a_1 {b_1}^3 \exp(-b_1 y_3) + \ddot{\lambda}_5 y_5 u_1 \exp(-res.\, y_7) \\
&+ \dot{\lambda}_5 \dot{y}_5 u_1 \exp(-res.\, y_7) - \dot{\lambda}_5 y_5 \dot{y}_7 .\, res.\, u_1 \exp(-res.\, y_7) \\
&+ \dot{\lambda}_5 \dot{y}_5 u_1 \exp(-res.\, y_7) + \lambda_5 \ddot{y}_5 u_1 \exp(-res.\, y_7) \\
&- \lambda_5 \dot{y}_5 \dot{y}_7 .\, res.\, u_1 \exp(-res.\, y_7) - \dot{\lambda}_5 y_5 \dot{y}_7 u_1 res \exp(-res.\, y_7) \\
&- \lambda_5 \dot{y}_5 \dot{y}_7 u_1 res \exp(-res.\, y_7) - \lambda_5 y_5 \ddot{y}_7 u_1 res \exp(-res.\, y_7) \\
&+ \lambda_5 y_5 {\dot{y}_7}^2 u_1 res^2 \exp(-res.\, y_7) + \ddot{\lambda}_3 a_1 \exp(-b_1 y_3) \\
&- \dot{\lambda}_3 \dot{y}_3 a_1 b_1 \exp(-b_1 y_3) - \dot{\lambda}_3 a_1 b_1 \dot{y}_3 \exp(-b_1 y_3) \\
&- \lambda_3 a_1 b_1 \ddot{y}_3 \exp(-b_1 y_3) + \lambda_3 a_1 {b_1}^2 {\dot{y}_3}^2 \exp(-b_1 y_3) \qquad (3.39)
\end{aligned}
$$

$$
\begin{aligned}
\frac{d^4\lambda_3}{dt^4} = & -\dddot{\lambda}_3 y_3 a_1 b_1 \exp(-b_1 y_3) - \ddot{\lambda}_3 \dot{y}_3 a_1 b_1 \exp(-b_1 y_3) + \ddot{\lambda}_3 y_3 \dot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
& - \ddot{\lambda}_3 \dot{y}_3 a_1 b_1 \exp(-b_1 y_3) - \dot{\lambda}_3 \ddot{y}_3 a_1 b_1 \exp(-b_1 y_3) \\
& + \dot{\lambda}_3 {\dot{y}_3}^2 a_1 {b_1}^2 \exp(-b_1 y_3) + \ddot{\lambda}_3 y_3 \dot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
& + \dot{\lambda}_3 {\dot{y}_3}^2 a_1 {b_1}^2 \exp(-b_1 y_3) + \dot{\lambda}_3 y_3 \ddot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
& - \dot{\lambda}_3 y_3 {\dot{y}_3}^2 a_1 {b_1}^3 \exp(-b_1 y_3) \\
& - \ddot{\lambda}_3 \dot{y}_3 a_1 b_1 \exp(-b_1 y_3) - \dot{\lambda}_3 \ddot{y}_3 a_1 b_1 \exp(-b_1 y_3) \\
& + \dot{\lambda}_3 {\dot{y}_3}^2 a_1 {b_1}^2 \exp(-b_1 y_3) - \dot{\lambda}_3 \ddot{y}_3 a_1 b_1 \exp(-b_1 y_3) \\
& - \lambda_3 \dddot{y}_3 a_1 b_1 \exp(-b_1 y_3) + \lambda_3 \ddot{y}_3 \dot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
& + \dot{\lambda}_3 {\dot{y}_3}^2 a_1 {b_1}^2 \exp(-b_1 y_3) + 2\lambda_3 \dot{y}_3 \ddot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
& - \lambda_3 {\dot{y}_3}^3 a_1 {b_1}^3 \exp(-b_1 y_3) + \ddot{\lambda}_3 y_3 \dot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
& + \dot{\lambda}_3 {\dot{y}_3}^2 a_1 {b_1}^2 \exp(-b_1 y_3) + \dot{\lambda}_3 y_3 {\dot{y}_3}^2 a_1 {b_1}^2 \exp(-b_1 y_3) \\
& - \dot{\lambda}_3 y_3 {\dot{y}_3}^2 a_1 {b_1}^3 \exp(-b_1 y_3) + \dot{\lambda}_3 {\dot{y}_3}^2 a_1 {b_1}^2 \exp(-b_1 y_3) \\
& + 2\lambda_3 \dot{y}_3 \ddot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) - \lambda_3 {\dot{y}_3}^3 a_1 {b_1}^3 \exp(-b_1 y_3) \\
& + \dot{\lambda}_3 y_3 \ddot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) + \lambda_3 \dot{y}_3 \ddot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) \\
& + \lambda_3 y_3 \dddot{y}_3 a_1 {b_1}^2 \exp(-b_1 y_3) - \lambda_3 y_3 \dot{y}_3 \ddot{y}_3 a_1 {b_1}^3 \exp(-b_1 y_3) \\
& - \dot{\lambda}_3 y_3 {\dot{y}_3}^2 a_1 {b_1}^3 \exp(-b_1 y_3) - \lambda_3 {\dot{y}_3}^3 a_1 {b_1}^3 \exp(-b_1 y_3) \\
& - 2\lambda_3 y_3 \dot{y}_3 \ddot{y}_3 a_1 {b_1}^3 \exp(-b_1 y_3) + \lambda_3 y_3 {\dot{y}_3}^3 a_1 {b_1}^4 \exp(-b_1 y_3) \\
& + \dddot{\lambda}_5 y_5 u_1 \exp(-res.y_7) + \ddot{\lambda}_5 \dot{y}_5 u_1 \exp(-res.y_7) \\
& - \ddot{\lambda}_5 y_5 \dot{y}_7.res.u_1 \exp(-res.y_7) + \ddot{\lambda}_5 \dot{y}_5 u_1 \exp(-res.y_7) \\
& + \dot{\lambda}_5 \ddot{y}_5 u_1 \exp(-res.y_7) - \dot{\lambda}_5 \dot{y}_5 \dot{y}_7 u_1.res.\exp(-res.y_7) \\
& - \ddot{\lambda}_5 y_5 \dot{y}_7.res.u_1 \exp(-res.y_7) - \dot{\lambda}_5 \dot{y}_5 \dot{y}_7.res.u_1 \exp(-res.y_7) \\
& - \dot{\lambda}_5 y_5 \ddot{y}_7.res.u_1 \exp(-res.y_7) + \dot{\lambda}_5 y_5 {\dot{y}_7}^2.res^2.u_1 \exp(-res.y_7) \\
& + \ddot{\lambda}_5 \dot{y}_5 u_1 \exp(-res.y_7) + \dot{\lambda}_5 \ddot{y}_5 u_1 \exp(-res.y_7) \\
& - \dot{\lambda}_5 \dot{y}_5 \dot{y}_7.res.u_1 \exp(-res.y_7)
\end{aligned}
$$

$$+\dot{\lambda}_5\ddot{y}_5u_1\exp(-res.y_7)\,\lambda_5\dddot{y}_5u_1\exp(-res.y_7)$$

$$-\lambda_5\ddot{y}_5\dot{y}_7u_1.res.\exp(-res.y_7)-\dot{\lambda}_5\dot{y}_5\dot{y}_7.res.u_1\exp(-res.y_7)$$

$$-\lambda_5\ddot{y}_5\dot{y}_7.res.u_1\exp(-res.y_7)-\lambda_5\dot{y}_5\ddot{y}_7.res.u_1\exp(-res.y_7)$$

$$+\lambda_5\dot{y}_5\dot{y}_7{}^2.res^2.u_1\exp(-res.y_7)-\ddot{\lambda}_5y_5\dot{y}_7u_1res\exp(-res.y_7)$$

$$-\dot{\lambda}_5\dot{y}_5\dot{y}_7u_1res\exp(-res.y_7)-\dot{\lambda}_5y_5\ddot{y}_7u_1res\exp(-res.y_7)$$

$$+\dot{\lambda}_5y_5\dot{y}_7{}^2u_1res^2\exp(-res.y_7)-\dot{\lambda}_5\dot{y}_5\dot{y}_7u_1res\exp(-res.y_7)$$

$$-\lambda_5\ddot{y}_5\dot{y}_7u_1res\exp(-res.y_7)-\lambda_5\dot{y}_5\ddot{y}_7u_1res\exp(-res.y_7)$$

$$+\lambda_5\dot{y}_5\dot{y}_7{}^2u_1res^2\exp(-res.y_7)-\lambda_5y_5\ddot{y}_7u_1res\exp(-res.y_7)$$

$$-\lambda_5y_5\ddot{y}_7u_1res\exp(-res.y_7)$$

$$+\lambda_5y_5\ddot{y}_7u_1res\exp(-res.y_7)\,\lambda_5y_5\ddot{y}_7u_1res\exp(-res.y_7)$$

$$+\dot{\lambda}_5y_5\dot{y}_7{}^2u_1res^2\exp(-res.y_7)+\lambda_5\dot{y}_5\dot{y}_7{}^2u_1res^2\exp(-res.y_7)$$

$$+2\lambda_5y_5\dot{y}_7\ddot{y}_7u_1res^2\exp(-res.y_7)-\lambda_5y_5\dot{y}_7{}^3u_1res^3\exp(-res.y_7)$$

$$+\dddot{\lambda}_3a_1\exp(-b_1y_3)-\ddot{\lambda}_3a_1b_1\dot{y}_3\exp(-b_1y_3)-\ddot{\lambda}_3\dot{y}_3a_1b_1\exp(-b_1y_3)$$

$$-\dot{\lambda}_3\ddot{y}_3a_1b_1\exp(-b_1y_3)+\dot{\lambda}_3\dot{y}_3{}^2a_1b_1{}^2\exp(-b_1y_3)$$

$$-\ddot{\lambda}_3a_1b_1\dot{y}_3\exp(-b_1y_3)-\dot{\lambda}_3a_1b_1\ddot{y}_3\exp(-b_1y_3)$$

$$+\dot{\lambda}_3a_1b_1{}^2\dot{y}_3{}^2\exp(-b_1y_3)-\dot{\lambda}_3a_1b_1\ddot{y}_3\exp(-b_1y_3)$$

$$-\lambda_3a_1b_1\dddot{y}_3\exp(-b_1y_3)+\lambda_3a_1b_1{}^2\ddot{y}_3\dot{y}_3\exp(-b_1y_3)$$

$$+\dot{\lambda}_3a_1b_1{}^2\dot{y}_3{}^2\exp(-b_1y_3)+2\lambda_3a_1b_1{}^2\dot{y}_3\ddot{y}_3\exp(-b_1y_3)$$

$$-\lambda_3a_1b_1{}^3\dot{y}_3{}^3\exp(-b_1y_3) \qquad (3.40)$$

As seen in the above the direct method to derivate the costates can be very long and prone to mistakes.

So instead of directly derivating the costates we take another approach:

$$\dot{\lambda}_3=-\lambda_3y_3a_1b_1\exp(-b_1y_3)+\lambda_5y_5u_1\exp(-res.y_7)+\lambda_3a_1\exp(-b_1y_3) \qquad (3.41)$$

$m = a_1\lambda_3$ (3.42)

$n = 1 - b_1 y_3$ (3.43)

$o = \exp(-b_1 y_3)$ (3.44)

$r = \exp(-res.\, y_7)$ (3.45)

$p = \lambda_5$ (3.46)

$q = y_5 u_1$ (3.47)

$\dot{\lambda}_3 = m.n.o + p.q.r$ (3.48)

$\ddot{\lambda}_3 = \dot{m}.n.o + m.\dot{n}.o + m.n.\dot{o} + \dot{p}.q.r + p.\dot{q}.r + p.q.\dot{r}$ (3.49)

$\dddot{\lambda}_3 = \ddot{m}.n.o + \dot{m}.\dot{n}.o + \dot{m}.n.\dot{o} + \dot{m}.\dot{n}.o + m.\ddot{n}.o + m.\dot{n}.\dot{o} + \dot{m}.n.\dot{o} + m.\dot{n}.\dot{o} +$

$m.n.\ddot{o} + \ddot{p}.q.r + \dot{p}.\dot{q}.r + \dot{p}.q.\dot{r} + \dot{p}.\dot{q}.r + p.\ddot{q}.r + p.\dot{q}.\dot{r} + \dot{p}.q.\dot{r} + p.\dot{q}.\dot{r} +$

$p.q.\ddot{r} = \ddot{m}.n.o + m.\ddot{n}.o + m.n.\ddot{o} + 2\dot{m}.\dot{n}.o + 2\dot{m}.n.\dot{o} + 2m.\dot{n}.\dot{o} + \ddot{p}.q.r + p.\ddot{q}.r +$

$p.q.\ddot{r} + 2\dot{p}.\dot{q}.r + 2\dot{p}.q.\dot{r} + 2p.\dot{q}.\dot{r}$ (3.50)

$$\frac{d^4\lambda_3}{dt^4} = \dddot{m}.n.o + \ddot{m}.\dot{n}.o + \ddot{m}.n.\dot{o} + +\dot{m}.\ddot{n}.o + m.\dddot{n}.o + m.\ddot{n}.\dot{o} + \dot{m}.n.\ddot{o} + m.\dot{n}.\ddot{o}$$

$$+ m.n.\dddot{o} + 2\ddot{m}.\dot{n}.o + 2\dot{m}.\ddot{n}.o + 2\dot{m}.\dot{n}.\dot{o} + 2\ddot{m}.n.\dot{o} + 2\dot{m}.\dot{n}.\dot{o}$$

$$+ 2\dot{m}.n.\ddot{o} + 2\dot{m}.\dot{n}.\dot{o} + 2m.\ddot{n}.\dot{o} + 2m.\dot{n}.\ddot{o} + \dddot{p}.q.r + \ddot{p}.\dot{q}.r + \ddot{p}.q.\dot{r}$$

$$+ \dot{p}.\ddot{q}.r + p.\dddot{q}.r + p.\ddot{q}.\dot{r} + \dot{p}.q.\ddot{r} + p.\dot{q}.\ddot{r} + p.q.\dddot{r} + 2\ddot{p}.\dot{q}.r$$

$$+ 2\dot{p}.\ddot{q}.r + 2\dot{p}.\dot{q}.\dot{r} + 2\ddot{p}.q.\dot{r} + 2\dot{p}.\dot{q}.\dot{r} + 2\dot{p}.q.\ddot{r} + 2\dot{p}.\dot{q}.\dot{r} + 2p.\ddot{q}.\dot{r}$$

$$+ 2p.\dot{q}.\ddot{r} \qquad (3.51)$$

We use the same method for λ_4 and λ_7

$\dot{\lambda}_4 = -\lambda_4 y_4 a_2 b_2 \exp(-b_2 y_4) + \lambda_6 y_6 u_2 + \lambda_4 a_2 \exp(-b_2 y_4)$

$$s = \lambda_6 u_2 \qquad (3.52)$$

$$w = y_6 \qquad (3.53)$$

$$x = \lambda_4 a_2 \qquad (3.54)$$

$$y = 1 - b_2 y_4 \qquad (3.55)$$

$$z = \exp(-b_2 y_4) \qquad (3.56)$$

$$\dot{\lambda}_4 = \mathrm{x.y.z + s.w} \qquad (3.57)$$

$$\ddot{\lambda}_4 = \dot{\mathrm{x}}.\mathrm{y}.\mathrm{z} + \mathrm{x}.\dot{\mathrm{y}}.\mathrm{z} + \mathrm{x}.\mathrm{y}.\dot{\mathrm{z}} + \dot{\mathrm{s}}.\mathrm{w} + \mathrm{s}.\dot{\mathrm{w}} \qquad (3.58)$$

$$\begin{aligned} \dddot{\lambda}_4 = {} & \ddot{\mathrm{x}}.\mathrm{y}.\mathrm{z} + \dot{\mathrm{x}}.\dot{\mathrm{y}}.\mathrm{z} + \dot{\mathrm{x}}.\mathrm{y}.\dot{\mathrm{z}} + \dot{\mathrm{x}}.\dot{\mathrm{y}}.\mathrm{z} + \mathrm{x}.\ddot{\mathrm{y}}.\mathrm{z} + \mathrm{x}.\dot{\mathrm{y}}.\dot{\mathrm{z}} + \dot{\mathrm{x}}.\mathrm{y}.\dot{\mathrm{z}} + \mathrm{x}.\dot{\mathrm{y}}.\dot{\mathrm{z}} + \mathrm{x}.\mathrm{y}.\ddot{\mathrm{z}} + \ddot{\mathrm{s}}.\mathrm{w} \\ & + \dot{\mathrm{s}}.\dot{\mathrm{w}} + \dot{\mathrm{s}}.\dot{\mathrm{w}} + \mathrm{s}.\ddot{\mathrm{w}} \\ = {} & \ddot{\mathrm{x}}.\mathrm{y}.\mathrm{z} + \mathrm{x}.\ddot{\mathrm{y}}.\mathrm{z} + \mathrm{x}.\mathrm{y}.\ddot{\mathrm{z}} + 2\dot{\mathrm{x}}.\dot{\mathrm{y}}.\mathrm{z} + 2\dot{\mathrm{x}}.\mathrm{y}.\dot{\mathrm{z}} + 2\mathrm{x}.\dot{\mathrm{y}}.\dot{\mathrm{z}} + \ddot{\mathrm{s}}.\mathrm{w} + \mathrm{s}.\ddot{\mathrm{w}} \\ & + 2\dot{\mathrm{s}}.\dot{\mathrm{w}} \qquad (3.59) \end{aligned}$$

$$\begin{aligned} \frac{d^4\lambda_4}{dt^4} = {} & \dddot{\mathrm{x}}.\mathrm{y}.\mathrm{z} + \ddot{\mathrm{x}}.\dot{\mathrm{y}}.\mathrm{z} + \ddot{\mathrm{x}}.\mathrm{y}.\dot{\mathrm{z}} + \dot{\mathrm{x}}.\ddot{\mathrm{y}}.\mathrm{z} + \mathrm{x}.\dddot{\mathrm{y}}.\mathrm{z} + \mathrm{x}.\ddot{\mathrm{y}}.\dot{\mathrm{z}} + \dot{\mathrm{x}}.\mathrm{y}.\ddot{\mathrm{z}} + \mathrm{x}.\dot{\mathrm{y}}.\ddot{\mathrm{z}} + \mathrm{x}.\mathrm{y}.\dddot{\mathrm{z}} \\ & + 2\ddot{\mathrm{x}}.\dot{\mathrm{y}}.\mathrm{z} + 2\dot{\mathrm{x}}.\ddot{\mathrm{y}}.\mathrm{z} + 2\dot{\mathrm{x}}.\dot{\mathrm{y}}.\dot{\mathrm{z}} + 2\ddot{\mathrm{x}}.\mathrm{y}.\dot{\mathrm{z}} + 2\dot{\mathrm{x}}.\dot{\mathrm{y}}.\dot{\mathrm{z}} + 2\dot{\mathrm{x}}.\mathrm{y}.\ddot{\mathrm{z}} + 2\dot{\mathrm{x}}.\dot{\mathrm{y}}.\dot{\mathrm{z}} \\ & + 2\mathrm{x}.\ddot{\mathrm{y}}.\dot{\mathrm{z}} + 2\mathrm{x}.\dot{\mathrm{y}}.\ddot{\mathrm{z}} + \dddot{\mathrm{s}}.\mathrm{w} + \ddot{\mathrm{s}}.\dot{\mathrm{w}} + \dot{\mathrm{s}}.\ddot{\mathrm{w}} + \mathrm{s}.\dddot{\mathrm{w}} + 2\ddot{\mathrm{s}}.\dot{\mathrm{w}} \\ & + 2\dot{\mathrm{s}}.\ddot{\mathrm{w}} \qquad (3.60) \end{aligned}$$

$$\dot{\lambda}_7 = \lambda_5 y_5 u_1 y_3 (-res) \exp(-res.y_7) \qquad (3.61)$$

$$e = y_5 \qquad (3.62)$$

$$f = y_3 \qquad (3.63)$$

$$g = \lambda_5 \qquad (3.64)$$

$$h = u_1.res.r \qquad (3.65)$$

$$r = \exp(-res.y_7) \qquad (3.66)$$

$$\dot{\lambda_7} = -e.f.g.h \qquad (3.67)$$

$$\ddot{\lambda_7} = -\dot{e}.f.g.h - e.\dot{f}.g.h - e.f.\dot{g}.h - e.f.g.\dot{h} \qquad (3.68)$$

$$\begin{aligned}\dddot{\lambda_7} = -(&\ddot{e}.f.g.h + \dot{e}.\dot{f}.g.h + \dot{e}.f.\dot{g}.h + \dot{e}.f.g.\dot{h} + \dot{e}.\dot{f}.g.h + e.\ddot{f}.g.h + e.\dot{f}.\dot{g}.h \\ &+ e.\dot{f}.g.\dot{h} + \dot{e}.f.\dot{g}.h + e.\dot{f}.\dot{g}.h + e.f.\ddot{g}.h + e.f.\dot{g}.\dot{h} + \dot{e}.f.g.\dot{h} \\ &+ e.\dot{f}.g.\dot{h} + e.f.\dot{g}.\dot{h} + e.f.g.\ddot{h}) \\ = -(&\ddot{e}.f.g.h + e.\ddot{f}.g.h + e.f.\ddot{g}.h + e.f.g.\ddot{h} + 2\dot{e}.\dot{f}.g.h \\ &+ 2\dot{e}.f.\dot{g}.h + 2\dot{e}.f.g.\dot{h} + 2e.\dot{f}.\dot{g}.h + 2e.\dot{f}.g.\dot{h} \\ &+ 2e.f.\dot{g}.\dot{h}) \qquad (3.70)\end{aligned}$$

$$\begin{aligned}-\frac{d^4\lambda_7}{dt^4} = &\dddot{e}.f.g.h + \ddot{e}.\dot{f}.g.h + \ddot{e}.f.\dot{g}.h + \ddot{e}.f.g.\dot{h} + \dot{e}.\ddot{f}.g.h + e.\dddot{f}.g.h + e.\ddot{f}.\dot{g}.h \\ &+ e.\ddot{f}.g.\dot{h} + \dot{e}.f.\ddot{g}.h + e.\dot{f}.\ddot{g}.h + e.f.\dddot{g}.h + e.f.\ddot{g}.\dot{h} + +\dot{e}.f.g.\ddot{h} \\ &+ e.\dot{f}.g.\ddot{h} + e.f.\dot{g}.\ddot{h} + e.f.g.\dddot{h} + 2\ddot{e}.\dot{f}.g.h + 2\dot{e}.\ddot{f}.g.h + 2\dot{e}.\dot{f}.\dot{g}.h \\ &+ 2\dot{e}.\dot{f}.g.\dot{h} + 2\ddot{e}.f.\dot{g}.h + 2\dot{e}.\dot{f}.\dot{g}.h + 2\dot{e}.f.\ddot{g}.h + 2\dot{e}.f.\dot{g}.\dot{h} \\ &+ 2\ddot{e}.f.g.\dot{h} + 2\dot{e}.\dot{f}.g.\dot{h} + 2\dot{e}.f.\dot{g}.\dot{h} + 2\dot{e}.f.g.\ddot{h} + 2\dot{e}.\dot{f}.\dot{g}.h \\ &+ 2e.\ddot{f}.\dot{g}.h + 2e.\dot{f}.\ddot{g}.h + 2e.\dot{f}.\dot{g}.\dot{h} + 2\dot{e}.\dot{f}.g.\dot{h} + 2e.\ddot{f}.g.\dot{h} \\ &+ 2e.\dot{f}.\dot{g}.\dot{h} + 2e.\dot{f}.g.\ddot{h} + 2\dot{e}.f.\dot{g}.\dot{h} + 2e.\dot{f}.\dot{g}.\dot{h} + 2e.f.\ddot{g}.\dot{h} \\ &+ 2e.f.\dot{g}.\ddot{h} \qquad (3.71)\end{aligned}$$

Now it is time to take care of the components of these derivations:

- $m = a_1\lambda_3$
- $n = 1 - b_1y_3$
- $o = \exp(-b_1y_3)$
- $r = \exp(-res.y_7)$
- $p = \lambda_5$
- $q = y_5u_1$
- $s = \lambda_6u_2$
- $w = y_6$
- $x = \lambda_4a_2$
- $y = 1 - b_2y_4$
- $z = \exp(-b_2y_4)$
- $e = y_5$
- $f = y_3$
- $g = \lambda_5$
- $h = u_1.res.r$

Necessary derivations of state variables:

- $\dot{y_2} = -k_ey_2 + \frac{k_a}{V}y_1$
- $\ddot{y_2} = -k_e\dot{y_2} + \frac{k_a}{V}\dot{y_1} = -k_e\dot{y_2} + \frac{k_a}{V}\left(-k_ay_1 + u(t)\right)$ (3.72)
- $\dot{y_3} = -a_1\exp(-b_1y_3)\,y_3 + (y_2 - c_1)$ (3.73)
- $\ddot{y_3} = -a_1\exp(-b_1y_3)\,\dot{y_3} + a_1b_1y_3\exp(-b_1y_3)\,\dot{y_3} + \dot{y_2}$ (3.74)
- $\dddot{y_3} = -a_1\exp(-b_1y_3)\,\ddot{y_3} + a_1b_1\exp(-b_1y_3)\,\dot{y_3}^2 + a_1b_1\exp(-b_1y_3)\,\dot{y_3}^2 +$
  $a_1b_1y_3\exp(-b_1y_3)\,\ddot{y_3} - a_1{b_1}^2y_3\exp(-b_1y_3)\,\dot{y_3}^2 + \ddot{y_2}$ (3.75)
- $\dot{y_4} = -a_2\exp(-b_2y_4)\,y_4 + (y_2 - c_2)$
- $\ddot{y_4} = -a_2\exp(-b_2y_4)\,\dot{y_4} + a_2b_2y_4\exp(-b_2y_4)\,\dot{y_4} + \dot{y_2}$ (3.76)

- $\dddot{y}_4 = -a_2 \exp(-b_2 y_4)\, \ddot{y}_4 + a_2 b_2 \exp(-b_2 y_4)\, \dot{y}_4{}^2 + a_2 b_2 \exp(-b_2 y_4)\, \dot{y}_4{}^2 +$

  $a_2 b_2 y_4 \exp(-b_2 y_4)\, \ddot{y}_4 - a_2 b_2{}^2 y_4 \exp(-b_2 y_4)\, \dot{y}_4{}^2 + \ddot{y}_2$ (3.77)
- $\dot{y}_5 = \lambda y_6 \log\left(\frac{K}{y_5}\right) y_5 - \exp(-res.\, y_7) u_1 y_3 y_5$
- $\ddot{y}_5 = \lambda \dot{y}_6 \log\left(\frac{K}{y_5}\right) y_5 - \lambda y_6 \dot{y}_5 + \lambda y_6 \log\left(\frac{K}{y_5}\right) \dot{y}_5 - \exp(-res.\, y_7)\, u_1 \dot{y}_3 y_5 -$

  $\exp(-res.\, y_7)\, u_1 y_3 \dot{y}_5 + res.\exp(-res.\, y_7)\, u_1 \dot{y}_7 y_5 y_3$ (3.78)
- $\dddot{y}_5 = \lambda \ddot{y}_6 \log\left(\frac{K}{y_5}\right) y_5 + \lambda \dot{y}_6 \log\left(\frac{K}{y_5}\right) \dot{y}_5 - \lambda \dot{y}_6 \dot{y}_5 - \lambda \dot{y}_6 \dot{y}_5 - \lambda y_6 \ddot{y}_5 +$

  $\lambda \dot{y}_6 \log\left(\frac{K}{y_5}\right) \dot{y}_5 + \lambda y_6 \log\left(\frac{K}{y_5}\right) \ddot{y}_5 - \lambda y_6 \frac{\dot{y}_5{}^2}{y_5} - \exp(-res.\, y_7)\, u_1 \ddot{y}_3 y_5 -$

  $\exp(-res.\, y_7)\, u_1 \dot{y}_3 \dot{y}_5 + res.\exp(-res.\, y_7)\, u_1 \dot{y}_7 \dot{y}_3 y_5 - \exp(-res.\, y_7)\, u_1 \dot{y}_3 \dot{y}_5 -$

  $\exp(-res.\, y_7)\, u_1 y_3 \ddot{y}_5 + res.\exp(-res.\, y_7)\, u_1 y_3 \dot{y}_7 \dot{y}_5 -$

  $res.\exp(-res.\, y_7)\, u_1 \ddot{y}_7 y_5 y_3 - res.\exp(-res.\, y_7)\, u_1 \dot{y}_7 \dot{y}_5 y_3 -$

  $res.\exp(-res.\, y_7)\, u_1 \dot{y}_7 y_5 \dot{y}_3 - res.\exp(-res.\, y_7)\, u_1 \dot{y}_7 y_5 y_3 +$

  $res.\exp(-res.\, y_7) u_1 \dot{y}_7 y_5 y_3$ (3.79)
- $\dot{y}_6 = R - (R + u_2 y_4) y_6$
- $\ddot{y}_6 = -(R + u_2 y_4) \dot{y}_6 - (u_2 \dot{y}_4) y_6$
- $\dddot{y}_6 = -(R + u_2 y_4) \ddot{y}_6 - (u_2 \dot{y}_4) \dot{y}_6 - (u_2 \ddot{y}_4) y_6 - (u_2 \dot{y}_4) \dot{y}_6$
- $\dot{y}_7 = (y_2 - c_1)$
- $\ddot{y}_7 = \dot{y}_2$ (3.80)
- $\dddot{y}_7 = \ddot{y}_2$ (3.81)

As can be seen control variable $u(t)$ shows up in the second derivation of $\ddot{y}_2$

$\ddot{y}_2$ is in the third derivation of y_7

$\dddot{y}_7$ is in the $\dddot{r}$

$\dddot{r}$ is in $\frac{d^4 \lambda_3}{dt^4}$

$\frac{d^4\lambda_3}{dt^4}$ is in $\frac{d^4A}{dt^4}$

$\frac{d^4A}{dt^4}$ is in $\frac{d^5\lambda_2}{dt^5}$

$\frac{d^5\lambda_2}{dt^5}$ is in $\frac{d^6\lambda_1}{dt^6}$

As seen in the equations above the highest derivate is the third order for each of these new variables.

- m

$$m = a_1\lambda_3 \qquad (3.82)$$

$$\dot{m} = a_1\dot{\lambda}_3 \qquad (3.83)$$

$$\ddot{m} = a_1\ddot{\lambda}_3 \qquad (3.84)$$

$$\dddot{m} = a_1\dddot{\lambda}_3 \qquad (3.85)$$

- $n = 1 - b_1y_3$

$$\dot{n} = -b_1\dot{y}_3 \qquad (3.86)$$

$$\dot{n} = -b_1(-a_1\exp(-b_1y_3)\,y_3 + (y_2 - c_1)) \qquad (3.87)$$

$$\ddot{n} = -b_1\ddot{y}_3 \qquad (3.88)$$

$$\dddot{n} = -b_1\dddot{y}_3 \qquad (3.89)$$

- $o = \exp(-b_1y_3)$

$$\dot{o} = -b_1\dot{y}_3 \exp(-b_1y_3) \qquad (3.90)$$

$$\ddot{o} = -b_1\ddot{y}_3 \exp(-b_1y_3) + {b_1}^2{\dot{y}_3}^2 \exp(-b_1y_3) \qquad (3.91)$$

$$\dddot{o} = -b_1\dddot{y}_3 \exp(-b_1y_3) + {b_1}^2\ddot{y}_3\dot{y}_3 \exp(-b_1y_3) + 2{b_1}^2\dot{y}_3\ddot{y}_3 \exp(-b_1y_3)$$
$$- {b_1}^3{\dot{y}_3}^3 \exp(-b_1y_3) \qquad (3.92)$$

- $r = \exp(-res.\,y_7)$

$$\dot{r} = -res.\,\dot{y}_7 \exp(-res.\,y_7) \qquad (3.93)$$

$$\ddot{r} = -res.\,\ddot{y}_7 \exp(-res.\,y_7) + res^2.\,{\dot{y}_7}^2 \exp(-res.\,y_7) \qquad (3.94)$$

$$\dddot{r} = -res.\,\dddot{y}_7 \exp(-res.\,y_7) + res^2.\,\ddot{y}_7\dot{y}_7 \exp(-res.\,y_7)$$
$$+ 2res^2.\,\dot{y}_7\ddot{y}_7 \exp(-res.\,y_7)$$
$$- res^3.\,{\dot{y}_7}^3 \exp(-res.\,y_7) \qquad (3.95)$$

- $p = \lambda_5$

$$\dot{p} = \dot{\lambda}_5 \qquad (3.96)$$

$$\dot{\lambda}_5 = -1 - \lambda_5\lambda y_6 \log\left(\frac{K}{y_5}\right) + \lambda_5\lambda y_6 + \lambda_5 u_1 y_3 \exp(-res.\,y_7) \qquad (3.97)$$

$$\ddot{p} = \ddot{\lambda}_5 = \dot{\dot{\lambda}}_5 = -\dot{\lambda}_5\lambda y_6 \log\left(\frac{K}{y_5}\right) - \lambda_5\lambda\dot{y}_6 \log\left(\frac{K}{y_5}\right) + \lambda_5\lambda y_6\left(\frac{\dot{y}_5}{y_5}\right) + \dot{\lambda}_5\lambda y_6$$
$$+ \lambda_5\lambda\dot{y}_6 + \dot{\lambda}_5 u_1 y_3 \exp(-res.\,y_7) + \lambda_5 u_1 \dot{y}_3 \exp(-res.\,y_7)$$
$$- res.\,\lambda_5 u_1 y_3 \dot{y}_7 \exp(-res.\,y_7) \qquad (3.98)$$

$$\dddot{p} = \dddot{\lambda}_5 = -\ddot{\lambda}_5 \lambda y_6 \log\left(\frac{K}{y_5}\right) - \dot{\lambda}_5 \lambda \dot{y}_6 \log\left(\frac{K}{y_5}\right) + \dot{\lambda}_5 \lambda y_6 \frac{\dot{y}_5}{y_5} - \dot{\lambda}_5 \lambda \dot{y}_6 \log\left(\frac{K}{y_5}\right)$$

$$- \lambda_5 \lambda \ddot{y}_6 \log\left(\frac{K}{y_5}\right) + \lambda_5 \lambda \dot{y}_6 \frac{\dot{y}_5}{y_5} + \dot{\lambda}_5 \lambda y_6 \left(\frac{\dot{y}_5}{y_5}\right) + \lambda_5 \lambda \dot{y}_6 \left(\frac{\dot{y}_5}{y_5}\right)$$

$$- \lambda_5 \lambda y_6 \left(\frac{\dot{y}_5{}^2}{y_5{}^2}\right) + \ddot{\lambda}_5 \lambda y_6 + \dot{\lambda}_5 \lambda \dot{y}_6 + \dot{\lambda}_5 \lambda \dot{y}_6 + \lambda_5 \lambda \ddot{y}_6$$

$$+ \ddot{\lambda}_5 u_1 y_3 \exp(-res. y_7) + \dot{\lambda}_5 u_1 \dot{y}_3 \exp(-res. y_7)$$

$$- res. \dot{\lambda}_5 u_1 y_3 \dot{y}_7 \exp(-res. y_7) + \dot{\lambda}_5 u_1 \dot{y}_3 \exp(-res. y_7)$$

$$+ \lambda_5 u_1 \ddot{y}_3 \exp(-res. y_7) - res. \lambda_5 u_1 \dot{y}_3 \dot{y}_7 \exp(-res. y_7)$$

$$- res. \dot{\lambda}_5 u_1 y_3 \dot{y}_7 \exp(-res. y_7) - res. \lambda_5 u_1 \dot{y}_3 \dot{y}_7 \exp(-res. y_7)$$

$$- res. \lambda_5 u_1 y_3 \ddot{y}_7 \exp(-res. y_7)$$

$$+ res^2. \lambda_5 u_1 y_3 \dot{y}_7{}^2 \exp(-res. y_7) \qquad (3.99)$$

- $q = y_5 u_1$

$$\dot{q} = \dot{y}_5 u_1 \qquad (3.100)$$

$$\ddot{q} = \ddot{y}_5 u_1 \qquad (3.101)$$

$$\dddot{q} = \dddot{y}_5 u_1 \qquad (3.102)$$

- $s = \lambda_6 u_2$

$$\dot{s} = \dot{\lambda}_6 u_2 = \lambda_6 R - \lambda_5 \lambda \log\left(\frac{K}{y_5}\right) + \lambda_6 y_4 u_2 \qquad (3.103)$$

$$\ddot{s} = \ddot{\lambda}_6 u_2 = \dot{\lambda}_6 R - \dot{\lambda}_5 \lambda \log\left(\frac{K}{y_5}\right) + \lambda_5 \lambda \frac{\dot{y}_5}{y_5} + \dot{\lambda}_6 y_4 u_2 + \lambda_6 \dot{y}_4 u_2 \qquad (3.104)$$

$$\dddot{s} = \dddot{\lambda}_6 u_2 = \ddot{\lambda}_6 R - \ddot{\lambda}_5 \lambda \log\left(\frac{K}{y_5}\right) + \dot{\lambda}_5 \lambda \frac{\dot{y}_5}{y_5} + \dot{\lambda}_5 \lambda \frac{\dot{y}_5}{y_5} + \lambda_5 \lambda \frac{\ddot{y}_5}{y_5} - \lambda_5 \lambda \frac{\dot{y}_5{}^2}{y_5{}^2}$$

$$+ \ddot{\lambda}_6 y_4 u_2 + \dot{\lambda}_6 \dot{y}_4 u_2 + \lambda_6 \ddot{y}_4 u_2 + \lambda_6 \dot{y}_4 \dot{u}_2 \qquad (3.105)$$

- $w = y_6$

$$\dot{w} = \dot{y}_6 \qquad (3.106)$$

$$\ddot{w} = \ddot{y}_6 \qquad (3.107)$$

$$\dddot{w} = \dddot{y}_6 \qquad (3.108)$$

- $x = \lambda_4 a_2$

$$\dot{x} = \dot{\lambda}_4 a_2 = a_2(-\lambda_4 y_4 a_2 b_2 \exp(-b_2 y_4) + \lambda_6 y_6 u_2 + \lambda_4 a_2 \exp(-b_2 y_4)) \qquad (3.109)$$

$$\begin{aligned}\ddot{x} &= -\dot{\lambda}_4 y_4 a_2{}^2 b_2 \exp(-b_2 y_4) + \lambda_4 y_4 \dot{y}_4 a_2{}^2 b_2{}^2 \exp(-b_2 y_4) + \dot{\lambda}_6 y_6 u_2 a_2 \\ &\quad + \lambda_6 \dot{y}_6 u_2 a_2 + \dot{\lambda}_4 a_2{}^2 \exp(-b_2 y_4) - b_2 \lambda_4 a_2{}^2 \dot{y}_4 \exp(-b_2 y_4) \\ &= a_2 \ddot{\lambda}_4 \qquad (3.110)\end{aligned}$$

$$\begin{aligned}\dddot{x} = \dddot{\lambda}_4 a_2 &= -\ddot{\lambda}_4 y_4 a_2{}^2 b_2 \exp(-b_2 y_4) - \dot{\lambda}_4 \dot{y}_4 a_2{}^2 b_2 \exp(-b_2 y_4) \\ &\quad + \dot{\lambda}_4 y_4 \dot{y}_4 a_2{}^2 b_2{}^2 \exp(-b_2 y_4) + \dot{\lambda}_4 y_4 \dot{y}_4 a_2{}^2 b_2{}^2 \exp(-b_2 y_4) \\ &\quad + \lambda_4 \dot{y}_4{}^2 a_2{}^2 b_2{}^2 \exp(-b_2 y_4) + \lambda_4 y_4 \ddot{y}_4 a_2{}^2 b_2{}^2 \exp(-b_2 y_4) \\ &\quad - \lambda_4 y_4 \dot{y}_4{}^2 a_2{}^2 b_2{}^3 \exp(-b_2 y_4) + \ddot{\lambda}_6 y_6 u_2 a_2 + \dot{\lambda}_6 \dot{y}_6 u_2 a_2 \\ &\quad + \dot{\lambda}_6 \dot{y}_6 u_2 a_2 + \lambda_6 \ddot{y}_6 u_2 a_2 + \ddot{\lambda}_4 a_2{}^2 \exp(-b_2 y_4) \\ &\quad + \dot{\lambda}_4 a_2{}^2 b_2 \dot{y}_4 \exp(-b_2 y_4) - b_2 \dot{\lambda}_4 a_2{}^2 \dot{y}_4 \exp(-b_2 y_4) \\ &\quad - b_2 \lambda_4 a_2{}^2 \ddot{y}_4 \exp(-b_2 y_4) \\ &\quad + b_2{}^2 \lambda_4 a_2{}^2 \dot{y}_4{}^2 \exp(-b_2 y_4) \qquad (3.111)\end{aligned}$$

- $y = 1 - b_2 y_4$

$$\dot{y} = -b_2 \dot{y}_4 \qquad (3.112)$$

$$\ddot{y} = -b_2 \ddot{y}_4 \qquad (3.113)$$

$$\dddot{y} = -b_2 \dddot{y}_4 \qquad (3.114)$$

- $z = \exp(-b_2 y_4)$

$$\dot{z} = -b_2 \dot{y}_4 \exp(-b_2 y_4) \qquad (3.115)$$

$$\ddot{z} = -b_2 \ddot{y}_4 \exp(-b_2 y_4) + {b_2}^2 {\dot{y}_4}^2 \exp(-b_2 y_4) \qquad (3.116)$$

$$\dddot{z} = -b_2 \dddot{y}_4 \exp(-b_2 y_4) + {b_2}^2 \ddot{y}_4 \dot{y}_4 \exp(-b_2 y_4) + 2{b_2}^2 \dot{y}_4 \ddot{y}_4 \exp(-b_2 y_4) - {b_2}^3 {\dot{y}_4}^3 \exp(-b_2 y_4) \qquad (3.117)$$

- $e = y_5$

$$\dot{e} = \dot{y}_5 \qquad (3.118)$$

$$\ddot{e} = \ddot{y}_5 \qquad (3.119)$$

$$\dddot{e} = \dddot{y}_5 \qquad (3.120)$$

- $f = y_3$

$$\dot{f} = \dot{y}_3 \qquad (3.121)$$

$$\ddot{f} = \ddot{y}_3 \qquad (3.122)$$

$$\dddot{f} = \dddot{y}_3 \qquad (3.123)$$

- $g = \lambda_5$

$$\dot{g} = \dot{\lambda}_5 \qquad (3.124)$$

$$\ddot{g} = \ddot{\lambda}_5 \qquad (3.125)$$

$$\dddot{g} = \dddot{\lambda}_5 \qquad (3.126)$$

- $h = u_1.res.r$

$$\dot{h} = u_1.res.\dot{r} \qquad (3.127)$$

$$\ddot{h} = u_1.res.\ddot{r} \qquad (3.128)$$

$$\dddot{h} = u_1.res.\dddot{r} \qquad (3.129)$$

$\frac{d^4\lambda_3}{dt^4}$ is calculated based on equations: (3.48) to (3.51) and (3.82) to (3.102).

$\frac{d^4\lambda_4}{dt^4}$ is calculated based on equations: (3.57) to (3.60) and (3.103) to (3.117)

$\frac{d^4\lambda_7}{dt^4}$ is calculated based on equations: (3.61) to (3.71) and (3.118) to (3.129)

According to (3.31) $\quad A = \lambda_4 + \lambda_3 + \lambda_7$

So A, $\dot{A}$, $\ddot{A}$, $\dddot{A}$, $\frac{d^4A}{dt^4}$ are calculated.

$\frac{d\lambda_2}{dt}, \frac{d^2\lambda_2}{dt^2}, \frac{d^3\lambda_2}{dt^3}, \frac{d^4\lambda_2}{dt^4}, \frac{d^5\lambda_2}{dt^5}$ are calculated from equations (3.31) to (3.36).

$\frac{d\lambda_1}{dt}, \frac{d^2\lambda_1}{dt^2}, \frac{d^3\lambda_1}{dt^3}, \frac{d^4\lambda_1}{dt^4}, \frac{d^5\lambda_1}{dt^5}, \frac{d^6\lambda_1}{dt^6}$ are then calculated from equations (3.26) to (3.31).

The terms in $\frac{d^6\lambda_1}{dt^6}$ that include $u(t)$ are:

$$B = \frac{k_a}{V}(-b_1).m.o + m.n.\frac{k_a}{V}(-b_1).\exp(-b_1 y_3) + p.q.\frac{k_a}{V}(-res)\exp(-res.y_7)$$

$$+ x.z.\frac{k_a}{V}(-b_2) - b_2 \exp(-b_2.y_4)\frac{k_a}{V} + e.g.h.\frac{k_a}{V}$$

$$+ e.f.g\frac{k_a}{V}u_1(-res^2)\exp(-res.y_7) \qquad (3.130)$$

The singular value for u is the obtained according to (3.31).

$$\frac{d^6\lambda_1}{dt^6} = k_a{}^5\left(k_a\lambda_1 - \frac{k_a}{V}\lambda_2\right) - \frac{k_a{}^5}{V}\dot{\lambda}_2 - \frac{k_a{}^4}{V}\ddot{\lambda}_2 - \frac{k_a{}^3}{V}\dddot{\lambda}_2 - \frac{k_a{}^2}{V}\frac{d^4\lambda_2}{dt^4}$$

$$- \frac{k_a}{V}\frac{d^5\lambda_2}{dt^5} \qquad (3.31)$$

note that in this equation $\lambda_1 = 0$ then $\frac{d^6\lambda_1}{dt^6}$ is considered to be zero well.

$$u_{singular} =$$

$$\frac{\left(\frac{k_a{}^6}{V}\lambda_2\right) + \frac{k_a{}^5}{V}\dot{\lambda}_2 + \frac{k_a{}^4}{V}\ddot{\lambda}_2 + \frac{k_a{}^3}{V}\dddot{\lambda}_2 + \frac{k_a{}^2}{V}\frac{d^4\lambda_2}{dt^4} + \frac{k_a}{V}(\frac{d^5\lambda_2}{dt^5} - B)}{B} \qquad (3.131)$$

3.1.1 optimality condition

$(-1)^p \frac{\delta}{\delta u}\left[\frac{d^{2p}}{dt^{2p}} H_u\right] \geq 0$ is the generalized Legendre-Clebsch condition as mentioned in the previous chapter.

$$H_u = \lambda_1$$

$$B = \frac{\delta}{\delta u}\left[\frac{d^{2p}}{dt^{2p}}\lambda_1\right]$$

$$(-1)^p \frac{\delta}{\delta u}\left[\frac{d^{2p}}{dt^{2p}} H_u\right] = -B$$

So to check the optimality we check the sign if the condition $-B \geq 0$ holds. Note that in order to obtain the control variable the H_u is derivated 6 times which means that $p = 3$.

3.2 Case 2

For $c_1 < y_2 < c_2$:

In this case according to (3.18) $\dot{\lambda_2} = \lambda_2 k_e - \lambda_4$

Then $A = \lambda_4$

λ_4 is the calculated just like case1:

$$\dot{\lambda_4} = -\lambda_4 y_4 a_2 b_2 \exp(-b_2 y_4) + \lambda_6 y_6 u_2 + \lambda_4 a_2 \exp(-b_2 y_4)$$

$$s = \lambda_6 u_2$$

$$w = y_6$$

$$x = \lambda_4 a_2$$

$$y = 1 - b_2 y_4$$

$$z = \exp(-b_2 y_4)$$

$$\dot{\lambda_4} = \mathrm{x.y.z + s.w}$$

$$\ddot{\lambda_4} = \mathrm{\dot{x}.y.z + x.\dot{y}.z + x.y.\dot{z} + \dot{s}.w + s.\dot{w}}$$

$$\ddot{\lambda}_4 = \ddot{x}.y.z + \dot{x}.\dot{y}.z + \dot{x}.y.\dot{z} + \dot{x}.\dot{y}.z + x.\ddot{y}.z + x.\dot{y}.\dot{z} + \dot{x}.y.\dot{z} + x.\dot{y}.\dot{z} + x.y.\ddot{z} + \ddot{s}.w$$
$$+ \dot{s}.\dot{w} + \dot{s}.\dot{w} + s.\ddot{w}$$
$$= \ddot{x}.y.z + x.\ddot{y}.z + x.y.\ddot{z} + 2\dot{x}.\dot{y}.z + 2\dot{x}.y.\dot{z} + 2x.\dot{y}.\dot{z} + \ddot{s}.w + s.\ddot{w}$$
$$+ 2\dot{s}.\dot{w}$$

$$\frac{d^4\lambda_4}{dt^4} = \dddot{x}.y.z + \ddot{x}.\dot{y}.z + \ddot{x}.y.\dot{z} + \dot{x}.\ddot{y}.z + x.\dddot{y}.z + x.\ddot{y}.\dot{z} + \dot{x}.y.\ddot{z} + x.\dot{y}.\ddot{z} + x.y.\dddot{z}$$
$$+ 2\ddot{x}.\dot{y}.z + 2\dot{x}.\ddot{y}.z + 2\dot{x}.\dot{y}.\dot{z} + 2\ddot{x}.y.\dot{z} + 2\dot{x}.\dot{y}.\dot{z} + 2\dot{x}.y.\ddot{z}$$
$$+ 2\dot{x}.\dot{y}.\dot{z} + 2x.\ddot{y}.\dot{z} + 2x.\dot{y}.\ddot{z} + \dddot{s}.w + \ddot{s}.\dot{w} + \dot{s}.\ddot{w} + s.\dddot{w} + 2\ddot{s}.\dot{w}$$
$$+ 2\dot{s}.\ddot{w}$$

Then $\dot{\acute{\lambda}}_2, \frac{d^2\acute{\lambda}_2}{dt^2}, \frac{d^3\acute{\lambda}_2}{dt^3}, \frac{d^4\acute{\lambda}_2}{dt^4}, \frac{d^5\acute{\lambda}_2}{dt^5}$ is calculated according to equations (3.32) to (3.36).

$\frac{d\acute{\lambda}_1}{dt}, \frac{d^2\acute{\lambda}_1}{dt^2}, \frac{d^3\acute{\lambda}_1}{dt^3}, \frac{d^4\acute{\lambda}_1}{dt^4}, \frac{d^5\acute{\lambda}_1}{dt^5}, \frac{d^6\acute{\lambda}_1}{dt^6}$ are then calculated from equations (3.26) to (3.31).

The terms in $\frac{d^6\acute{\lambda}_1}{dt^6}$ that include $u(t)$ are:

$$\acute{B} = x.z.\frac{k_a}{V}(-b_2) - b_2\exp(-b_2.y_4)\frac{k_a}{V}$$

$$\acute{u}_{singular} = \frac{\left(\frac{k_a}{V}^6\acute{\lambda}_2\right) + \frac{k_a}{V}^5\dot{\acute{\lambda}}_2 + \frac{k_a}{V}^4\ddot{\acute{\lambda}}_2 + \frac{k_a}{V}^3\dddot{\acute{\lambda}}_2 + \frac{k_a}{V}^2\frac{d^4\acute{\lambda}_2}{dt^4} + \frac{k_a}{V}\left(\frac{d^5\acute{\lambda}_2}{dt^5} - \acute{B}\right)}{\acute{B}}$$

3.2.1 Optimality condition

$(-1)^p\frac{\delta}{\delta u}\left[\frac{d^{2p}}{dt^{2p}}H_u\right] \geq 0$ is the generalized Legendre-Clebsch condition as mentioned in the previous chapter.

$$H_u = \lambda_1$$

$$\acute{B} = \frac{\delta}{\delta u}\left[\frac{d^{2p}}{dt^{2p}}\,\lambda_1\right]$$

$$(-1)^p\,\frac{\delta}{\delta u}\left[\frac{d^{2p}}{dt^{2p}}\,H_u\right] = -\acute{B}$$

So to check the optimality we check the sign if the condition $-\acute{B} \geq 0$ holds. Note that in order to obtain the control variable the H_u is derivated 6 times which means that $p = 3$.

3.3 case 3: infinite order singular arc

When $y_2 < c_1$ then $\dot{\lambda}_2 = \lambda_2 k_e$; meaning control variable will not show up in the derivatives of the switching function no matter how many times it is derivated. This is, as discussed before infinite order singular arc. If we rewrite equations (3.1) to (3.7) the new ODEs are as follows:

$$\dot{y_1} = -k_a y_1 + u(t) \qquad (3.1)$$

$$\dot{y_2} = -k_e y_2 + \frac{k_a}{V} y_1 \qquad (3.2)$$

$$\dot{y_3} = -a_1 \exp(-b_1 y_3)\, y_3 \qquad (3.3)$$

$$\dot{y_4} = -a_2 \exp(-b_2 y_4)\, y_4 \qquad (3.4)$$

$$\dot{y_5} = \lambda y_6 \log\left(\frac{K}{y_5}\right) y_5 - N_1 y_5 \qquad (3.5)$$

$$\dot{y_6} = R - (R + N_2) y_6 \qquad (3.6)$$

$$\dot{y_7} = 0 \qquad (3.7)$$

y_2 is the state variable that relates the control variable and the rest of the variables. When y_2 is not available in $y_3 \; or \; y_4$ it means that the control variable and cancer cells are independent and the control variable has no effect on the cancer cells. This situation emerges when $y_2 < .3(c_2)$. In order to calculate the infinite order value assumptions about $\dot{y_2}$ and $\dot{y_1}$ are made as follows:

$$\dot{y_2} = 0 \; and \; \dot{y_1} = 0 \qquad when \; y_2 = 0.3$$

The assumption is made to make sure that y_2 never drops below 0.3 because as explained earlier when y_2 is less than 0.3 then the medication will have no effect on tumour cells.

The simulation is run for each day then after rewriting the values for K_a and K_v as:

$$K_a \; for \; 24 \; hours = 2.4 * 24 = 57.6$$

$$K_e \; for \; 24 \; hours = 0.39 * 24 = 9.36$$

$$\dot{y_1} = -k_a y_1 + u(t) = 0$$

$$\dot{y_2} = -k_e y_2 + \frac{k_a}{V} y_1 = 0 \qquad y_2 = 0.3$$

u is then calculated for the case of infinite order singular arc.

$$0 = -9.36 * 0.3 + \left(\frac{57.6}{14}\right) y_1 \rightarrow \; y_1 = 0.6825$$

$$-9.36 * 0.6825 + u(t) = 0 \rightarrow u_{infinite_{order_{singular}}} = 39.312$$

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Introduction

In this chapter we use MATLAB to simulate the results.for solving non stiff ODEs the ODE45 in MATLAB and for stiff ODEs ODE15s is used. MATLAB ODE solvers can solve equations of the form : $\acute{y} = f(y,t)$. Solving the ODE equations and obtaining the optimal control theory control variable is iterated and each iteration develops the control variable for the next iteration. In this simulation the number of iterations is set to 20. Different variables are taken into account and changed to obtain the results provided in this chapter. The variables changed in order to test the results are maximum dosage and the singular range. First we test the algorithm by applying maximum dosage of 50 then the dosage is changed to 10. Note that in all results the dosage of 39.312(almost 40 in the figures) means infinite order singular arc is happening and the dosage is set to the solution provided in the previous chapter for the infinite order singular arc.

4.1.1 Changing maximum dosage:

4.1.1.1 $\boldsymbol{u_{max} = 10}$

The first set of results has the values:

$$u_{max} = 10 \qquad number\ of\ days = 350$$

$$singular\ range = (-0.000505\ , 0.000505)$$

Note that in this simulation the values for finite order singular arc are out of bound(the maximum dosage in [5] which is 85) so the values for finite singular arc is either 0 or u_{max}.

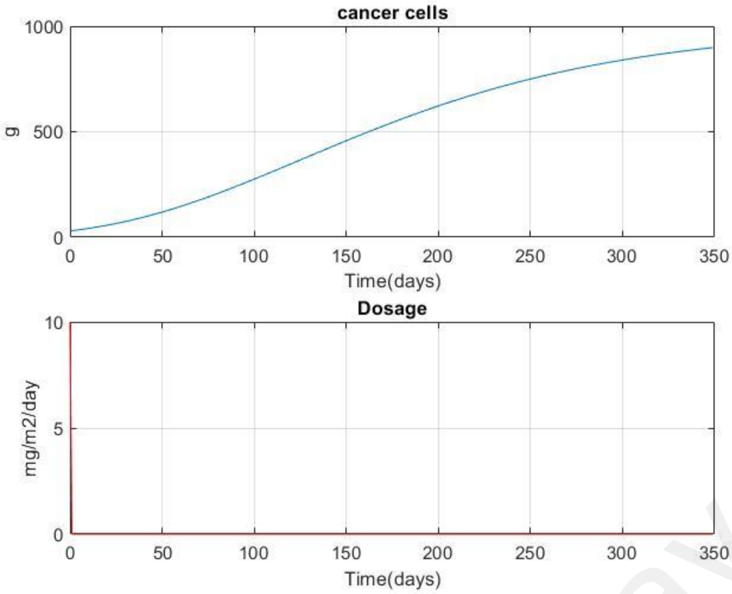

Figure 4.1 (First Iteration)

Figure 4.1 shows how cancer cells grow without any medication applied. Which is the first iteration.

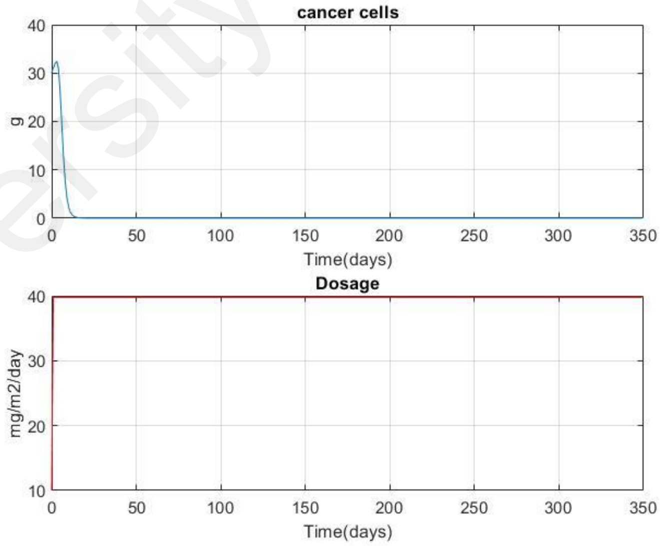

Figure 4.2(Second Iteration)

Figure 4.2 shows the second iteration when the algorithm is trying to minimize the cancer cells by applying the maximum dosage all the time which is obviously not the best option.

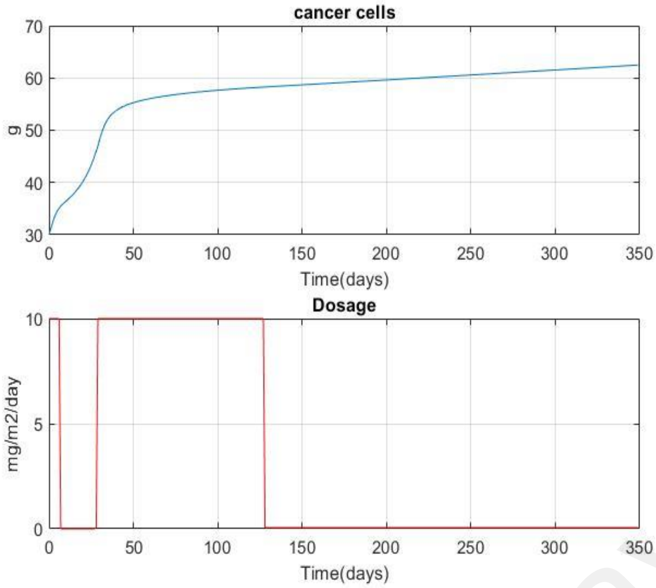

Figure 4.3(Third Iteration)

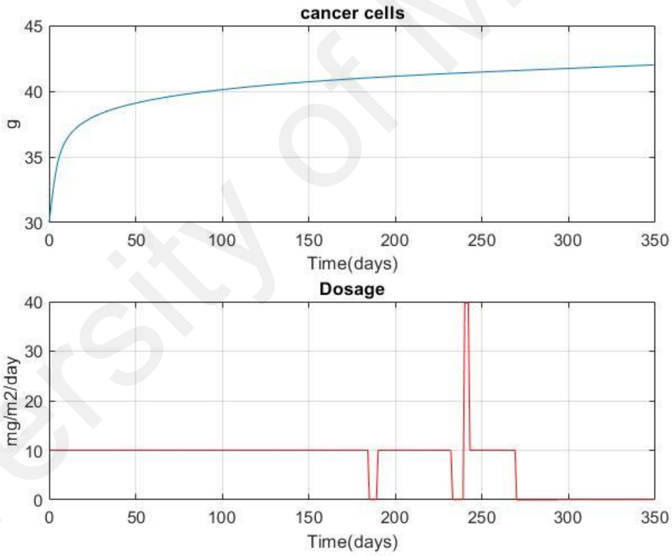

Figure 4.4(19th Iteration)

Figure 4.3 shows the third iteration and figure 4.4 shows the 19th iteration. As can be seen in the figures these iterations are not minimizing the cancer cells and thorough the whole 20 iterations it can be seen that the odd iterations cannot minimize the cancer cells.

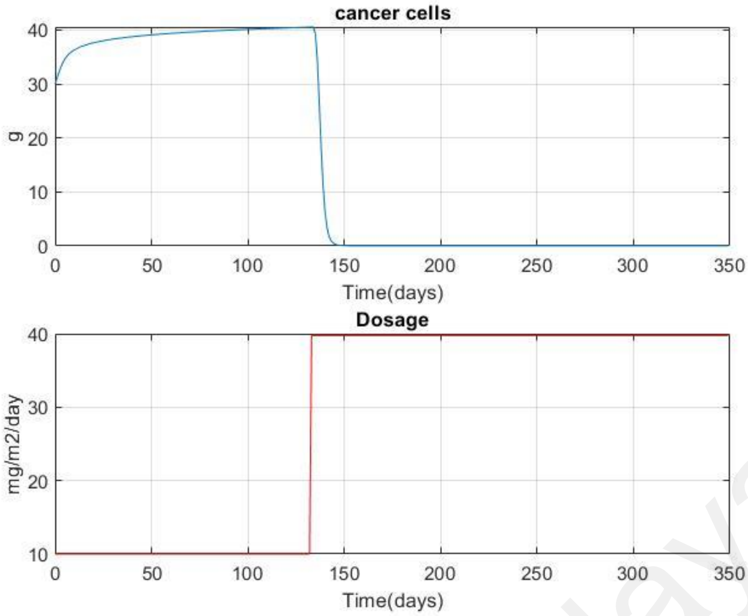

Figure 4.5(4th Iteration)

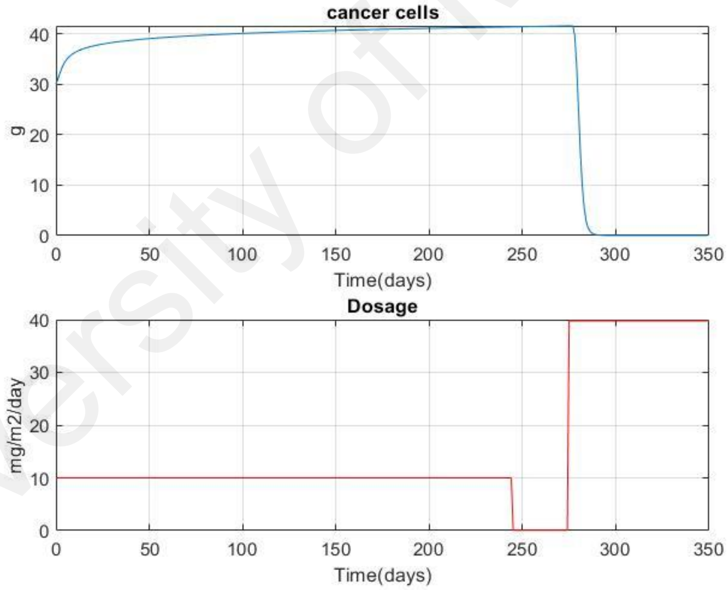

Figure 4.6(20th Iteration)

Figure 4.5 and figure 4.6 show the 4th and the 20th iteration respectively. As it can be seen both can make the cancer cells reach zero.

Note that in [5] it states that when cancer cells reach below 1, the cancer is considered cured. So as it can be seen both these iterations are curing cancer.

The difference is that in the 4th iteration the algorithm is minimizing the cancer cells by bang-bang plus infinite order singular arc and in this case when the maximum dosage is 10 it is greater that the value obtained for infinite order singular arc which is 39.3.

As the algorithm iterates the infinite order singular arc becomes less and the control becomes combination of bang-bang plus finite order singular arc plus infinite order singular arc.

Also note that when infinite order singular arc the cancer cells drop faster and reach 0 sooner than when both finite and infinite order singular arcs are present.

To choose between these two drug regimens should be left to the chemo doctors. One regimen uses less medication but cures slower another regimen uses more chemo but cures faster.

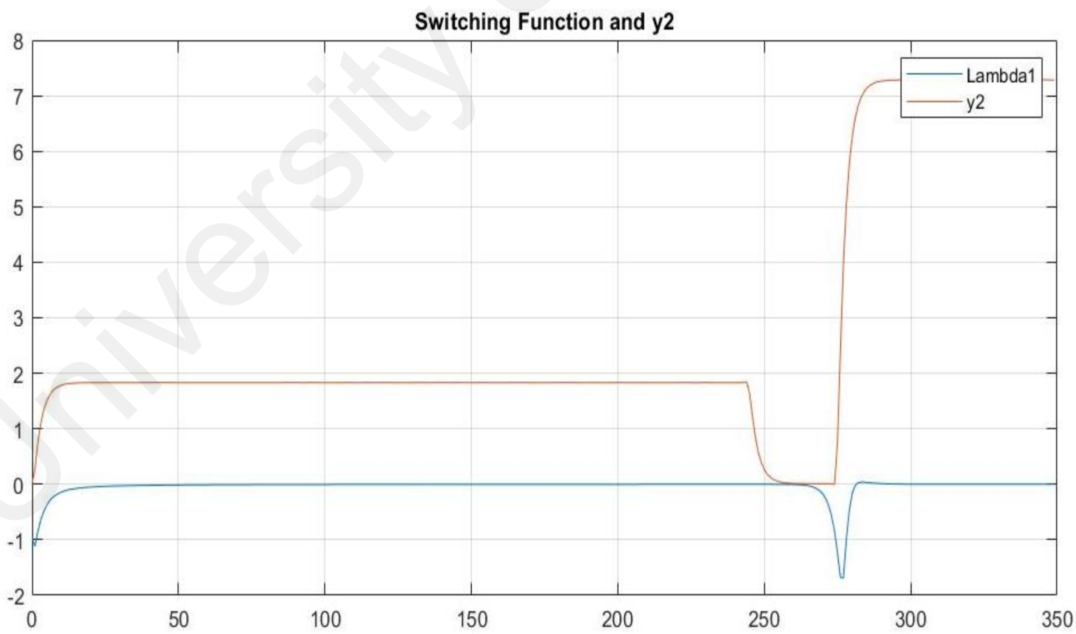

Figure 4.7

Figure 4.7 shows λ_1 which is the switching function and y_2. As discussed in the previous section the value of y_2 determines the case of singular arc.

As it can be seen in the figure 4.7 most of the control in this system of ODEs is singular control. λ_1 has very small values for most of the time. So another variable that can be changed here and will affect the control is the range of λ_1 that we define different cases of bang-bang, singular control and infinite order singular arc.

4.1.1.2 $u_{max} = 50$

The next set of results depict different iterations when $u_{max} = 50$ the rest of the variables are left the same. Like before the first iteration when no chemo is applied is the same and the cancer cells just increase. As it can be seen in the figures 4.8 and 4.9 the even iterations take the extreme case of applying chemo almost constantly.

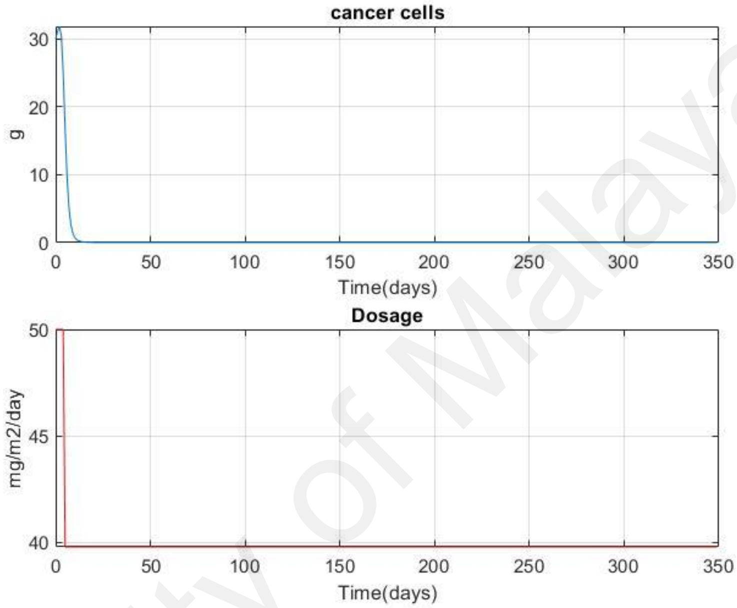

Figure 4.8(Second Iteration)

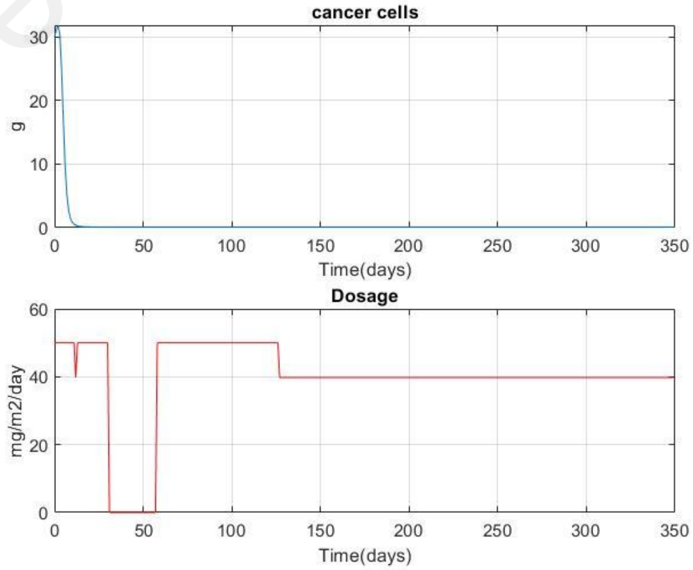

Figure 4.9 (20th Iteration)

The figures 4.10 and 4.11 show two sample of odd iterations. it can be seen that the odd iterations are better options because they are not applying chemo all the time. The difference between the third iteration and the 19^{th} one is that in the latter infinite order singular arc decreases the amount of chemo administrated. But in the third iteration the cancer drops below 1 sooner than the 19^{th} iteration which is an obvious observation.

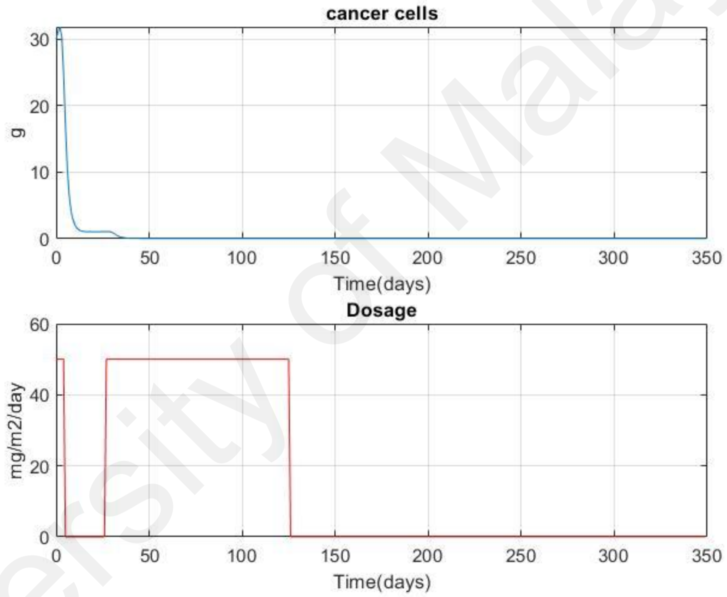

Figure 4.10 (Third Iteration)

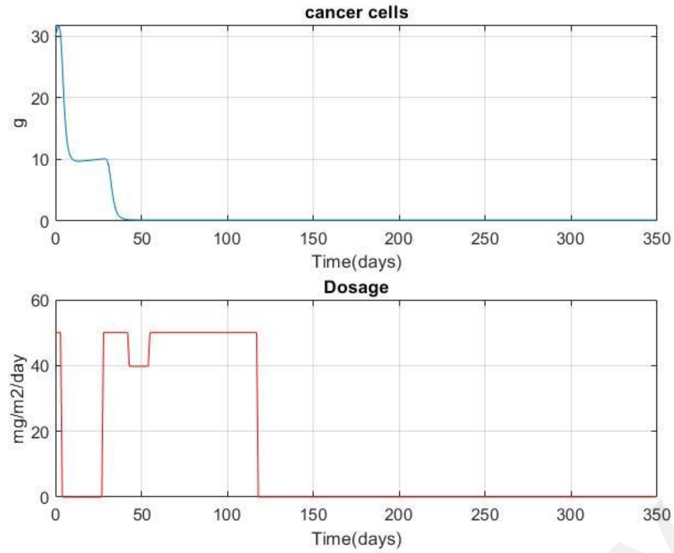

Figure 4.11 (19^{th} Iteration)

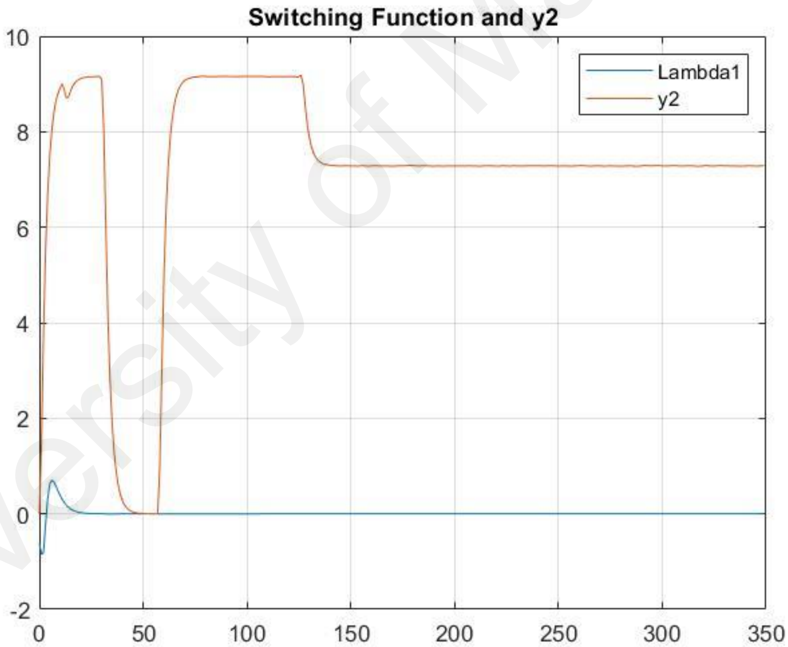

Figure 4.12

Again here according to the plot of the switching function and y_2 it can be seen that

Almost all of the control is singular control.

4.1.2 Changing the singular range

in this section the range for singular value is changed and the consequences are discussed. This range determines if the switching function is small enough to be considered singular arc or not. u_{max} is set to 50. Number of days is 350 as before. The range of singular arc is changed to $(-0.00001\ ,\ 0.00001)$ which is a smaller range than before. Note that as seen in previous sections the switching function in this particular control has mostly very small value. So this range can change the results drastically. In previous section it was seen that odd iterations are better options than the even ones. Figure 4.13 and 4.14 show the third and the 19th iteration after the range is changed.

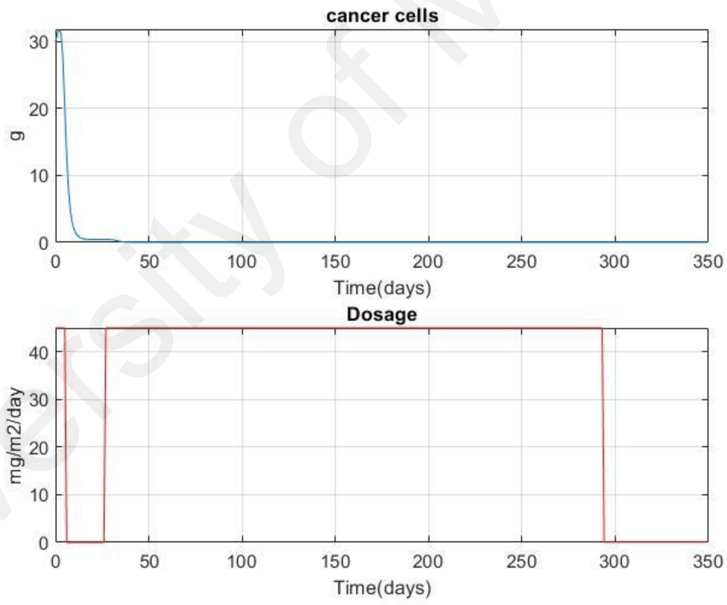

Figure 4.13 (Third Iteration)

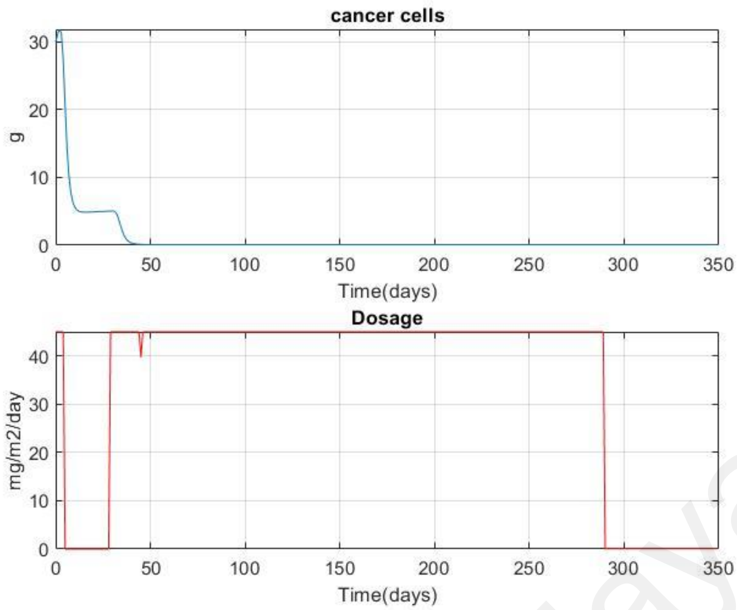

Figure 4.14(19th iteration)

As can be seen in the two figures 4.13 and 4.14 when this range changes a lot of points that were considered singular control in previous range now are not singular anymore. As a result, the chemo is administrated much more but the results on the cancer cells are almost the same.

4.2 Generalized Legendre-Clebsch condition

The generalized Legendre-Clebsch condition: $(-1)^p \frac{\delta}{\delta u}\left[\frac{d^{2p}}{dt^{2p}} H_u\right] \geq 0$ is checked for the cases discussed earlier where: $u_{max} = 50$ and $singular\ range = (-0.000505, 0.000505)$

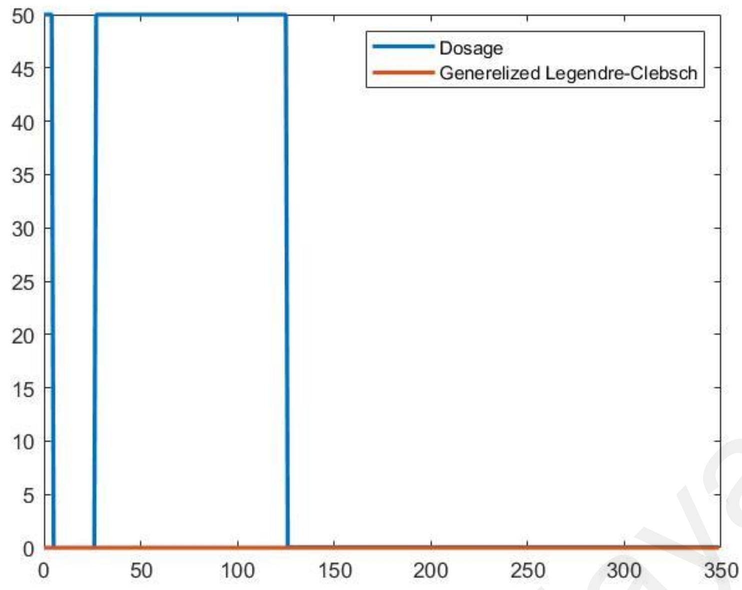

Figure 4.15(third iteration)

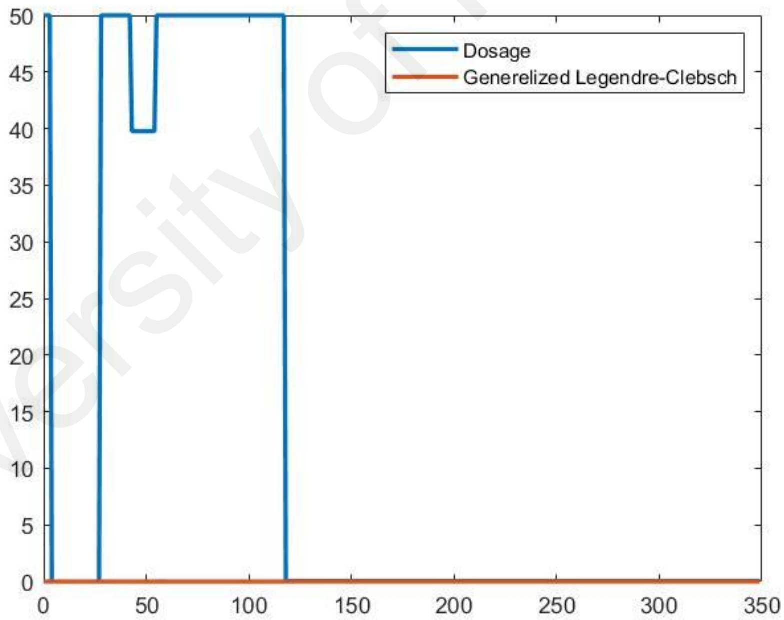

Figure 4.16(19th iteration)

As can be seen in the figures 4.15 and 4.16 the generalized Legendre-Clebsch condition for both iterations 3 and 19 is zero which means that the optimality condition is satisfied.

For $u_{max} = 10$ and $singular\ range = (-0.000505, 0.000505)$ figures 4.17 and 4.18 show the dosage and the generalized Legendre-Clebsch condition for iterations 4 and 20 respectively. As it can be seen the condition holds and the optimality condition is satisfied here too.

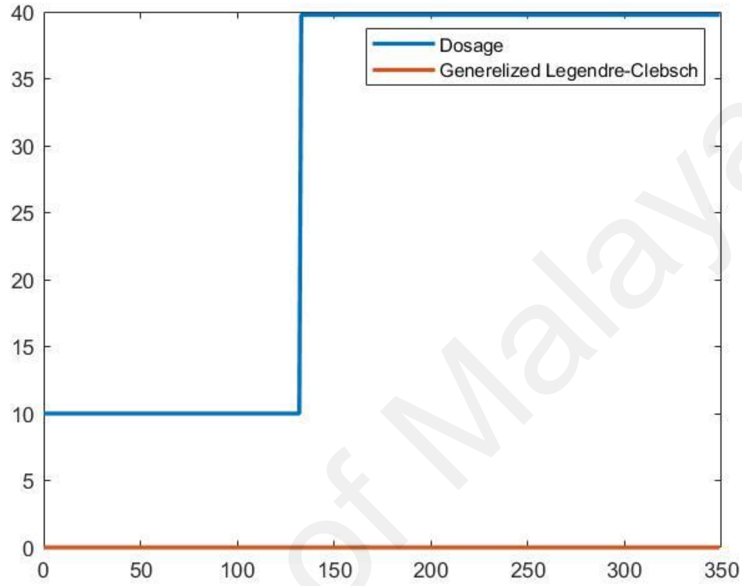

Figure 4.17(4th iteration)

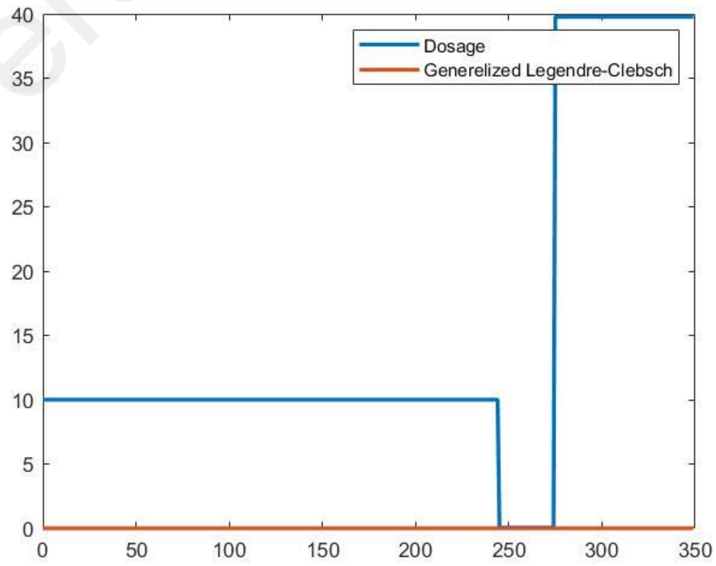

Figure 4.18(20th iteration)

CHAPTER 5: CONCLUSION AND FUTURE WORK

5.1 Conclusion

In this research paper a mathematical model of administrating chemotherapy is studied and OCT is used to obtain the optimal input (the chemotherapy). As discussed earlier it can be seen that this control contains singular control in addition to bang-bang control. The singular control includes both finite and infinite order singular arc. Favier et al in [5] is using $\frac{60\frac{mg}{m^2}}{day}$ or $\frac{85\frac{mg}{m^2}}{day}$ for the chemotherapy. In this work the maximum dosage is set to $\frac{10\frac{mg}{m^2}}{day}$ and $\frac{50\frac{mg}{m^2}}{day}$. and the results indicate that both these dosages can minimize the cancer cells. As mentioned before the cancer is considered cured when y_5 is less than 1. The cancer cells drop below 1 with both maximum dosages.

In the process of iterating the whole algorithm it can be seen that odd iterations follow the same pattern and even iterations follow a different pattern. When the maximum dosage is as low as $\frac{10\frac{mg}{m^2}}{day}$ either one of the algorithms fail to minimize the cancer cells and choosing between even and odd iterations becomes quite easy. But for $\frac{50\frac{mg}{m^2}}{day}$ both odd and even iterations are minimizing the cancer cells to less than 1. But it can be seen that one set of the iterations is using much more chemotherapy than the other. So when both set of iterations are curing the cancer and the results on the cancer cells are almost the same then it only makes sense to choose the one which administrate less chemotherapy.

Another important observation is the range in which we consider singular arc is happening. The algorithm is very sensitive to this range. Is order to get better and more optimal results (less chemotherapy and cure cancer) this range has to be chosen carefully. The range in this work was chosen based on trial and error.

This range becomes important because the switching function is mostly close to zero which means that the control is mostly singular control. And a threshold of error has to be considered for the switching function because this function is calculated after 14 ODEs are solved in MATLAB. Some of which are stiff ODEs. This is the reason why an error threshold has to be considered for the switching function. if this range is very small then the control becomes bang-bang instead of singular control and as it was discussed earlier when the control becomes bang-bang instead of singular more chemotherapy is used but the results are the same. So it is important to choose a range which allows the singular arc to take care of the control when the switching function is close enough to zero.

This work also includes infinite order singular arc. It was discussed that infinite order singular arc in this system means that the cancer cells become totally independent of the chemotherapy. A simple solution was offered to avoid this situation. Again it can be seen that this amount plus the finite order singular amounts plus bang-bang control minimize the cancer cells.

5.2 Recommendation for future work:

1- as discussed in chapter 3 there has been a lot of work on necessary and sufficient conditions for optimality. This work studies generalized Legendre-Clebsch condition. Also a Hessian matrix can be developed to check the optimality at each point.

2- this work choose two maximum dosage values based on the values in [5]. This value can be chosen more diligently. Using intelligent algorithms this value can be set differently.

3- the objective in this work is set to be minimizing the cancer cells only. It is a single objective OCT algorithm. It can be changed to a multi objective algorithm with the second objective being minimizing the dosage as well as the cancer cells.

4- when facing infinite order singular arc the solution adapted in this work is to avoid the situation. Again using intelligent algorithm, a different and maybe more accurate value for infinite order singular arc can be calculated.

APPENDICES

```
Main.m
clc;

V=14;
Ka=57.6/24;
Ke=9.36/24;
a1=.7;
b1=.31;
c111=3.7;
a2=.27;
b2=.31;
c222=.3;
res=.07;
u1= .15;
K=1000;
R=1;
u2=.6;
lamda=.01;


lll1=zeros(350,20);
u_coeff1=zeros(350,20);
u_coeff2=zeros(350,20);
%%   ODES
total_day=350;
z=20;
 %the inside loop determines how many times the ode i
gonna run
tspan1=[0 :1:total_day-1];
tspan2=[total_day-1:-1: 0];
options=odeset('RelTol',1e-7,'AbsTol',1e-7);
INITIAL_VALUE_Y= [0 0 0 0 30 1 0];
INITIAL_LAMDA=[0 0 0 0 0 0 0];
 options1='';
options2 = odeset('RelTol',1e-8,'RelTol',1e-10);
max=50;
singular_value=40;
Dosage=zeros(total_day,z+1);
Dosage(1,:)=max;
  for i=1:z


[T_Y1,Y1(:,i)]=ode45(@(t1,y1)dy1(Dosage(:,i),y1,t1,(0:
total_day-
1)),tspan1,INITIAL_VALUE_Y(1),options1);%u,Y1,t_y,t_u)
```

```
[T_Y2,Y2(:,i)]=ode45(@(t2,y2)dy2(Y1(:,i),y2,T_Y1,t2),t
span1,INITIAL_VALUE_Y(2),options1);%y1,y2,t1,t2)

[T_Y3,Y3(:,i)]=ode15s(@(t3,y3)dy3(Y2(:,i),y3,T_Y2,t3),
tspan1,INITIAL_VALUE_Y(3),options1);%y2,y3,t2,t3)

[T_Y4,Y4(:,i)]=ode15s(@(t4,y4)dy4(Y2(:,i),y4,T_Y2,t4),
tspan1,INITIAL_VALUE_Y(4),options1);%(y2,y4,t2,t4)

[T_Y7,Y7(:,i)]=ode15s(@(t7,y7)dy7(Y2(:,i),T_Y2,t7),tsp
an1,INITIAL_VALUE_Y(7),options1);%y2,t2,t7)

[T_Y6,Y6(:,i)]=ode15s(@(t6,y6)dy6(Y4(:,i),y6,T_Y4,t6),
tspan1,INITIAL_VALUE_Y(6),options1);%y4,y6,t4,t6)

[T_Y5,Y5(:,i)]=ode15s(@(t5,y5)dy5(Y3(:,i),y5,Y6(:,i),Y
7(:,i),T_Y3,t5,T_Y6,T_Y7),tspan1,INITIAL_VALUE_Y(5),op
tions2);%y3,y5,y6,y7,t3,t5,t6,t7)

[T_L5,L5(:,i)]=ode15s(@(tl5,l5)dl5(l5,Y3(:,i),Y5(:,i),
Y6(:,i),Y7(:,i),tl5,T_Y3,T_Y5,T_Y6,T_Y7),tspan2,0,opti
ons);%l5,y3,y5,y6,y7,tl5,ty3,ty5,ty6,ty7)

[T_L6,L6(:,i)]=ode15s(@(tl6,l6)dl6(L5(:,i),l6,Y4(:,i),
Y5(:,i),T_L5,tl6,T_Y4,T_Y5),tspan2,0,options);%l5,l6,y
4,y5,tl5,tl6,ty4,ty5)

[T_L4,L4(:,i)]=ode15s(@(tl4,l4)dl4(l4,L6(:,i),Y4(:,i),
Y6(:,i),tl4,T_L6,T_Y4,T_Y6),tspan2,0,options);
%l4,l6,y4,y6,tl4,tl6,ty4,ty6)

[T_L3,L3(:,i)]=ode15s(@(tl3,l3)dl3(l3,L5(:,i),Y3(:,i),
Y5(:,i),Y7(:,i),tl3,T_L5,T_Y3,T_Y5,T_Y7),tspan2,0,opti
ons);%l3,l5,y3,y5,y7,tl3,tl5,ty3,ty5,ty7)

[T_L7,L7(:,i)]=ode15s(@(tl7,l7)dl7(L5(:,i),Y3(:,i),Y5(
:,i),Y7(:,i),tl7,T_L5,T_Y3,T_Y5,T_Y7),tspan2,0,options
);%l5,y3,y5,y7,tl7,tl5,ty3,ty5,ty7)

[T_L2,L2(:,i)]=ode15s(@(tl2,l2)dl2(l2,L3(:,i),L4(:,i),
L7(:,i),Y2(:,i),tl2,T_L3,T_L4,T_L7,T_Y2),tspan2,0,opti
ons);%l2,l3,l4,l7,y2,tl2,tl3,tl4,tl7,ty2)

[T_L1,L1(:,i)]=ode15s(@(tl1,l1)dl1(l1,L2(:,i),tl1,T_L2
),tspan2,0,options);
      L22=fliplr(L2(:,i)')';
      L33=fliplr(L3(:,i)')';
      L44=fliplr(L4(:,i)')';
```

```
        L55=fliplr(L5(:,i)')';
        L66=fliplr(L6(:,i)')';
        L77=fliplr(L7(:,i)')';
        %%
          ttl=ceil(length(T_Y1)/total_day);
          tt = decimate(T_Y1,ttl);
          while length(tt)<total_day
              tt=[tt; T_Y1(end)];
          end
          T_Y1=tt;
          yy=[];
          while length(yy1)<total_day
              yy1=[yy1; Y1(end,i)];
          end
          ttl=ceil(length(T_Y2)/total_day);
          tt = decimate(T_Y2,ttl);
          while length(tt)<total_day
              tt=[tt; T_Y2(end)];
          end
          T_Y2=tt;
          yy2 =
decimate(Y2(:,i),ceil(length(Y2)/total_day));
          while length(yy2)<total_day
              yy2=[yy2; Y2(end,i)];
          end
          ttl=ceil(length(T_Y3)/total_day);
          tt = decimate(T_Y3,ttl);
          while length(tt)<total_day
              tt=[tt; T_Y3(end)];
          end
          T_Y3=tt;
          yy3 =
decimate(Y3(:,i),ceil(length(Y3)/total_day));
          while length(yy3)<total_day
              yy3=[yy3; Y3(end,i)];
          end
           ttl=ceil(length(T_Y4)/total_day);
           tt = decimate(T_Y4,ttl);
           while length(tt)<total_day
              tt=[tt; T_Y4(end)];
           end
           T_Y4=tt;
           yy4 =
decimate(Y4(:,i),ceil(length(Y4)/total_day));
           while length(yy4)<total_day
               yy4=[yy4; Y4(end,i)];
           end

           ttl=ceil(length(T_Y5)/total_day);
```

```
        tt = decimate(T_Y5,ttl);
        while length(tt)<total_day
            tt=[tt; T_Y5(end)];
        end
        T_Y5=tt;
        yy5 =
decimate(Y5(:,i),ceil(length(Y5)/total_day));
        while length(yy5)<total_day
            yy5=[yy5; Y5(end,i)];
        end


        ttl=ceil(length(T_Y6)/total_day);
        tt = decimate(T_Y6,ttl);
        while length(tt)<total_day
            tt=[tt; T_Y6(end)];
        end
        T_Y6=tt;
        yy6 =
decimate(Y6(:,i),ceil(length(Y6)/total_day));
        while length(yy6)<total_day
            yy6=[yy6; Y6(end,i)];
        end


        while length(tt)<total_day
            tt=[tt; T_Y7(end)];
        end
        T_Y7=tt;
        yy7 =
decimate(Y7(:,i),ceil(length(Y7)/total_day));
        while length(yy7)<total_day
            yy7=[yy7; Y7(end,i)];
        end


       while length(tt)<total_day
           tt=[tt; T_L1(end)];
       end
       T_L1=tt;
       ll=[];

       while length(ll1)<total_day
           ll1=[ll1; L1(end)];
       end
       lll1(:,i)=ll1;



       while length(tt)<total_day
```

```
            tt=[tt; T_L2(end)];
        end
        T_L2=tt;
        ll2 =
decimate(L22,ceil(length(L22)/total_day));
        while length(ll2)<total_day
            ll2=[ll2; L2(end)];
        end


        ttl=ceil(length(T_L3)/total_day);
        tt = decimate(T_L3,ttl);
        while length(tt)<total_day
            tt=[tt; T_L3(end)];
        end
        T_L3=tt;
        ll3 =
decimate(L33,ceil(length(L33)/total_day));
        while length(ll3)<total_day
            ll3=[ll3; L3(end)];
        end


         ttl=ceil(length(T_L4)/total_day);
        tt = decimate(T_L4,ttl);
        while length(tt)<total_day
            tt=[tt; T_L4(end)];
        end
        T_L4=tt;
        ll4 =
decimate(L44,ceil(length(L44)/total_day));
        while length(ll4)<total_day
            ll4=[ll4; L4(end)];
        end

         ttl=ceil(length(T_L5)/total_day);
        tt = decimate(T_L5,ttl);
        while length(tt)<total_day
            tt=[tt; T_L5(end)];
        end
        T_L5=tt;
        ll5 =
decimate(L55,ceil(length(L55)/total_day));
        while length(ll5)<total_day
            ll5=[ll5; L5(end)];
        end


         ttl=ceil(length(T_L6)/total_day);
        tt = decimate(T_L6,ttl);
```

```
        while length(tt)<total_day
            tt=[tt; T_L6(end)];
        end
        T_L6=tt;
        ll6 =
decimate(L66,ceil(length(L66)/total_day));
        while length(ll6)<total_day
            ll6=[ll6; L6(end)];
        end

        ttl=ceil(length(T_L7)/total_day);
        tt = decimate(T_L7,ttl);
        while length(tt)<total_day
            tt=[tt; T_L7(end)];
        end
        T_L7=tt;
        ll7 =
decimate(L77,ceil(length(L77)/total_day));
        while length(ll7)<total_day
            ll7=[ll7; L7(end)];
        end

      %%
      oo=abs(ll1)<5.05e-4;
      ooo=yy2<.3;
      o1(:,i)=  bitand(oo,ooo);
      ooo1=(yy2>.3)&(yy2<3.7);
      o2(:,i)=  bitand(oo,ooo1);
      ooo2=(yy2>3.7);
      o3(:,i)=  bitand(oo,ooo2);
      for m=1:length(ll1)

         if (ll1(m))<-(5.05e-4)

             Dosage(m,i+1)=max;

         elseif (ll1(m))>5.05e-4

             Dosage(m,i+1)=0;

         elseif ((abs(ll1(m))<5.05e-4)&&(yy2(m)>3.7))


[u_coeff1(m,i),Dosage(m,i+1)]=singular_arc1_1(ll1(m),l
l2(m),ll3(m),ll4(m),ll5(m),ll6(m),ll7(m),yy1(m),yy2(m)
,yy3(m),yy4(m),yy5(m),yy6(m),yy7(m),Dosage(m));

         elseif ((abs(ll1(m))<5.05e-
4)&&(yy2(m)<3.7)&&(yy2(m)>.3))
```

```
[u_coeff2(m,i),Dosage(m,i+1)]=singular_arc2_1(ll1(m),l
l2(m),ll3(m),ll4(m),ll5(m),ll6(m),ll7(m),yy1(m),yy2(m)
,yy3(m),yy4(m),yy5(m),yy6(m),yy7(m),Dosage(m,i));
         elseif(yy2(m)<.3)&&(abs(ll1(m))<5.05e-4)
             if(m>1)
                 Dosage(m,i+1)=39.77327;
             end
        end



      end
  end
 end of main.m


singular_arc_case1.m
function
[u_coEff,out]=singular_arc1_1(~,l2,l3,l4,l5,l6,l7,y1,y
2,y3,y4,y5,y6,y7,u)

global V
global lamda
global  Ke
global a1
global  b1
global  c111
global  a2
global  Ka
global  b2
global  c222
global  res
global  u1
global K
global R
global u2
V=14;
Ka=57.6/24;
Ke=9.36/24;
a1=.7;
b1=.31;
c111=3.7;
a2=.27;
b2=.31;
c222=.3;
res=.07;
u1= .15;
K=1000;
```

```
R=1;
u2=.6;
lamda=.01;
%%
max=50;
m=a1*l3;
n=1-b1*y3;
o=exp(-b1*y3);
r=exp(-res*y7);
p=l5;
q=u1*y5;

%%
s=l6*u2;
w=y6;
x=l4*a2;
yy=1-b2*y4;
z=exp(-b2*y4);
%%
e1=y5;
f=y3;
g=l5;
h=u1*res*r;
%%
dy1=-Ka*y1+u;
dy2=-Ke*y2+(Ka*y1)/V;
ddy2=-Ke*dy2+(Ka*dy1)/V;
%%
x2=-Ke*dy2-(((Ka)^2)/V)*y1;
%%
dy3=-a1*y3*o+y2-c111;
ddy3=-a1*dy3*o+dy2+(a1*b1*y3*dy3)*o;
dddy3=-a1*ddy3*o+a1*b1*((dy3)^2)*o+ddy2+...
(a1*b1*(dy3)^2)*o+a1*b1*y3*ddy3*o-
a1*b1*b1*y3*((dy3)^2)*o;
%%
x1=-a1*ddy3*o+a1*b1*((dy3)^2)*o+...
(a1*b1*(dy3)^2)*o+a1*b1*y3*ddy3*o-
a1*b1*b1*y3*((dy3)^2)*o;
%%
dy4=-a2*y4*z+y2-c222;
ddy4=-a2*dy4*z+dy2+a2*b2*dy4*y4*z;
dddy4=-
a2*ddy4*z+a2*b2*(dy4^2)*z+a2*b2*ddy4*y4*z+a2*b2*(dy4^2
)*z-a2*b2*b2*(dy4^2)*y4*z+ddy2;
%%
x5=-
a2*ddy4*z+a2*b2*(dy4^2)*z+a2*b2*ddy4*y4*z+a2*b2*(dy4^2
)*z-a2*b2*b2*(dy4^2)*y4*z;
```

```
%%
dy6=R-R*y6-u2*y4*y6;
ddy6=-R*dy6-u2*dy4*y6-u2*y4*dy6;
dddy6=-R*ddy6-u2*ddy4*y6-u2*dy4*dy6-u2*dy4*dy6-
u2*y4*ddy6;
%%
dy7=y2-c111;
ddy7=dy2;
dddy7=ddy2;
%%
dy5=lamda*y6*y5*log(K/y5)-u1*y3*y5*r;
ddy5=lamda*dy6*y5*log(K/y5)+lamda*y6*dy5*log(K/y5)-
lamda*y6*dy5-u1*dy3*y5*r...
    -u1*y3*dy5*r+u1*y3*y5*dy7*res*r;
dddy5=lamda*ddy6*y5*log(K/y5)+lamda*dy6*dy5*log(K/y5)-
lamda*dy6*dy5+lamda*dy5*dy6*log(K/y5)...
    +lamda*y6*ddy5*log(K/y5)-lamda*y6*dy5*dy5/y5-
lamda*dy6*dy5-lamda*y6*ddy5...
    -u1*ddy3*y5*exp(-res*y7)-u1*dy3*dy5*exp(-
res*y7)+res*u1*dy3*y5*dy7*exp(-res*y7)...
    -u1*dy3*dy5*exp(-res*y7)-u1*y3*ddy5*exp(-
res*y7)+res*u1*y3*dy5*dy7*exp(-res*y7)...
    +u1*dy3*y5*dy7*res*exp(-
res*y7)+res*u1*y3*dy5*dy7*exp(-
res*y7)+res*u1*y3*y5*ddy7*exp(-res*y7)...
    -u1*res*res*y3*y5*dy7*dy7*exp(-res*y7);
%%
dn=-dy3;
ddn=-ddy3;
dddn=-dddy3;
%%
do=-b1*dy3*o;
ddo=-b1*ddy3*o+b1*b1*((dy3)^2)*o;
dddo=-
b1*dddy3*o+b1*b1*ddy3*dy3*o+2*b1*b1*dy3*ddy3*o...
-b1*b1*b1*((dy3)^3)*exp(-b1*y3);
x3=b1*b1*ddy3*dy3*o+2*b1*b1*dy3*ddy3*o...
-b1*b1*b1*((dy3)^3)*exp(-b1*y3);
%%
dr=-res*dy7*r;
ddr=res^2*(dy7^2)*r-res*ddy7*r;
dddr=2*(res^2)*dy7*ddy7*r-res^3*(dy7^3)*r-
res*dddy7*r+res^2*ddy7*dy7*r;
x4=2*(res^2)*dy7*ddy7*r-
res^3*(dy7^3)*r+res^2*ddy7*dy7*r;
%%
dl5=-1 + lamda*l5*y6 + l5*u1*y3*r -
l5*lamda*y6*log(K/y5);
```

```
ddl5=lamda*dl5*y6 + lamda*l5*dy6 + dl5*u1*y3*r +
l5*u1*dy3*r...
    + l5*u1*y3*dr - dl5*lamda*y6*log(K/y5) -
l5*lamda*dy6*log(K/y5)...
    + l5*lamda*y6*dy5/y5;
dddl5=lamda*ddl5*y6 + 2*lamda*dy6*dl5 +
lamda*l5*ddy6...
    + ddl5*u1*y3*r + dl5*
 l5*u1*ddy3*r + l5*u1*dy3*dr...
    + dl5*u1*y3*dr + l5*u1*dy3*dr + l5*u1*y3*ddr...
    - ddl5*lamda*y6*log(K/y5) -
dl5*lamda*dy6*log(K/y5) + dl5*lamda*y6*dy5/y5...
    - dl5*lamda*dy6*log(K/y5) -
l5*lamda*ddy6*log(K/y5) + l5*lamda*dy6*dy5/y5...
    + dl5*lamda*y6*dy5/y5 + l5*lamda*dy6*dy5/y5 +
l5*lamda* - l5*lamda*y6*dy5 *y5);
%%
dp=dl5;
ddp=ddl5;
dddp=dddl5;
%%
dq=u1*dy5;
ddq=u1*ddy5;
dddq=u1*dddy5;
%%
dl6= - l5*lamda*y5*log(K/y5)+l6*(R+u2*y4);
ddl6= dl6*R + dl6*u2*y4 + l6*u2*dy4 -
lamda*dl5*y5*log(K/y5) - lamda*l5*dy5*log(K/y5)...
    +lamda*l5*dy5;
dddl6= ddl6*R + ddl6*u2*dy4 + 2*dl6*u2*dy4 +
l6*u2*ddy4 -lamda*ddl5*y5*log(K/y5)...
    - lamda*dl5*dy5*log(K/y5) + 2*lamda*dl5*dy5-
lamda*dl5*dy5*log(K/y5)...
    -
lamda*l5*ddy5*log(K/y5)+lamda*l5*dy5*dy5/y5+lamda*l5*d
dy5;
%%
ds=u2*dl6;
dds=u2*ddl6;
ddds=u2*dddl6;
%%
dw=dy6;
ddw=ddy6;
dddw=dddy6;
%%

%%
dyy=-b2*dy4;
ddyy=-b2*ddy4;
```

```
dddyy=-b2*dddy4;
%%
dz=-b2*dy4*z;
ddz=-b2*ddy4*z+b2*b2*((dy4)^2)*z;
dddz=-
b2*dddy4*z+b1*b1*ddy4*dy4*z+2*b2*b2*dy4*ddy4*z...
-b2*b2*b2*((dy4)^3)*exp(-b2*y4);
x6=b1*b1*ddy4*dy4*z+2*b2*b2*dy4*ddy4*z...
-b2*b2*b2*((dy4)^3)*exp(-b2*y4);
%%
de1=dy5;
dde1=ddy5;
ddde1=dddy5;
%%
df=dy3;
ddf=ddy3;
dddf=dddy3;
%%
dg=dl5;
ddg=ddl5;
dddg=dddl5;
%%
dh=u1*res*dr;
ddh=u1*res*ddr;
dddh=u1*res*dddr;
%%
%-------------------------------------------------------
-----------------------------%
%%
dl3=m*n*o+p*q*r ;
dm=a1*dl3;
%%
ddl3=dm*n*o+m*dn*o+m*n*do+dp*q*r+p*dq*r+p*q*dr;
ddm=a1*ddl3;
%%
dddl3=ddm*n*o+dm*dn*o+dm*n*do...
    +dm*dn*o+m*ddn*o+m*dn*do...
    +dm*n*do+m*dn*do+m*n*ddo...
    +ddp*q*r+dp*dq*r+dp*q*dr...
    +dp*dq*r+p*ddq*r+p*dq*dr...
    +dp*q*dr+p*dq*dr+p*q*ddr;

dddm=a1*dddl3;
%%
ddddl3=dddm*n*o+ddm*dn*o+ddm*n*do...
    +ddm*dn*o+dm*ddn*o+dm*dn*do...
    +ddm*n*do+dm*dn*do+dm*n*ddo...
    +ddm*dn*o+dm*ddn*o+dm*dn*do...
    +dm*ddn*o+m*dddn*o+m*ddn*do...
```

```
     +dm*dn*do+m*ddn*do+m*dn*ddo...
     +ddm*n*do+dm*dn*do+dm*n*ddo...
     +dm*dn*do+m*ddn*do+m*dn*ddo...
     +dm*n*ddo+m*dn*ddo+m*n*dddo...
     +dddp*q*r+ddp*dq*r+ddp*q*dr...
     +ddp*dq*r+dp*ddq*r+dp*dq*dr...
     +ddp*q*dr+dp*dq*dr+dp*q*ddr...
     +ddp*dq*r+ dq*dr...
     +dp*ddq*r+p*dddq*r+p*ddq*dr...
     +dp*dq*dr+p*ddq*dr+p*dq*ddr...
     +ddp*q*dr+dp*dq*dr+dp*q*ddr...
     +dp*dq*dr+p*ddq*dr+p*dq*ddr...
     +dp*q*ddr+p*dq*ddr+p*q*dddr;

ddddl3_1=dddm*n*o+ddm*dn*o+ddm*n*do...
     +ddm*dn*o+dm* dm*dn*do...
     +ddm*n*do+dm*dn*do+dm*n*ddo...
     +ddm*dn*o+dm*ddn*o+dm*dn*do...
     +dm*ddn*o+m*ddn*do...
     +dm*dn*do+m*ddn*do+m*dn*ddo...
     +ddm*n*do+dm*dn*do+dm*n*ddo...
     +dm*dn*do+m*ddn*do+m*dn*ddo...
     +dm*n*ddo+m*dn*ddo...
     +dddp*q*r+ddp*dq*r+ddp*q*dr...
     +ddp*dq*r+dp*ddq*r+dp*dq*dr...
     +ddp*q*dr+dp*dq*dr+dp*q*ddr...
     +ddp*dq*r+dp*ddq*r+dp*dq*dr...
     +dp*ddq*r+p*dddq*r+p*ddq*dr...
     +dp*dq*dr+p*ddq*dr+p*dq*ddr...
     +ddp*q*dr+dp*dq*dr+dp*q*ddr...
     +dp*dq*dr+p*ddq*dr+p*dq*ddr...
     +dp*q*ddr+p*dq*ddr...
     +m*o*(-b1)*(x1+x2) ...%m.dddn.o
     +m*n*x3 + m*n*(x1+x2)*(-b1)*exp(-
b1*y3)...%m.n.dddo
     +p*q*x4 + p*q*x2*(-res*exp(-res*y7));%p.q.dddr
%%-------------------------------------------%
%%
p1=s;
dp1=ds;
ddp1=dds;
dddp1=ddds;
q1=w;
dq1=dw;
ddq1=ddw;
dddq1=dddw;
m1=x;
n1=yy;
dn1=dyy;
```

```
ddn1=ddyy;
dddn1=dddyy;
o1=z;
do1=dz;
ddo1=ddz;
dddo1=dddz;
a=e1;
da=de1;
dda=dde1;
ddda=ddde1;
b=f;
db=df;
ddb=ddf;
dddb=dddf;
c=g;
dc=dg;
ddc=ddg;
dddc=dddg;
e=h;
de=dh;
dde=ddh;
ddde=dddh;
%%
Dl4=m1*n1*o1+p1*q1;
dm1=a2*Dl4;
ddl4=dm1*n1*o1+m1*dn1*o1+m1*n1*do1+dp1*q1+p1*dq1;
ddm1=ddl4*a2;
dddl4=ddm1*n1*o1+dm1*dn1*o1+dm1*n1*do1...
    +dm1*dn1*o1+m1*ddn1*o1+m1*dn1*do1...
    +dm1*n1*do1+m1*dn1*do1+m1*n1*ddo1...
    +ddp1*q1+dp1*dq1...
    +dp1*dq1+p1*ddq1;
dddm1=dddl4*a2;
ddddl4=dddm1*n1*o1+ddm1*dn1*o1+ddm1*n1*do1...
    +ddm1*dn1*o1+dm1*ddn1*o1+dm1*dn1*do1...
    +ddm1*n1*do1+dm1*dn1*do1+dm1*n1*ddo1...
    +ddm1*dn1*o1+dm1*ddn1*o1+dm1*dn1*do1...
    +dm1*ddn1*o1+ do1...% m1*dddn1*o1
    +dm1*dn1*do1+m1*ddn1*do1+m1*dn1*ddo1...
    +ddm1*n1*do1+dm1*dn1*do1+dm1*n1*ddo1...
    +dm1*dn1*do1+m1*ddn1*do1+m1*dn1*ddo1...
    +dm1*n1*ddo1+m1*dn1*ddo1...%m1*n1*dddo1
    +dddp1*q1+ddp1*dq1...
    +2*ddp1*dq1+2*dp1*ddq1...
    +dp1 *dddq1...
    + m1*o1*(-b2)*(x5+x2)...% m1*dddn1*o1
    + m1*n1*x6 + m1*n1*(-b2*exp(-
b2*y4)*(x5+x2));%m1*n1*dddo1
dx=a2*Dl4;
```

```
ddx=a2*ddl4;
dddx=a2*dddl4;
%%
dl7=a*b*c*e;
ddl7=da*b*c*e+a*db*c*e+a*b*dc*e+a*b*c*de;
dddl7=
da*db*c*e+2*da*b*dc*e+2*da*b*c*de+a*ddb*c*e+2*a*db*dc*
e+...
    2*a*db*c*de+a*b*ddc*e+2*a*b*dc*de+a*b*c*dde;
ddddl7=ddda*b*c*e+dda*db*c*e+dda*b*dc*e+dda*b*c*de...
    +2*(dda*db*c*e+da *dc*e+da*db*c*de)...

+2*(dda*b*dc*e+da*db*dc*e+da*b*ddc*e+da*b*dc*de)...

+2*(dda*b*c*de+da*db*c*de+da*b*dc*de+da*b*c*dde)...
    +da*ddb*c*e+a*dddb*c*e+a*ddb*dc*e+a*ddb*c*de...
    +2*(da*db*dc*e+a*ddb*dcdb*ddc*e+a*db*dc*de)...

+2*(da*db*c*de+a*ddb*c*de+a*db*dc*de+a*db*c*dde)...
    +da*b*ddc*e+a*db*ddc*e+a*b*dddc*e+a*b*ddc*de...

+2*(da*b*dc*de+a*db*dc*de+a*b*ddc*de+a*b*dc*dde)...
    +da*b*c*dde+a*db*c*dde+a*b*dc*dde+a*b*c*ddde;
ddddl7_1=ddda*b*c*e+dda*db*c*e+dda*b*dc*e+dda*b*c*de..
.

+2*(dda*db*c*e+da*ddb*c*e+da*db*dc*e+da*db*c*de)...

+2*(dda*b*dc*e+da*db*dc*e+da*b*ddc*e+da*b*dc*de)...

+2*(dda*b*c*de+da*db*c*de+da*b*dc*de+da*b*c*dde)...
    +da*ddb*c*e + a*ddb*dc*e +
a*ddb*c*de...%a*dddb*c*e

+2*(da*db*dc*e+a*ddb*dc*e+a*db*ddc*e+a*db*dc*de)...

+2*(da*db*c*de+a*ddb*c*de+a*db*dc*de+a*db*c*dde)...
    +da*b*ddc*e + a*db*ddc*e + a*b*dddc*e +
a*b*ddc*de...
    +2*(da*b*dc*de+a*db*dc *b*ddc*de+a*b*dc*dde)...
    +da*b*c*dde + a*db*c*dde + a*b*dc*dde ...%+
a*b*c*ddde
    +a*c*e*(x1+x2)...
    +a*b*c*u1*res*(x4+x2*(exp(-res*y7)));

%%
Z=l3+l4-l7;
dZ=dl3+Dl4-dl7;
ddZ=ddl3+ddl4-ddl7;
```

```
dddZ=dddl3+dddl4-dddl7;
ddddZ_1=-ddddl7_1 + ddddl4 + ddddl3_1;
%%
u_coEff=(m*o*(-b1)*Ka/V) + m*n*(-b1)*(Ka/V)*exp(-
b1*y3) + p*q*(Ka/V)*(-res*exp(-res*y7))...
    + m1*o1*(-b2)*(Ka/V) + m1*n1* (Ka/V)*(-b2)*(exp(-
b2*y4)) - a*c*e* (Ka/V) - a*b*c*(Ka/V)*(-res*exp(-
res*y7));
%%
dl2=Ke*l2-Z;
ddl2=(Ke^2)*l2-Ke*Z-dZ;
dddl2=(Ke^3)*l2-(Ke^2)*Z-Ke*dZ-ddZ;
ddddl2=(Ke^4)*l2-(Ke^3)*Z-(Ke^2)*dZ-(Ke^1)*ddZ-dddZ;
dddddl2=(Ke^5)*l2-(Ke^4)*Z-(Ke^3)*dZ-(Ke^2)*ddZ-
(Ke^1)*dddZ-ddddZ_1;
%%
rest=((Ka^6)/V)*l2 + ((Ka^5)/V)*dl2 +
((Ka^4)/V)*ddl2...
     + ((Ka^3)/V)*dddl2 + ((Ka^2)/V)*ddddl2 +
((Ka)/V)*dddddl2;
%%

if (SA<0)
    SA=0.056897;
elseif (SA>max)
    SA=max;
end
out=SA;
u_coEff=(mV)*exp(-b1*y3) + p*q*(Ka/V)*(-res*exp(-
res*y7))...
    + m1*o1*(Ka/V) + m1*n1* (Ka/V)*(-b2)*(exp(-b2*y4))
- a*c*e* (Ka/V) - a*b*c*(Ka/V)*(-res*exp(-res*y7));


End of singular_arc_case1.m
```

Singular_arc_case2.m

```
function
[u_coEff,out]=singular_arc2_1(lll1,lll2,lll3,lll4,lll5
,lll6,lll7,yy1,yy2,yy3,yy4,yy5,yy6,yy7,u)


V=14;
Ka=57.6/24;
Ke=9.36/24;
a1=.7;
b1=.31;
c111=3.7;
a2=.27;
b2=.31;
c222=.3;
res=.07;
u1= .15;
K=1000;
R=1;
u2=.6;
lllamDa=.01;
%%
max=50;
s=lll6*u2;
w=yy6;
x=lll4*a2;
yyyyyy=1-b2*yy4;
z=exp(-b2*yy4);
%%
Dyy1=-Ka*yy1+u;
Dyy2=-Ke*yy2+(Ka*yy1)/V;
DDyy2=-Ke*Dyy2+(Ka*Dyy1)/V;
%%
x2=-Ke*Dyy2-(((Ka)^2)/V)*yy1;
%%

%%
Dyy4=-a2*yy4*z+yy2-c222;
DDyy4=-a2*Dyy4*z+Dyy2+a2*b2*Dyy4*yy4*z;
DDDyy4=-
a2*DDyy4*z+a2*b2*(Dyy4^2)*z+a2*b2*DDyy4*yy4*z+a2*b2*(D
yy4^2)*z-a2*b2*b2*(Dyy4^2)*yy4*z+DDyy2;
%%
x5=-
a2*DDyy4*z+a2*b2*(Dyy4^2)*z+a2*b2*DDyy4*yy4*z+a2*b2*(D
yy4^2)*z-a2*b2*b2*(Dyy4^2)*yy4*z;
%%
Dyy6=R-R*yy6-u2*yy4*yy6;
DDyy6=-R*Dyy6-u2*Dyy4*yy6-u2*yy4*Dyy6;
```

```
DDDyy6=-R*DDyy6-u2*DDyy4*yy6-u2*Dyy4*Dyy6-
u2*Dyy4*Dyy6-u2*yy4*DDyy6;
%%
Dyy7=yy2-c111;
DDyy7=Dyy2;
DDDyy7=DDyy2;
%%
r=exp(-res*yy7);
Dr=-res*Dyy7*r;
DDr=res^2*(Dyy7^2)*r-res*DDyy7*r;
DDDr=2*(res^2)*Dyy7*DDyy7*r-res^3*(Dyy7^3)*r-
res*DDDyy7*r+res^2*DDyy7*Dyy7*r;
%%
o=exp(-b1*yy3);


%%
Dyy3=-a1*yy3*o+yy2-c111;
DDyy3=-a1*Dyy3*o+Dyy2+(a1*b1*yy3*Dyy3)*o;
DDDyy3=-a1*DDyy3)^2)*o+DDyy2+...
(a1*b1*(Dyy3)^2)*o+a1*b1*yy3*DDyy3*o-
a1*b1*b1*yy3*((Dyy3)^2)*o;

%%
Do=-b1*Dyy3*o;
DDo=-b1*DDyy3*o+)*o;
DDDo=-
b1*DDDyy3*o+b1*b1*DDyy3*Dyy3*o+2*b1*b1*Dyy3*DDyy3*o...
-b1*b1*b1*(( b1*yy3);
x3=b1*b1*DDyy3*Dyy3*o+2*b1*b1*Dyy3*DDyy3*o...
-b1*b1*b1*((Dyy3)^3)*exp(-b1*yy3);
%%
Dyy5=lllamDa*yy6*yy5*log(K/yy5)-u1*yy3*yy5*r;
DDyy5=lllamDa*Dyy6*yy5*log(K/yy5)+lllamDa*yy6*Dyy5*log
(K/yy5)-lllamDa*yy6*Dyy5-u1*Dyy3*yy5*r...
    -u1*yy3*Dyy5*r+u1*yy3*yy5*Dyy7*res*r;
DDDyy5=lllamDa*DDyy6*yy5*log(K/yy5)+lllamDa*Dyy6*Dyy5*
log(K/yy5)-
lllamDa*Dyy6*Dyy5+lllamDa*Dyy5*Dyy6*log(K/yy5)...
    +lllamDa*yy6*DDyy5*log(K/yy5)-
lllamDa*yy6*Dyy5*Dyy5/yy5-lllamDa*Dyy6*Dyy5-
lllamDa*yy6*DDyy5...
    -u1*DDyy3*yy5*exp(-res*yy7)-u1*Dyy3*Dyy5*exp(-
res*yy7)+res*u1*Dyy3*yy5*Dyy7*exp(-res*yy7)...
    -u1*Dyy3*Dyy5*exp(-res*yy7)-u1*yy3*DDyy5*exp(-
res*yy7)+res*u1*yy3*Dyy5*Dyy7*exp(-res*yy7)...
    +u1*Dyy3*yy5*Dyy7*res*exp(-
res*yy7)+res*u1*yy3*Dyy5*Dyy7*exp(-
res*yy7)+res*u1*yy3*yy5*DDyy7*exp(-res*yy7)...
```

```
    -u1*res*res*yy3*yy5*Dyy7*Dyy7*exp(-res*yy7);
%%
Dlll5=-1 + lllamDa*lll5*yy6 + lll5*u1*yy3*r - 
lll5*lllamDa*yy6*log(K/yy5);
DDlll5=lllamDa*Dlll5*yy6 + lllamDa*lll5*Dyy6 + 
Dlll5*u1*yy3*r + lll5*u1*Dyy3*r...
    + lll5*u1*yy3*Dr - Dlll5*lllamDa*yy6*log(K/yy5) - 
lll5*lllamDa*Dyy6*log(K/yy5)...
    + lll5*lllamDa*yy6*Dyy5/yy5;
DDDlll5=lllamDa*DDlll5*yy6 + 2*lllamDa*Dyy6*Dlll5 + 
lllamDa*lll5*DDyy6...
    + DDlll5*u1*yy3*r + Dlll5*u1*Dyy3*r + 
Dlll5*u1*yy3*Dr...
    + Dlll5 *r + lll5*u1*DDyy3*r + lll5*u1*Dyy3*Dr...
    + Dlll5*u1*yy3*Dr + lll5*u1*Dyy3*Dr + 
lll5*u1*yy3*DDr...
    - DDlll5*lllamDa*yy6*log(K/yy5) - 
Dlll5*lllamDa*Dyy6*log(K/yy5) + Dlll5*lllamDa*...
    - Dlll5*lllamDa*Dyy6*log(K/yy5) - 
lll5*lllamDa*DDyy6*log(K/yy5) + 
lll5*lllamDa*Dyy6*Dyy5/yy5...
    + Dlll5*lllamDa*yy6*Dyy5/yy5 + 
lll5*lllamDa*Dyy6*Dyy5/yy5 + 
lll5*lllamDa*yy6*DDyy5/yy5 - 
lll5*lllamDa*yy6*Dyy5*Dyy5/(yy5*yy5);

%%
Dlll6= - lll5*lllamDa*yy5*log(K/yy5)+lll6*(R+u2*yy4);
DDlll6= Dlll6*R + Dlll6*u2*yy4 + lll6*u2*Dyy4 - 
lllamDa*Dlll5*yy5*log(K/yy5) - 
lllamDa*lll5*Dyy5*log(K/yy5)...
    +lllamDa*lll5*Dyy5;
DDDlll6= DDlll6*R + DDlll6*u2*Dyy4 + 2*Dlll6*u2*Dyy4 + 
lll6*u2*DDyy4 -lllamDa*DDlll5*yy5*log(K/yy5)...
    - lllamDa*Dlll5*Dyy5*log(K/yy5) + 
2*lllamDa*Dlll5*Dyy5-
lllamDa*lll5*DDyy5*log(K/yy5)+lllamDa*lll5*Dyy5*Dyy5/y
y5+lllamDa*lll5*DDyy5;
%%
Ds=u2*Dlll6;
DDs=u2*DDlll6;
DDDs=u2*DDDlll6;
%%
Dw=Dyy6;
DDw=DDyy6;
DDDw=DDDyy6;
%%

%%
```

```
Dyyyyyy=-b2*Dyy4;
DDyyyyyy=-b2*DDyy4;
DDDyyyyyy=-b2*DDDyy4;
%%
Dz=-b2*Dyy4*z;
DDz=-b2*DDyy4*z+b2*b2*((Dyy4)^2)*z;
DDDz=-
b2*DDDyy4*z+b1*b1*DDyy4*Dyy4*z+2*b2*b2*Dyy4*DDyy4*z...
-b2*b2*b2*((Dyy4)^3)*exp(-b2*yy4);
x6=b1*b1*DDyy4*Dyy4*z+2*b2*b2*Dyy4*DDyy4*z...
-b2*b2*b2*((Dyy4)^3)*exp(-b2*yy4);
%%
p1=s;
Dp1=Ds;
DDp1=DDs;
DDDp1=DDDs;
q1=w;
Dq1=Dw;
DDq1=DDw;
DDDq1=DDDw;
m1=x;
n1=yyyyyy;
Dn1=Dyyyyyy;
DDn1=DDyyyyyy;
DDDn1=DDDyyyyyy;
o1=z;
Do1=Dz;
DDo1=DDz;
DDDo1=DDDz;
%%
Dlll4=m1*n1*o1+p1*q1;
Dm1=a2*Dlll4;
DDlll4=Dm1*n1*o1+m1*Dn1*o1+m1*n1*Do1+Dp1*q1+p1*Dq1;
DDm1=DDlll4*a2;
DDDlll4=DDm1*n1*o1+Dm1*Dn1*o1+Dm1*n1*Do1...
    +Dm1*Dn1*o1+m1*DDn1*o1+m1*Dn1*Do1...
    +Dm1*n1*Do1+m1*Dn1*Do1+m1*n1*DDo1...
    +DDp1*q1+Dp1*Dq1...
    +Dp1*Dq1+p1*DDq1;
DDDm1=DDDlll4*a2;
DDDDlll4_1=DDDm1*
Dn1*Do1...
    +DDm1*n1*Do1+Dm1*Dn1*Do1+Dm1*n1*DDo1...
    +DDm1*Dn1*o1+Dm1*DDn1*o1+Dm1*Dn1*Do1...
    +Dm1*DDn1*o1+m
*Dn1*DDo1...
    +DDm1*n1*Do1+Dm1*Dn1*Do1+Dm1*n1*DDo1...
    +Dm1*Dn1*Do1+m1*DDn1*Do1+m1*Dn1*DDo1...
    +Dm1*n1*DDo1+m1*Dn1*DDo1...%m1*n1*DDDo1
```

```
    +DDDp1*q1+DDp1*Dq1...
    +2*DDp1*Dq1+2*Dp1*DDq1...
    +Dp1*DDq1+p1*DDDq1...
    + m1*o1*(-b2)*(x5+x2)...% m1*DDDn1*o1
    + m1*n1*x6 + m1*n1*(-b2*exp(-
b2*yy4)*(x5+x2));%m1*n1*DDDo1
Dx=a2*Dlll4;
DDx=a2*DDlll4;
DDDx=a2*DDDlll4;
%%
Z=lll4;
DZ=Dlll4;
DDZ=DDlll4;
DDDZ=DDDlll4;
DDDDZ_1=DDDDlll4_1 ;
%%
u_coEff= m1*o1*(-b2)*(Ka/V) + m1*n1* (Ka/V)*(-
b2)*(exp(-b2*yy4)) ;
%%
Dlll2=Ke*lll2-Z;
DDlll2=(Ke^2)*lll2-Ke*Z-DZ;
DDDlll2=(Ke^3)*lll2-(Ke^2)*Z-Ke*DZ-DDZ;
DDDDlll2=(Ke^4)*lll2-(Ke^3)*Z-(Ke^2)*DZ-(Ke^1)*DDZ-
DDDZ;
DDDDDlll2=(Ke^5)*lll2-(Ke^4)*Z-(Ke^3)*DZ-(Ke^2)*DDZ-
(Ke^1)*DDDZ-DDDDZ_1;
%%
rest=((Ka^6)/V)*lll2 + ((Ka^5)/V)*Dlll2 +
((Ka^4)/V)*DDlll2+
V)*DDDDlll2 + ((Ka)/V)*DDDDDlll2;
%%

if (SA<0)
    SA=0.056897;
elseif (SA>max)
    SA=max;
end
out=SA;



end of singular_arc_case2.m
```

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