SILESIAN UNIVERSITY OF TECHNOLOGY

FACULTY OF AUTOMATIC CONTROL, ELECTRONICS AND COMPUTER SCIENCE

Final Project

Sub-optimal Periodic Control For Cancer Treatment

Author: Ismail KALAY

Supervisor: Dr hab. inż. Jarosław ŚMIEJA

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GENERIC REPORT STRUCTURE

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Lastly,I want to say that thank you to my beloved family.

Abstract

Before Isaac Newton, everybody had known that apples were falling down.But Newton formulate this fact in mathematical equations due to his experiments.Now we know cancer proliferates fastly but we dont know what the exact formula in time domain.And we know some treatment methods(chemotherapy, radiation therapy etc) but isn't known what is the best periodic therapy.

In this report, optimization of antiangiogenic periodic therapy for three mathematical model of cancer growth with vascularization from literature is considered as a nonlinear control problem.After continuous therapy of these three ordinary differential equation (ODE) models of cancer growth, to see the all performance index (sum of cancer volume and dose of chemotherapy) with or without patient resistance according to periodic therapy parameters, you can find my programme written in Matlab.

Lastly, finding optimal periodic therapy is showed in Matlab with Optimization Toolbox.

Keywords: Angiogenesis, Cancer model, Periodic Control, Optimize Ordinary Differential Equations, Tumour, Chemotherapy,

Table of Contents

List of Abbreviations

N	Tumor Cell number at any moment
K	Endothelial Cell number at any moment
S	Sensitive cancer cells
R	Resistant cancer cells
M	Mature Vessels
I	Immature Vessels
u	Dose of angiogenic inhibitor
v	Dose of cytotoxic drugs
E	Endothelial
C	Cancer
Compart	Comparment
Tou	Wide of Therapy for Angiogenic Inhibitor(days)
Tu	Period of Therapy for Angiogenic Inhibitor (days)
k1	Patient Resistance to Cancer Cells
k2	Patient Resistance to Angiogenic Inhibitor
k3	Patient Resistance to Cytotoxic Drugs
P.R.	Patient Resistance
Lb	Lower-band
Ub	Upper-band
İnitials	inits
Jval	Performance index value
E. T.	Elapsed Time [s]
interior-p	Interior-point algorithm in fmincon
Med-scl	Medium-scale sqp algorithm in fmincon
Sqp	Sequential Quadratic Programming
First-O.	`First-Order`
LMin	Local Minimum
PDE	Partial Differential Equations
LQ	Linear quadratic
ODE	Ordinary Differential Equation
TCP	Treatment Cure Probability
CSCs	Cancer Stem Cells
JAKs	Janus Kina
STATses	Signal Transducers and Activating of Transcription
TNF	Tumor Necroz Factor
APC	Antigen Presenting Cell
NK	Natural Killer Cell
aCTL	Alloreactive Cytotoxic-T-Lymphocytes
Malignant Gliomas	MG brain tumor
MHC	Major Histo-compability Complex
BBB	Blood Brain Barrier
Anaplastic astroytoma	uncontrolled growing tumor in Brain
CNS	Central Nervous System
C	Total number of CTL
TAA	Tumor Associated Antigens

Parameters used in simulation

model	parameter	description	value and unit
hahnfeldt et al. [1]	β	Tumor growth parameter	$0.192\ day^{-1}$
	γ	Endothelial stimulation parameter	$5.85\ day^{-1}$
	λ	Endothelial inhibition parameter	$873\,10^{-5}\,day^{-1}\,mm^{-2/3}$
	μ	Natural mortality of endothelial	$0\ day^{-1}$
	η	Antiangiogenic killing parameter	$0.15\ kg\,mg^{-1}$
	ξ	Cytostatic killing parameter for k	$0.26\ kg\,mg^{-1}$
	ψ	Cytostatic killing parameter for n	$0.34\ kg\,mg^{-1}$
	u	Dose of angiogenic inhibitor	$2\text{mg}\,kg^{-1}\,day^{-1}$
	v	Dose of cytotoxic drugs	$2\text{mg}\,kg^{-1}\,day^{-1}$
benzekry et al. [2]	β	Tumor growth parameter	$0.192\ day^{-1}$
	γ	I. endothelial stimulation parameter	$5.85\ day^{-1}$
	λ	I. endothelial inhibition parameter	$873\,10^{-5}\,day^{-1}\,mm^{-2/3}$
	ϵ	Unstable vessels maturation parameter	$0.0756\ day^{-1}$
	τ	Natural mortality of mature e. cells	$0.075\ day^{-1}$
	η	Antiangiogenic killing parameter	$6.85\,10^{-7}\,mg^{-1}\,mm^{-1}$
	ψ	Cytostatic killing parameter for c. cells	$1.37\,10^{-5}\,mg^{-1}\,mm^{-1}$
	u	Dose of angiogenic inhibitor	$525\,mg\,day^{-1}$
	v	Dose of cytotoxic drugs	$525\,mg\,week^{-1}$
Note: Half dose during continuous therapy for Benzekry Model			
Three compartment [3]	a	Average transit times through Compart.	$0.02\ day$
	c	Average transit times through Compart.	$0.2\ day$
	q	Probability of mutation to resistant cell	0.9
	r	Probability of mutation to sensitive cell	0
	γ	Endothelial stimulation parameter	$5.85\ day^{-1}$
	λ	Endothelial inhibition parameter	$873\,10^{-5}\,day^{-1}\,mm^{-2/3}$
	μ	Antiangiogenic killing parameter	$9.1\ kg\,mg^{-1}$
	ξ	Cytostatic killing parameter for K	$4.7\ kg\,mg^{-1}$
	u	Dose of angiogenic inhibitor	$1\,mg\,kg^{-1}\,day^{-1}$
	v	Dose of cytotoxic drugs	$1\,mg\,kg^{-1}\,day^{-1}$

INTRODUCTION

The model proposed by Hahnfeldt et al. (1999) describes the growth of a tumour assuming that tumour growth is strictly controlled by the evolution of the vascular network that supplies oxygen and nutrients to tumour cells.

After a certain size (1-2 mm diameter) tumor development stops, because a part of the tumor gets too far from capillaries and can't pick up enough oxygen. Tumor needs own blood vessels – the process of forming new blood vessels is called angiogenesis.

The aim of antiangiogenic cancer therapy is to prevent tumors from forming new blood vessels, because without angiogenesis tumor growth is inhibited. Several angiogenic inhibitors are known in medical practice, for example endostatin or bevacizumab.

To develop these therapies, it's required to analyze tumor growth and explore causal factors – this process belongs to the science of molecular oncology. The aim of targeted molecular therapies is not to eliminate the whole tumor, but to control the tumor into a given state and keep it there. This task belongs to the science of control engineering.

This report aim is to show optimal periodic therapies which are much better than giving chemotherapy everyday according to patient resistances.And also this report can be a good starting step for who wants to study on optimization in Bioinformatic areas.

In chapters; after showing continuous therapy for three mathematical model of cancer growth with vascularization, finding all performance indexes according to patient resistance to compare optimization toolbox solver's results in chapter 3.After chapter 1 Only Three-Compartment model has got whole code explanation.Because other models can be written with same logic.

Chapter 1: Analysis of Models with Cancer Growth in Continuous Therapy

In this part , Continuous Therapy is described as Figure 1 at the bottom

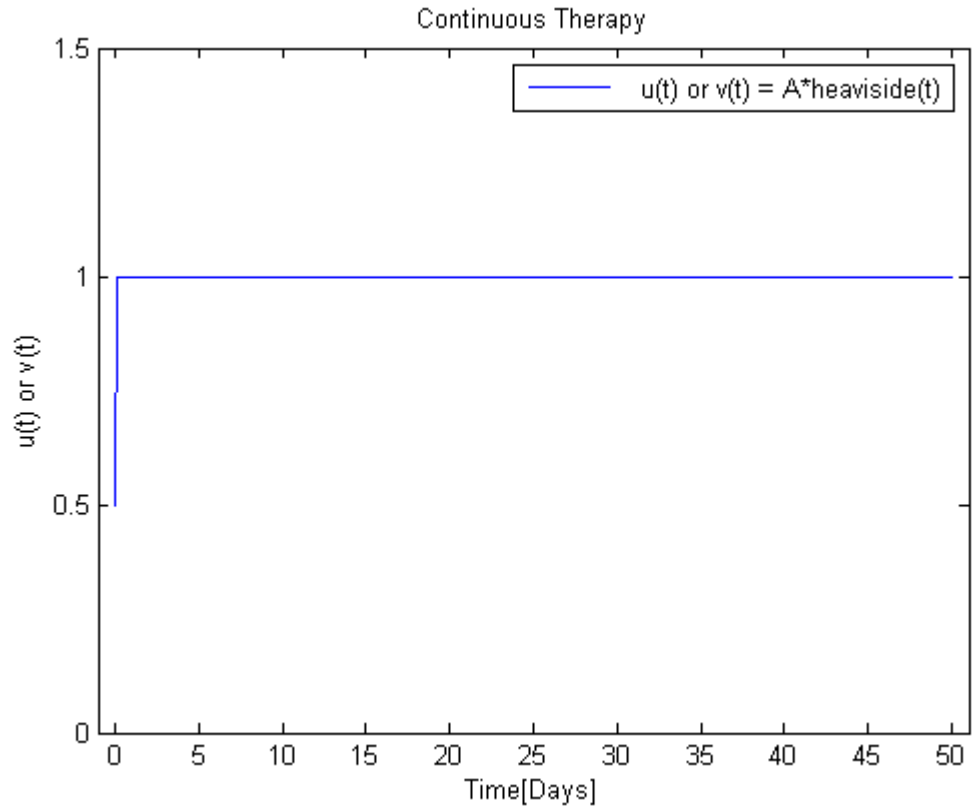


Figure 1:Continuous Therapy

1.1 Hahnfeldt Model (1999)

Two ordinary differential equations describe tumor and vascular interaction. The first shows dynamics of the tumor growth.The second equation describes vascular network growth, including stimulators of angiogenesis (characterized by parameter (γ), inhibitory factors secreted by tumor cells (λ) and natural mortality of the endothelial cells (μ). In this model, N represents cancer volume, β the proliferation ability of the cells, and K the vascular network volume.

$$\dot{N} = -\beta N \ln\left(\frac{N}{K}\right) - \psi v N$$
$$\dot{K} = \gamma N - \lambda K N^{(2/3)} - \mu K - \eta u K - \xi v K$$

The coefficients ψ, η, ξ and are nonnegative constants (conversion factors) that relate the dosages of antiangiogenic(u) and cytostatic(v) agents as based on the Hahnfeldt et al. model, d'Onofrio and Gandolfi [4] proposed some modifications.

solcontinuous.m

```
f=continuous;
    f.hahnfeldt
```

continuous.m

```
classdef continuous
 methods (Static)
     function hahnfeldt
     inits=[8000 10000];tspan=[0 50];f=continuous;
     [tout,yout]=ode23(@f.hahnfeldtmodel,tspan,inits);
     f.PlotHahnfeldt(tout,yout)
     end
     function Dy = hahnfeldtmodel(t,y)
         % constants hahnfeldt in A.Swierniak 2013
         beta=0.192;gama=5.85;lamda=0.00873;
         mu=0;eta=0.15;eps=0.26;psi=0.34;u=1;v=1;N=y(1);K=y(2);
         Dy=[-beta*N*log(N/K)-psi*v*N;
             gama*N-lamda*K*(N^(2/3))-mu*K-eta*u*K-eps*v*K];end
     function PlotHahnfeldt(T,Y)
     plot(T,Y(:,1),'-',T,Y(:,2),'-');
     title('Hahnfeldt Model');xlabel('Time[Days]');
     ylabel('Volume[mm^3]');
     legend('N:Cancer Volume','K:EndothelialVolume');end
     end end
```

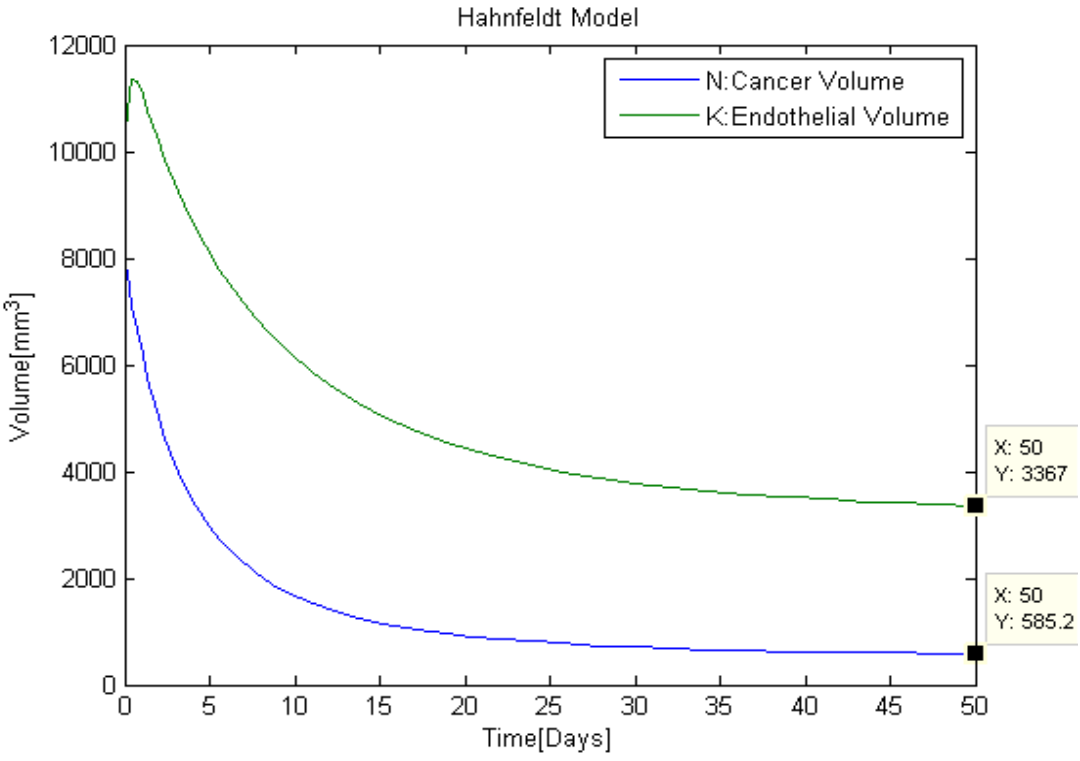


Figure 2:Hahnfeldt Model Contunious Therapy

1.2 Benzekry Model (2012)

In [2], a new modification was proposed by Benzekry et al. as:

$$\dot{N} = -\beta N \ln\left(\frac{N}{M}\right) - \psi v N Q M$$

$$\dot{M} = \epsilon I - \tau M \qquad Q(t) = \frac{M(t)}{M(t)+I(t)}$$

$$\dot{I} = -\epsilon I + \gamma N - \lambda I N^{(2/3)} - \eta u I Q M$$

Their idea was based on the original model of Hahnfeldt et al., which includes stable (*M*—mature) and unstable (*I*—immature) vessels. Only stable vessels supply nutrients and oxygen and they are the carrying capacity for cancer cells.Unstable vessels mature with a constant rate denoted by ϵ ,and mature vessels have natural mortality τ .Stable vessels transport antiangiogenic and cytostatic agents.The quality of the vascular network (Q) is calculated and included in factors determining the efficiency of the therapy.

solcontinuous.m

```
f=continuous;
    f.benzekry
```

continuous.m

```
classdef continuous
 methods (Static)
    function benzekry
    inits=[7900 2000 6000];tspan=[0 50];f=continuous;
    [tout,yout]=ode23(@f.benzekrymodel,tspan,inits);
    f.PlotBenzekry(tout,yout)
    end
    function Dy = benzekrymodel(t,y)
    % constants Benzekry in A.Swierniak 2013
       beta=0.192;gama=5.85;lamda=0.00873;
       eps=7.56e-3;tou=7.5e-3;eta=6.85e-7;psi=1.37e-5;
       N=y(1);M=y(2);I=y(3);Q=(M/(M+I));
       u=525/2*heaviside(t);
       v=(212/2)/7*heaviside(t);
       Dy=[-beta*N*log(N/M)-psi*v*N*Q*M;
            eps*I-tou*M;
            -eps*I+gama*N-lamda*I*(N^(2/3))-eta*u*I*Q*M];end
    function PlotBenzekry(T,Y)
          plot(T,Y(:,1),'-',T,Y(:,2),'-',T,Y(:,3),'-');
          title('benzekry Model');
          xlabel('Time[Days]');ylabel('Volume[mm^3]');
          legend('N:Cancer Volume','M:Mature Vessels',...
          'I:Immature Vessels');end
    end    end
```

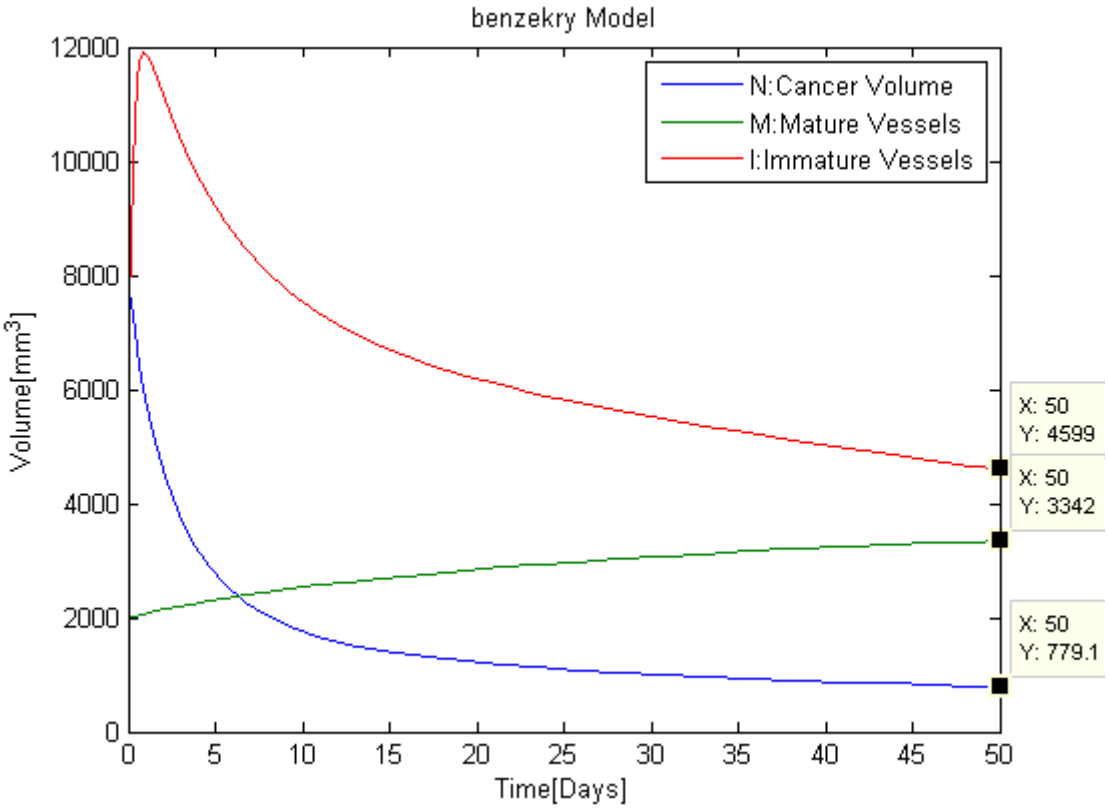


Figure 3:Benzekry Model Continuous Therapy

1.3 Three Comparment Model (2013)

A typical problem observed in chemotherapy is cancer cell resistance to chemotherapy.A three-compartment model was proposed in [3] and includes the Hahnfeldt et al. model of vessel growth and two more equations. The first describes sensitive cancer cells (*S*), and the second resistant cancer cells (*R*). *N* is the sum of all cancer cells as:

$$\dot{S} = -a\,S + (1 - v - \frac{S}{K})(2-q)\,a\,S + r\,c\,R$$

$$\dot{R} = -c\,R + (2-q)\,c\,R(1-\frac{R}{K}) + (1-v)\,q\,a\,S$$

$$\dot{K} = \gamma N - \lambda K N^{(2/3)} - \mu K - \eta u K - \xi v K$$

The coefficients *a* and *c* stand for the inverse of the average transit times through compartments.The probability of mutations occurring during the process is described by *(q)*, the probability of mutation into the resistive compartment, and (*r)*, the probability of mutation into the sensitive one. Chemotherapy and antiangiogenic therapy are already incorporated into the equations, with (*v)* representing the dose of cytostatic killing agent,*0≤ v ≤ 1* and u representing the dose of antiangiogenic drug, and *0 ≤ u ≤ 1*. As in the originalHahnfeldt model, the coefficients η, ξ are nonnegative constants (conversion factors) that relate the dosages of antiangiogenic (*u*) and cytostatic (*v*) agents.

solcontinuous.m

```
f=continuous;
    f.compartment
```

continuous.m

```
classdef continuous

 methods (Static)

     function out = compartment
            inits=[4500 3500 6000];% initial values
            tspan=0:0.1:50;% time step is 0.1- therapy time is 50
            f=continuous;
            [tout,yout]=ode23(@f.compartmentmodel,tspan,inits);
            f.PlotCompartment(tout,yout);
            end

     function Dy = compartmentmodel(t,y)
      % constants in A.SwierSiak 2013
      a=0.02;c=0.2;q=0.9;r=0;gama=5.85;lamda=0.00873;
      eta=9.1;eps=4.7;
      S=y(1);R=y(2);K=y(3);
       v=1;% Dose of cytotoxic drugs
       u=1;% Dose of angiogenenic drugs

      % Ode System in A.SwierSiak 2013
      Dy=[-a*S+(1-v-S/K)*(2-q)*a*S+r*c*R;
          -c*R+(2-r)*c*R*(1-R/K)+(1-v)*q*a*S;
          gama*(S+R)-lamda*K*((S+R)^(2/3))-eta*u*K-eps*v*K];end

      function PlotCompartment(T,Y)
      plot(T,Y(:,1),'-',T,Y(:,2),'-',T,Y(:,3),'-');
      title('Tree-compartmentmodel');
      xlabel('Time[Days]');ylabel('Volume[mm^3]');
      legend('S:Sensitive Cancer','R:Resistant...
            Cancer','K:Endothelial Volume');end
     end
end
```

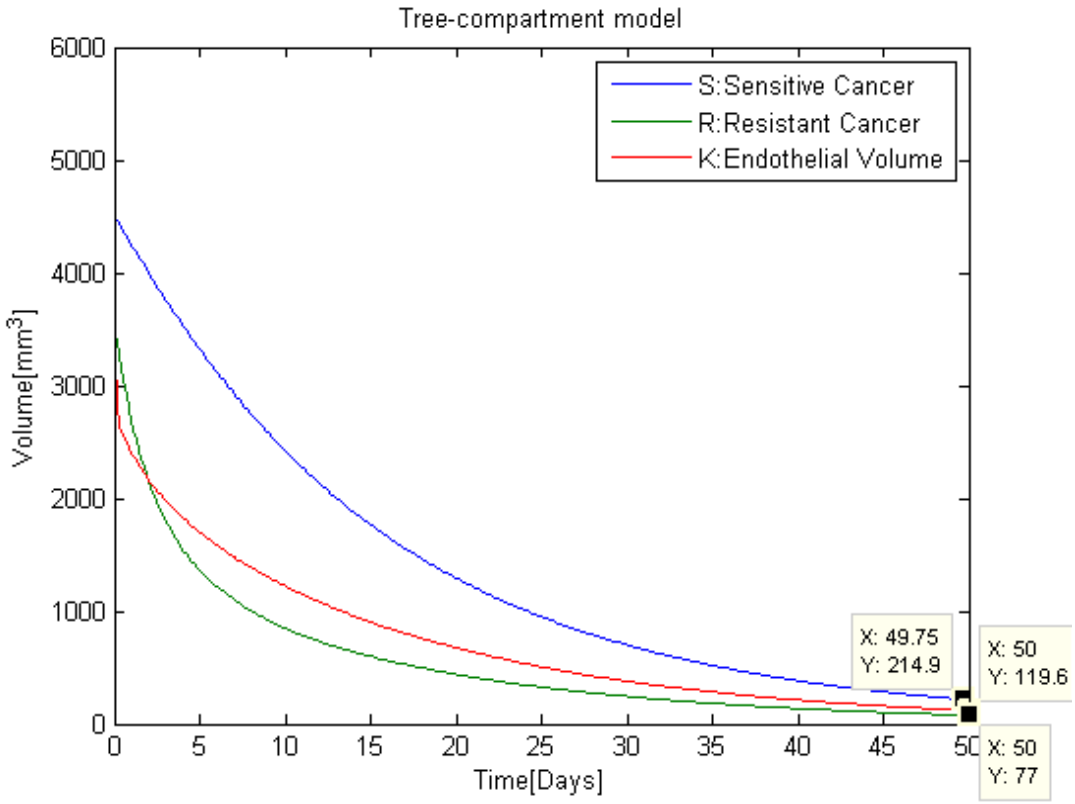


Figure 4:Three Compartment Model Continuous Therapy

The total dose of antiangiogenic drug $u_{total} = Total\ Therapy\ Days\ \ x\ \ u_{daily}$

$u_{total} = 50\ \ x\ \ 1\,mg\,kg^{-1}\,day^{-1} = 50\mathrm{mgkg}^{-1}$

The total dose of cytostatic killing agent can calculate same as (u) . $v_{total} = 50\mathrm{mgkg}^{-1}$

Yout values after continuous therapy:

Sensitive Cell (S)	Resistive Cell (R)	Endothelial (K)
211,7	77	119,5
288.7		

Sum of the cancer cells(N=S+R=211.7+77=288.7) and dose of angiogenenic inhibitor (50) is (338,7).This value is our performance index which will use to compare periodic Therapy.

Chapter 2A: Finding All performance Indexes With Patient Resistance

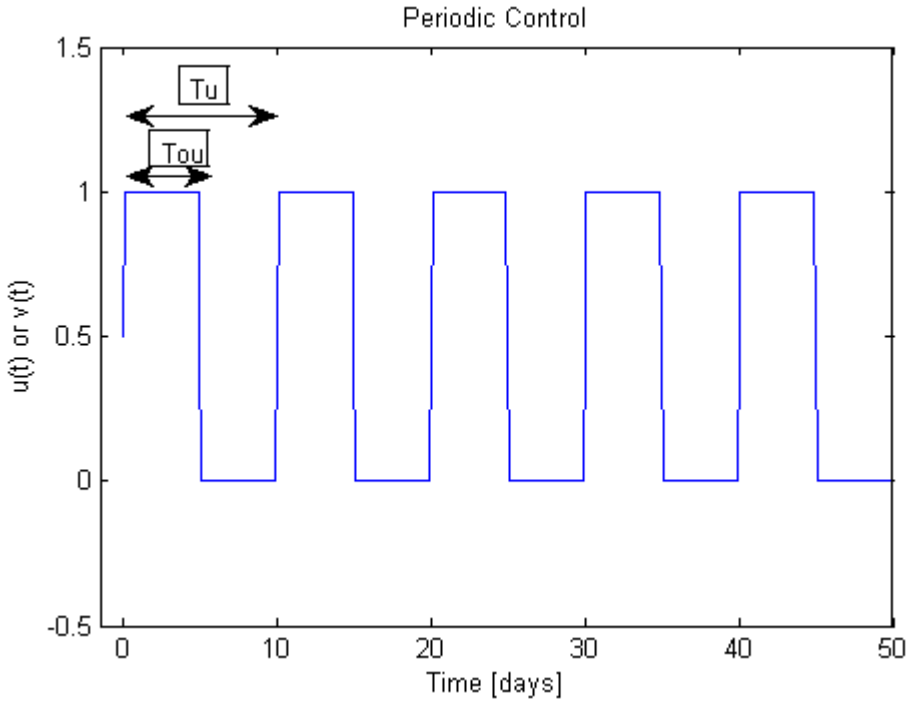
Next pages, we will see 3D performance indexes with or without patient resistance for three mathematical models which has got valleys.Valleys mean that there are more optimal performance indexes (J) in periodic therapy than continuous therapy.

Patient resistance k1 related with cancer last volume can be explain as Patient resistance to Cancer and k2 related with angiogenenic inhibitor can be explain as Patient resistance to angiogenenic inhibitor.

In this report k3 equal zero (0).Because in periodic therapy we will use cytostatics inhibitors continuously.when we considered without patient resistances, k1 and k2 can be taken one (1).It means the patient shows **same resistance** to cancer and angiogenenic drugs volume.

$$J = k_1 N(t_f) + k_2 \int_0^{t_f} u(t)\,dt + k_3 \int_0^{t_f} v(t)\,dt$$

In addition, Tou=Tu line always shows us continuous therapy.For this reason we always get same results on this line.while looking 3D performance indexes graphs ,we should keep this in our minds.



Tou is equal five (5).And total treatment time is always equal 50 in this report.

Chapter 2B: Finding All performance Indexes With Patient Resistance

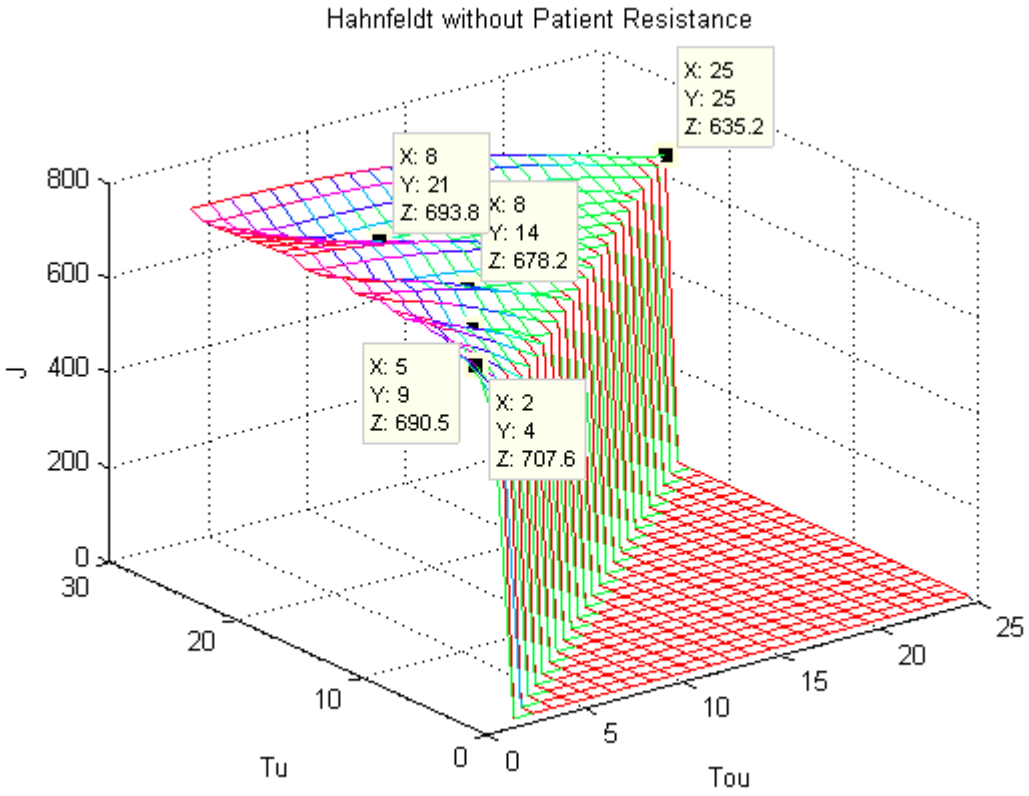
The performance index with patient resistance is :

In this report k3 equal zero (0).Because in periodic therapy we will use cytostatics inhibitors continuously.when we considered with patient resistances, k1(0.5) and k2 can be taken (2). It means that patient has got different resistance to cancer and angiogenenic drugs volume .

U and N values are inversely proportional.when we give more medicine we can find less Cancer volume at the end of therapy.if our patient body resistance is high ,it should effects performance index positively(decreased).So performance index is decreased.if our patient resistance to chemotherapy's side effect is low , it should effects performance index negatively(increased).So performance is increased.For this reason,I give k1(0.5) and k2(2).

In chapter 3,according to patient resistance we can find optimal periodic therapies much better than continuous therapy for three mathematical models.

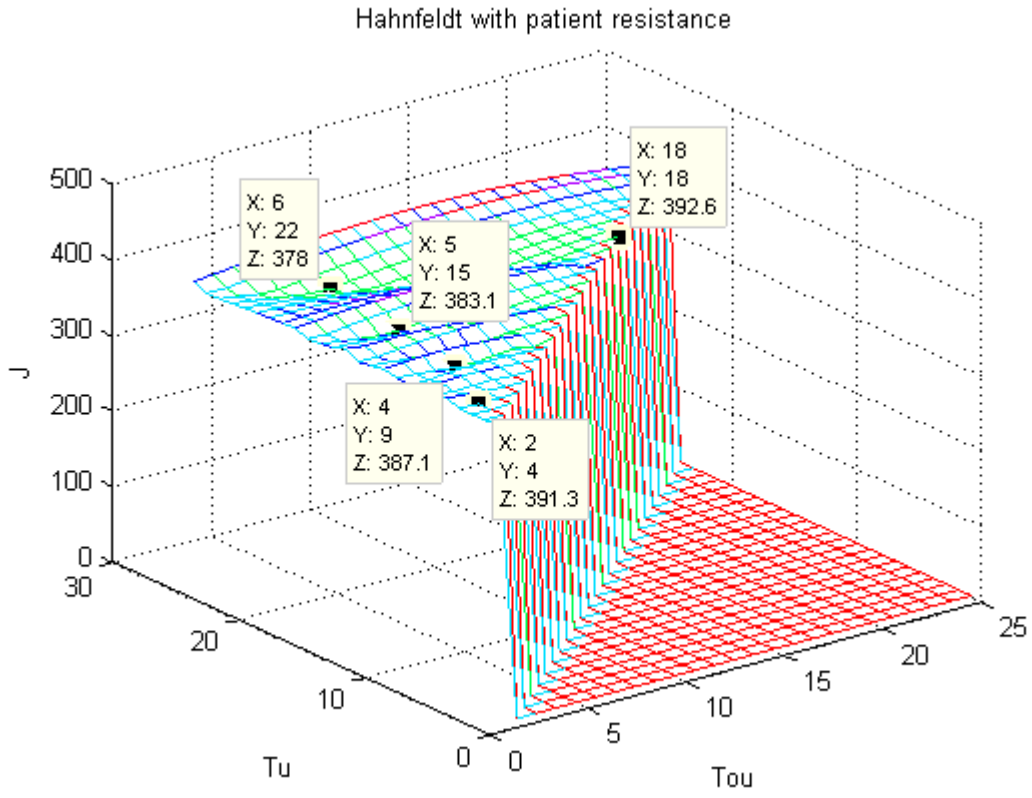
2.1.a Hahnfeldt Model without Patient Resistance



From 1.1 Hahnfeldt results we got (585.2 mm^3) for Cancer volume in after continuous therapy.if we add U (50 mg), we can reach Performance index J(685.2) when Tou is equal Tu.

On this Hahnfeldt model ,according to performance index without patient resistance there isn't more optimal periodic therapy than continuous therapy.

2.1.b Hahnfeldt Model with Patient Resistance

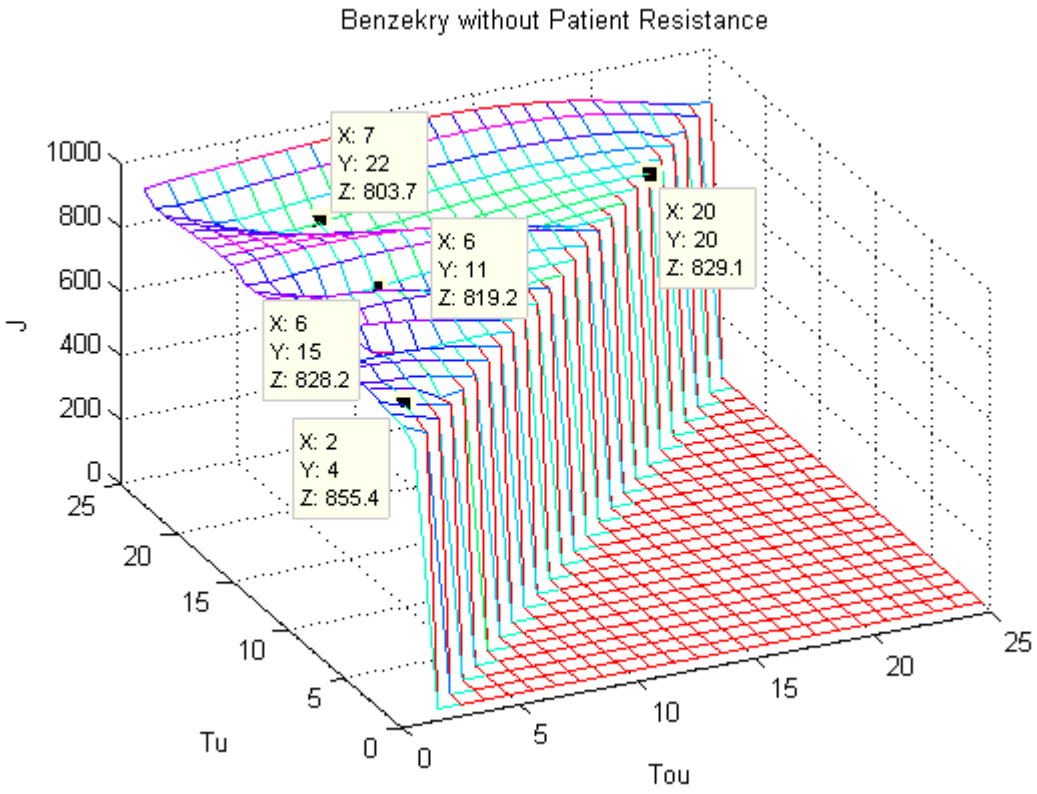


when we check 2.1 Hahnfeldt Model results ,there isnt more optimal periodic therapy than continuous therapy but according to patient resistance (k1=0.5, k2=2) there are more optimal therapies as you see.

For example: when Tou=6 days and period of the therapy Tu=22 days , we reach performance index with patient resistance (J=378) on Graph.

As you see there is one more green valley which has got (J=383.1)

2.2.a Benzekry Model without Patient Resistance



From 1.1 Hahnfeldt results we got (779.1 mm^3) for Cancer volume after therapy.if we add U (50 mg), we can reach Performance index J(829.1) when Tou is equal Tu.

$$For\ Periodic\ Therapy\ without\ Patient\ Resistance$$

$$J = N + Total\ Therapy\ Time\ x \frac{Tou}{Tu}$$

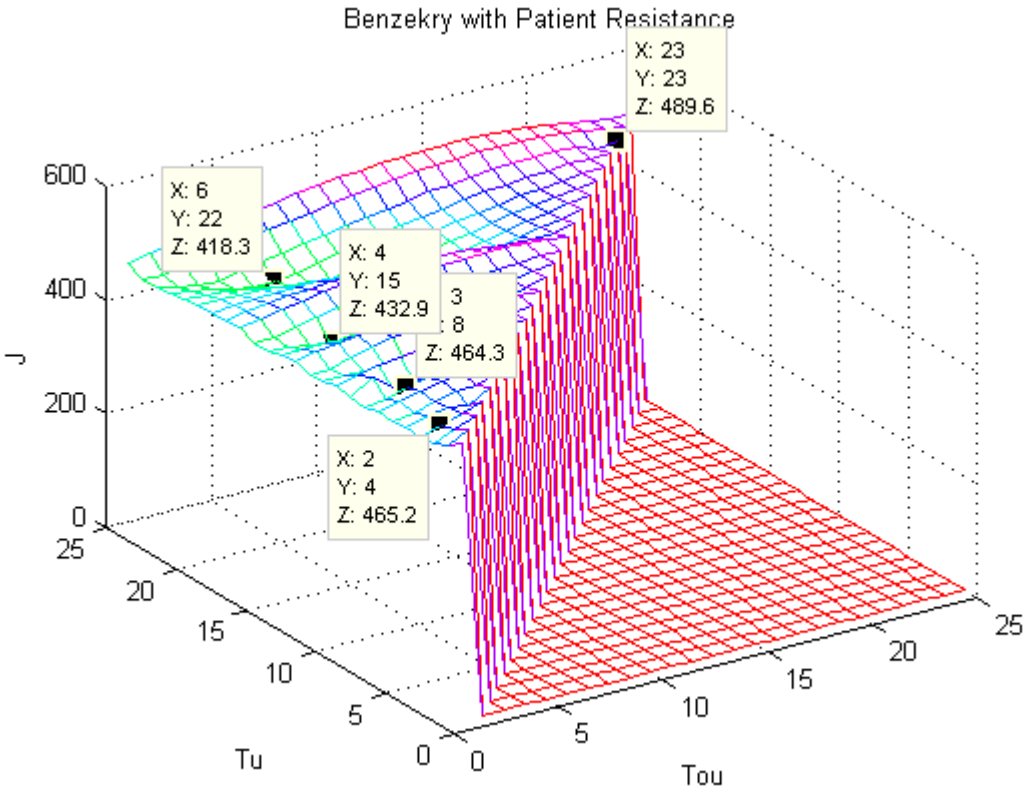
In Graph, there are two more optimal therapy which are J=803(Tou=7, Tu=22) and J=819 (Tou=6, Tu=11). So if we give medicine 7 days in 22 days period on condition that total period of tharepy is 50 days, the cancer volume decreased to this value:

$$N = J - 50\,x \frac{7}{22}$$

$$N = 803 - 50\,x \frac{7}{22}$$

$$N = 787.1$$

2.2.b Benzekry Model with Patient Resistance



Due to patient resistance we can find optimal periodic therapy with less dose of angiogenic inhibitor. This is good for patient to prevent from side effects of chemotherapy.

2.3.a Three-Compartment Model without Patient Resistance

Finding All performance Indexes (J) between Gu-Tu: 0-25

FindallJ.m

```
a=0.02;c=0.2;q=0.9;r=0;gama=5.85;lamda=0.00873;eta=9.1;eps=4.7;
        k1=0.5;%Patient resistance to Cancer
        k2=2;%Patient resistance to Chemotherapy
        inits=[4500 3500 6000];tspan=0:1:50;
        counter=0;
        tic
        for j=1:1:25
            Tu=j;
             for k=1:1:25
             Tou=k;%Tou:open time of U.[days]
             if Tou<=Tu
            [tout,yout]=ode23(@(t,y)compartment3(t,y,Tu,Tou),tspan,inits);
             S=yout(end,1);R=yout(end,2);
             N=S+R;%total last value of Tumor
             U=50*Tou/Tu;%total Angiogenic Inhibitor
             J(j,k) = k1*N + k2*U;
             else
                 counter = counter + 1;
             end
             end
        end
        toc
        figure(1)
        mesh(J);
        colormap(hsv)
        xlabel('Tou')
        ylabel('Tu')
        zlabel('J')
```

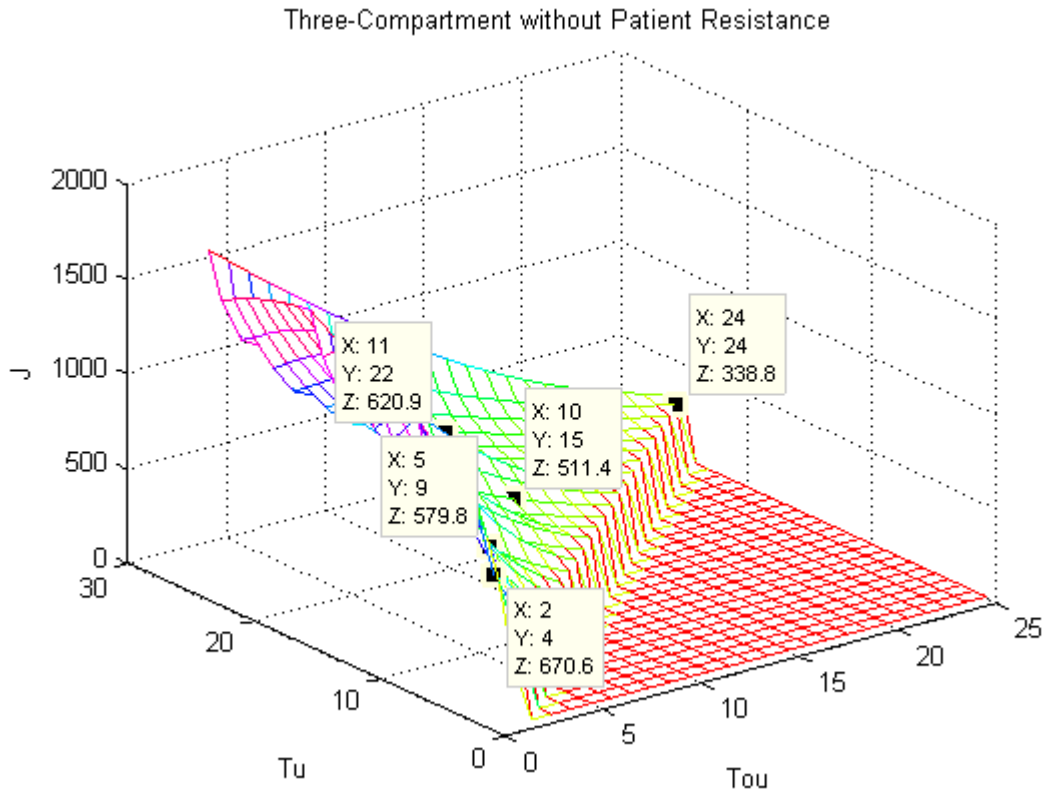
compartment3.m

```
function Dy = compartment3(t,y,Tu,Tou)
               % constants in A.SwierSiak 2013
                at=0;
               for k=0:Tu:50
                at=at + heaviside(t-k)-heaviside(t-(k+Tou));
               end
               global a c q r gama lamda eta eps
               S=y(1);R=y(2);K=y(3);v=heaviside(t);u=at;
               Dy=[-a*S+(1-v-S/K)*(2-q)*a*S+r*c*R;
                   -c*R+(2-r)*c*R*(1-R/K)+(1-v)*q*a*S;
                   gama*(S+R)-lamda*K*((S+R)^(2/3))-eta*u*K-eps*v*K];end
```

Matlab output:

counter = 300

So, impossible condition's number is (300) while the programme runs for Tou and Tu: 0:1:25.Our constraint is Tou<=Tu. In the case of impossible conditions, Tou is higher than period time (Tu).



When we look at the three-compartment graph , we cant observe deep valleys that more optimal periodic therapy than continuous therapy.

To check my codes work properly, we should look 1.3 Three-Compartment Model results in continuous therapy.

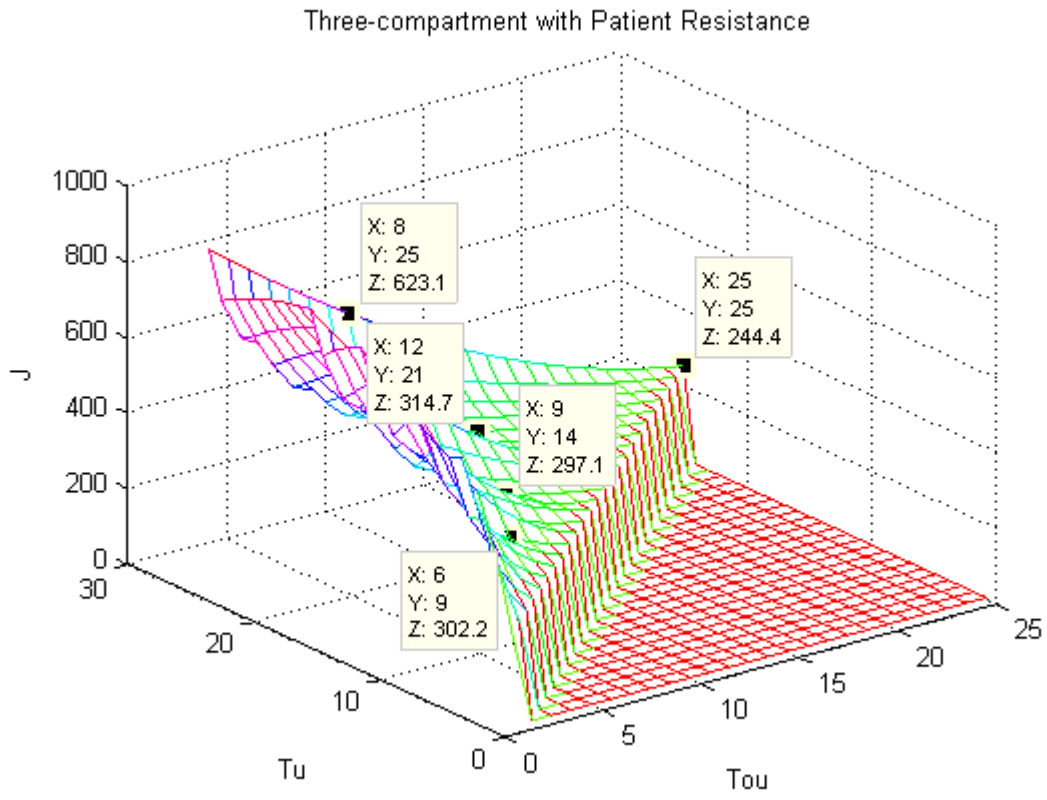
$$N = J - 50x\frac{7}{22}$$

$$N = 338.8 - 50x\frac{24}{24}$$

$$N = 288.8$$

As we find before cancer volume is equal 288.8 mm^3

2.3.b Three-Compartment Model with Patient Resistance




```
k1=0.5; %Patient resistance to Cancer
k2=2;   %Patient resistance to Chemotherapy
```

Chapter 4: Optimization Periodic Therapy without Patient Resistance

In this chapter ,Optimization solver algorithms and obtaining objective function for performance index are explained.

To understand the structure of my codes , you can glance over which I inspired by MathWorks documentation from "Optimize an ODE in Parallel"[5].

The Structure of Objective Function For Optimization Performance Index

main.m

```
f=myfun;%global model constants
        global ..
        .. ..
        %    Tou;Tu
        lb = [0;5];%lower-band
        ub = [3;7];%upper-band
        x0 = [2,6];% initial guess
        [xsol,Jval,eflag,outpt] = patternsearch(@f.objective,x0,...
            [],[],[],[],lb,ub,@f.constraint,opts)
```

myfun.m

```
classdef myfunc
        methods (Static)
         function J = objective(x)
           Tou = x(1);
           Tu = x(2);
           f=myfun
           ..
           ..
            %taking values after therapy for J
           [tout,yout]=ode23(@(t,y)f.odesystem(t,y,Tu,Tou),tspan,inits);
            ...
            J = k1*N + k2*U; %performance index J
         end
         function [c,ceq] = constraint(x)
           Tou = x(1);Tu = x(2);
           ceq = [];
           c = Tou-Tu; %nonlinear constraint Tou-tu<=0 for Periodic
         end
         function Dy = odesystem(t,y,Tu,Tou)
              ..
               Dy=[...%Mathematical model
                   ..  .. ];end
        end
end
```

Whole Optimization Codes with Explanation

main.m

```
clc;clear;
        f=compart;%three compartment model
        global a c q r gama lamda eta eps v
        a=0.02;c=0.2;q=0.9;r=0;gama=5.85;lamda=0.00873;eta=9.1;
        eps=4.7;v=1;
        %  Tou;Tu
        lb=[0;0];
        ub=[12;25];
        x0=[10,15];
        opts = psoptimset('Display','iter')
        tic % solution time
        [xsol,Jval,eflag,outpt] = patternsearch(@f.objective,x0,...
            [],[],[],[],lb,ub,@f.constraint,opts)
        toc
```

myfun.m

```
classdef myfun
         methods (Static)
          function J = objective(x)
            Tou = x(1);
            Tu = x(2);
            f=myfun;k1=1;k2=1;%Patient Resistance
            inits=[4500 3500 6000];tspan=0:0.1:50;
            [tout,yout]=ode45(@(t,y)f.odesystem(t,y,Tu,Tou),tspan,inits);
             S=yout(end,1);R=yout(end,2);
             N=S+R;%last total value of Tumor
             U=50*Tou/Tu;%total dose of Angiogenic Inhibitor
             J = k1*N + k2*U;
          end
          function [c,ceq] = constraint(x)
            Tou = x(1);Tu = x(2);
            ceq = [];
            c = Tou-Tu; %nonlinear constraint
          end
          function Dy = odesystem(t,y,Tu,Tou)
                global a c q r gama lamda eta eps v
                at=0;
                for k=0:Tu:50
                 at=at + heaviside(t-k)-heaviside(t-(k+Tou));
                end
                u=at;
                S=y(1);R=y(2);K=y(3);
                Dy=[-a*S+(1-v-S/K)*(2-q)*a*S+r*c*R;
                -c*R+(2-r)*c*R*(1-R/K)+(1-v)*q*a*S;
                gama*(S+R)-lamda*K*((S+R)^(2/3))-eta*u*K-eps*v*K];end
         end
        end
```

Optimization Solvers

1. **Pattern Search**

Pattern Search is a Global Optimization Toolbox function.The function patternsearch accepts the objective function as a function handle of the form @fun. The function fun accepts a vector input and returns a scalar function value[6].

x = patternsearch(problem) finds the minimum for problem, where problem is a structure containing the following fields:

objective — Objective function
X0 — Starting point
Aineq — Matrix for linear inequality constraints
bineq — Vector for linear inequality constraints
Aeq — Matrix for linear equality constraints
beq — Vector for linear equality constraints
lb — Lower bound for x
ub — Upper bound for x
nonlcon — Nonlinear constraint function
Solver — 'patternsearch'
options — Options structure created with psoptimset
rngstate — Optional field to reset the state of the random number generator

```
Main codes for PatternSearch solver:
lb=[0;0];
ub=[12;25];
x0=[10,15];

opts = psoptimset('Display','iter')
[xsol,Jval,eflag,outpt] = patternsearch(@f.objective,x0,...
[],[],[],[],lb,ub,@f.constraint,opts)
```

PatternSearch Output:

```
xsol =  1.1997e+001  1.2016e+001
Jval =  3.3869e+002
eflag =     1
outpt =
         function: @(varargin)f.objective(varargin{:})
      problemtype: 'nonlinearconstr'
       pollmethod: 'gpspositivebasis2n'
     searchmethod: []
       iterations: 5
        funccount: 214
         meshsize: 8.9125e-007
    maxconstraint: 0
          message: [1x115 char]
Elapsed time is 123.495522 seconds.
```

2. Fmincon

Fmincon Matlab solver can be use to find minimum of constrained nonlinear multivariable function.

All four algorithms use these options:

- 'trust-region-reflective' (default) [7]
- 'active-set' [8]
- 'interior-point'[9]
- 'sqp'[10]

```
Main codes for Fmincon solver:
options = optimset('Algorithm','sqp','Display','iter');
[x,fval,exitflag,output]=fmincon(@f.objective,x0,[],[],[],...
 [],lb,ub,@f.constraint,options)
```

Note 1:when I tried to use 'trust-region-reflective' algorithm, I got this warning.Automatically Matlab uses 'active-set' algorithm.

```
"Warning: Trust-region-reflective algorithm does not solve this
type of problem, using active-set algorithm. You could also try the
interior-point or sqp algorithms"
```

Note 2:when I tried to use 'active-set' , I got this as an output.
algorithm: 'medium-scale: SQP, Quasi-Newton, line-search'

Note3: If one of these Gradient options ('GradObj','off','GradConstr','off') is on,

Matlab can't solve the problem.its output like that:

```
Too many output arguments.

Caused by:

    Failure in initial user-supplied objective function
evaluation. FMINCON cannot continue.
```

3. MultiStart

For a MultiStart problem, use these algorithms: 'fmincon', 'fminunc', 'lsqcurvefit' or 'lsqnonlin'.

Main codes for MultiStart solver:

```
options = optimset('Algorithm','sqp','Display','iter');

problem = createOptimProblem('fmincon','x0',x0,...
    'objective',@f.objective,'lb',lb,'ub',ub,'options',options);

[x,fval,exitflag,output,solutions] = run(MultiStart,problem,3)
```

LMin	Iter	F-count	f(x)	Feasibility	Steplength	Norm of step	First-O. optimality
1	4	125	5.11e+002	0.000e+000	9.0e-007	9.54e-006	3.33e+000
2	6	195	9.85e+002	0.000e+000	9.0e-007	6.318e-006	2.08e+000
3	6	185	6.82e+002	0.000e+000	9.0e-007	1.240e-005	2.07e+000

MultiStart Output for Three-Compartment Model:

```
MultiStart completed the runs from all start points.

All 3 local solver runs converged with a positive local solver
exit flag.

x =  9.9959e+000  1.5002e+001
fval =  5.1151e+002
exitflag =     1
output =
                funcCount: 508
          localSolverTotal: 3
        localSolverSuccess: 3
    localSolverIncomplete: 0
    localSolverNoSolution: 0
                  message: [1x127 char]
solutions =  1x3 GlobalOptimSolution

Elapsed time is 323.717330 seconds.
```

Tou ,Tu

Lmin2 x = [6.94,23.94]

Lmin3 x = [13.61,24.12]

3.1.a Hahnfeldt Model

LMin	Iter	F-count	f(x)	Feasibility	Steplength	Norm of step	First-O. optimality
1	4	133	6.87e+002	0.000e+000	9.0e-007	9.54e-006	4.33e+000
2	7	200	7.67e+002	0.000e+000	2.2e-005	7.00e-005	4.07e+000
3	4	124	6.54e+002	0.000e+000	9.0e-007	1.69e-005	3.38e+000

```
                Tou  ,Tu
Lmin1 x = [9.9,15.0]
Lmin2 x = [-,-]
Lmin3 x  = 1.8240e+001  2.0850e+001
Lmin3 fval =  6.5437e+002
```

Elapsed time is 74.479199 seconds.

Because of function evaluation limit (200) ,matlab didn't accept (J=767) this value as a local minimum.In solution there wasnt no x vector (Tou,Tu).

Hahnfeld Model without P.R.(k1=1,k2=1)								
Solver	Algorithm	Lb	Ub	inits	Tou	Tu	Jval	E.T. [s]
Pattern S.	Default	[0;13]	[7;25]	[3;20]	6.9	21.1	700	32
Pattern S.	Default	[0;13]	[10;25]	[5;20]	9.9	19.6	674	28
Pattern S.	Default	[0;10]	[8;15]	[5;12]	7.99	10.3	657	48
Pattern S.	Default	[0;0]	[25;25]	[10;15]	14.8	15.1	634	21
MultiStart(3)	T.R.R.	[0;0]	[25;25]	[10;15]	9.8	17.5	710	88
MultiStart(3)	active-set	[0;0]	[25;25]	[10;15]	9.7	20	688	79
MultiStart(3)	Interior-p	[0;0]	[25;25]	[10;15]	9.0	10.3	647	93
MultiStart(3)	Sqp	[0;0]	[25;25]	[10;15]	18.2	20.8	654	74
Fmincon	T.R.R.	[0;0]	[25;25]	[10;15]	9.9	15	687	36
Fmincon	active-set	[0;0]	[25;25]	[10;15]	9.9	15	687	35
Fmincon	Interior-p	[0;0]	[25;25]	[10;15]	9.9	15	687	25
Fmincon	Sqp	[0;0]	[25;25]	[10;15]	9.9	15	687	23

3.1.b Hahnfeldt Model with Patient Resistance

Hahnfeldt Model with P.R. (k1=0.5,k2=2)								
Solver	Algorithm	Lb	Ub	inits	Tou	Tu	Jval	E.T. [s]
Pattern S.	Default	[0;13]	[7;25]	[3;20]	6.8	21.2	375	33
Pattern S.	Default	[0;13]	[10;25]	[5;20]	9.7	20	374	32
Pattern S.	Default	[0;10]	[8;15]	[5;12]	4.4	11.2	384	70
Pattern S.	Default	[0;0]	[25;25]	[10;10]	11.6	19	376	33
Pattern S.	Default	[0;0]	[25;25]	[10;15]	7.2	21	374	38
MultiStart(3)	T.R.R.	[0;0]	[25;25]	[10;20]	9.9	20	375	55
MultiStart(3)	active-set	[0;0]	[25;25]	[10;20]	9.9	20	375	136
MultiStart(5)	Interior-p	[0;0]	[25;25]	[10;15]	4.0	22.8	381	91
MultiStart(3)	Sqp	[0;0]	[25;25]	[10;15]	9.9	15.0	393	29
Fmincon	T.R.R.	[0;0]	[25;25]	[10;15]	2	15.8	389	34
Fmincon	active-set	[0;0]	[25;25]	[10;15]	2	15.8	389	33
Fmincon	Interior-p	[0;0]	[25;25]	[10;15]	9.9	15.0	393	21
Fmincon	Sqp	[0;0]	[25;25]	[10;15]	9.9	15.0	393	23

3.2.a Three-Compartment Model

Three-Compartment without P.R.								
Solver	Algorithm	Lb	Ub	inits	Tou	Tu	Jval	E.T. [s]
Pattern S.		[0;5]	[3;7]	[2,6]	2.99	5.21	586	559
Pattern S.		[0;0]	[4;10]	[2,6]	3.99	4.01	338	521
Pattern S.		[0;0]	[1;10]	[0.5,5]	0.99	1.008	337	2461
Pattern S.		[0;2]	[1;10]	[0.5,6]	0.99	2.04	694.8	1789
Pattern S.		[0;0]	[25;25]	[10;15]	14.9	15	338	125
Pattern S.		[0;0]	[12;25]	[10;15]	11.9	12	338	210
MultiStart(2)		[0;4]	[3;6]	[2,5]	2.44	5.81	773.8	420
MultiStart(2)		[0;5]	[3;7]	[2,6]	1.99	5.99	869.3	320
MultiStart(4)		[0;5]	[3;7]	[2,6]	1.99	5.99	869.3	718
MultiStart(2)		[0;0]	[4;10]	[2,6]	1.99	5.98	868.3	340
MultiStart(2)		[0;0]	[1;10]	[0.5,5]	0.95	4.85	1159.5	342
MultiStart(2)		[0;0]	[1;10]	[0.5,5]	0.46	5.31	1500.3	359
MultiStart(3)	Sqp	[0;0]	[12;25]	[10;15]	9.99	15	511.5	323
Fmincon	Interior-p	[0;0]	[1;10]	[0.5,5]	0.35	4.30	1507.2	521
Fmincon	Med-scl sqp	[0;5]	[3;7]	[2,6]	2.00	5.99	869.3	243
Fmincon	Interior-p	[0;0]	[4;10]	[2,6]	2.69	7.99	867.3	428
Fmincon	active-set	[0;0]	[4;10]	[2,6]	2.99	8.00	823.5	269
Fmincon	Sqp	[0;0]	[4;10]	[2,6]	3.20	9.39	823.1	108
Fmicon	Sqp	[0;0]	[25;25]	[10;10]	9.99	15	511.5	96
Fmincon	T.R.R.	Can't solve with T.R.R. Matlab use active-set algorithm						

3.2.b Three-Compartment Model

Three-Compartment with P.R. (k1=0.5,k2=2)								
Solver	Algorithm	Lb	Ub	inits	Tou	Tu	Jval	E.T. [s]
Pattern S.	Default	[0;5]	[3;7]	[2,6]	2.99	5.21	586	482
Pattern S.	Default	[0;0]	[4;10]	[2,6]	3.9	4.0	338	383
Pattern S.	Default	[0;0]	[25;25]	[10;15]	14.9	15	338	84
Pattern S.	Default	[0;15]	[12;25]	[10;20]	11.9	18.9	477	95
Pattern S.	Default	[0;13]	[10;25]	[7;17]	9.9	13.3	4.3	137
MultiStart(3)	T.R.R.	[0;0]	[25;25]	[10;15]	9.9	15	305	34
MultiStart(3)	active-set	[0;0]	[25;25]	[10;15]	9.9	15	305	33
MultiStart(3)	active-set	[0;0]	[25;25]	[5;20]	14.9	15	244	123
MultiStart(3)	active-set	[0;0]	[25;15]	[12;15]	11.9	15	276	144
MultiStart(3)	interior-p	[0;0]	[25;25]	[12;10]	9.8	10	245	184
MultiStart(3)	Sqp	[0;0]	[4;10]	[2,6]	1.99	5.98	459	238
MultiStart(3)	Sqp	[0;0]	[25;25]	[10;15]	9.9	15	305	64
Fmincon	Interior-p	[0;0]	[25;25]	[10;15]	9.9	15	305	66
Fmincon	active-set	[0;10]	[8;25]	[5,15]	4.99	14.9	413	114
Fmincon	Interior-p	[0;0]	[25;25]	[10;15]	2.18	2.49	280	61
Fmincon	Sqp	[0;0]	[25;25]	[10;15]	2.49	2.5	244	44
Fmincon	T.R.R.	Can't solve with T.R.R. Matlab use active-set algorithm						

Conclusion

We got same performance index results in continuous therapy when we compare 3D performance indexes graphs in chapter 2.And also more deep valleys appears with patient resistances.Patient resistance to cancer volume in their body is high level(Immune system strong for cancer).And resistance to angiogenenic drug's side effect is low level (patient body weak for drugs).These situations which I counted above are considered while choosing patient resistance.More deep valleys like dimples mean that there is more optimal periodic therapies than continuous therapy.

Three-Compartment's more linear performance index graph is observed after comparing Three-Compartment and Hahnfeldt model graphs.while appearing more deep valleys(dimples) on Hanhnfeldt and Benzekry graphs, there is no dimple on three-compartment graph as you see.After patient resistance flat areas occured on Three-Compartment with P.T graph.

In chapter 3, how to use Matlab solvers(functions) such as PatternSearch,MultiStart and Fmincon with four different algorithms are showed to find best periodic therapy point which we couldn't see on 3D graphs in chapter 2. To find more local minimum point you can give more multistart starting point with displaying iterations.The minimum Jval(performance index values) are near continuous therapy(Tou=Tu).For this reason the solvers find always same value which means that giving angiogenenic drugs everyday ($1\,mg\,kg^{-1}day^{-1}$) because of lack of dimples.

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12. Comparison of Simple Models of Periodic Protocols for Combined Anticancer Therapy Marzena DoBbniak and Andrzej Swierniak

Appendix1

MultiStart output:

```
       MultiStart completed the runs from all start points.
       All 2 local solver runs converged with a positive local
solver exit flag.
       xmin =  2.4439e+000  5.8116e+000
       fmin =  7.7384e+002
       outpt =
                      funcCount: 246
                localSolverTotal: 2
              localSolverSuccess: 2
          localSolverIncomplete: 0
          localSolverNoSolution: 0
                        message: [1x127 char]
       Elapsed time is 420.885243 seconds.
```

Fmincon output:

```
       lb=[0;5];
       ub=[3;7];
       x0=[2,6];
       [xmin,fmin,flag,outpt] = fmincon(problem)

xmin =  2.0000e+000  5.9998e+000
fmin =  8.6938e+002
flag =    5
outpt =
         iterations: 7
          funcCount: 150
       lssteplength: 1.1921e-007
           stepsize: 1.2568e-007
          algorithm: 'medium-scale: SQP, Quasi-Newton, line-search'
      firstorderopt: 8.3335e+000
    constrviolation: -9.9985e-001
            message: [1x781 char]
Elapsed time is 243.383404 seconds.
```

Appendix2

Fmincon output2:

```
lb = [0;0];%lower-band
ub = [1;10];%upper-band
x0 = [0.5,5];% initial guess
options = optimset('Algorithm','interior-point',...
       'Display','iter','GradObj','off','GradConstr','off');

[x,fval,exitflag,output]=fmincon(@f.objective,x0,[],[],[]...
,[],lb,ub,@f.constraint,options)
```

Iter	F-count	f(x)	Feasibility	First-order optimality	Norm of step
0	3	1.529418e+003	0.000e+000	1.453e+003	
1	8	1.528710e+003	0.000e+000	1.255e+002	7.128e-001
2	14	1.524360e+003	0.000e+000	1.235e+002	1.059e-002
3	23	1.512706e+003	0.000e+000	3.637e+000	6.427e-003
4	34	1.507159e+003	0.000e+000	3.593e+000	2.794e-003
5	51	1.507159e+003	0.000e+000	3.593e+000	1.904e-005
6	56	1.507158e+003	0.000e+000	3.592e+000	5.396e-005
7	67	1.507158e+003	0.000e+000	3.592e+000	8.331e-006
8	71	1.507158e+003	0.000e+000	3.591e+000	4.721e-005
9	83	1.507157e+003	0.000e+000	3.591e+000	3.644e-006
10	93	1.507157e+003	0.000e+000	3.591e+000	3.189e-006
11	106	1.507157e+003	0.000e+000	4.272e+007	3.488e-007
12	109	1.507157e+003	0.000e+000	2.442e+004	2.018e-006
13	116	1.507157e+003	0.000e+000	3.590e+000	4.012e-006
14	121	1.507157e+003	0.000e+000	3.590e+000	1.404e-005
15	131	1.507157e+003	0.000e+000	3.590e+000	3.510e-006
16	141	1.507157e+003	0.000e+000	3.590e+000	3.072e-006
17	158	1.507157e+003	0.000e+000	3.590e+000	2.100e-008
18	168	1.507157e+003	0.000e+000	3.590e+000	1.846e-008
19	176	1.507157e+003	0.000e+000	3.590e+000	6.494e-008
20	184	1.507157e+003	0.000e+000	3.590e+000	2.297e-007
21	194	1.507157e+003	0.000e+000	4.272e+007	2.432e-007
22	199	1.507157e+003	0.000e+000	4.272e+007	5.010e-007

```
Local minimum possible. Constraints satisfied.
fmincon stopped because the size of the current step is less than
the default value of the step size tolerance and constraints are
satisfied to within the default value of the constraint tolerance.
<stopping criteria details>
x =  3.5767e-001  4.3039e+000
fval =  1.5072e+003
exitflag =  2
output =
         iterations: 23
          funcCount: 215
    constrviolation: 0
           stepsize: 3.7073e-010
          algorithm: 'interior-point'
      firstorderopt: 4.2721e+007
       cgiterations: 118
            message: [1x722 char]
Elapsed time is 523.705345 seconds.
```