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```
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%-----
%%
%                               Modelação e Simulação em Medicina
%                               Docente: Professora Raquel Conceição | 2017/2018
%
%                               Íris Isabel Coimbra Damião    | 45297
%                               João Pedro Fernandes Peixoto  | 46727
%
%                               The Simulation of the Influence of Two-Compartment Model
%                               Parameters on the Plasma Drug Concentration and Drug Effect
%
%                               Part 1 | Influence on Plasma Drug Concentration
%
%-----
%%
clc;
clearvars;
close all;
```

## Tabled Values

```
Vc = 961;      % Volume of the central compartment [mL]
CL = 75;       % clearance [L.h-1]
K12 = 0.126;   % transfer rate constant from the central compartment
               % to the peripheral compartment [h-1]
K21 = 0.062;   % transfer rate constant from the peripheral compartment
               % to the central compartment[h-1]
E_max = 37.7;  % max drug effect (no units)
C_E50 = 3.2;   % concentration of the drug that produces half of the
               % maximum effect[ng.mL-1]
F = 0.75;      % bioavailability (% of D0)
```

## Studie 1 - Changes in C with Ka

This study aims to simulate the changes in the concentration of the drug, in time, with changing values of Ka (absorption rate), while fixing the elimination rate (K10) and the oral dose (D0)

```
% setting initial variables
K10 = CL/Vc;      % fixing elimination rate
Ka = 0.1:0.1:5;   % absorption rate varies from 0.1h-1 to 5h-1 with a
step
```

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```

                                % of  $0.1h^{-1}$ 

% definition of the hybrid constants using the function f_r
[alpha_1, alpha_2] = f_r(-1,K10+K21+K12,-K10*K21);
alpha = max(alpha_1,alpha_2);
beta = K10+K21+K12-alpha;

% a) simulation using C(t)
%dt = 1/365; %temporal step
dt = 0.1;
t = 0:dt:12; %time vector

% initiation of the concentration vector
C = zeros(length(t),length(Ka));
C(1,:) = 0;

% definition of the oral dose vector
D0 = zeros(1,length(t));
D0(1) = 0;
D0(2:length(t)) = 40;

% initiation of the L, M and N vectors
L = zeros(1,length(Ka));
M = zeros(1,length(Ka));
N = zeros(1,length(Ka));

% calculation, using a for loop, of the concentration values with
    fixed
% oral dose and elimination rate
for i=1:length(t)
    for j= 1:length(Ka)
        L(j) = (K21-alpha)/((beta-alpha)*(Ka(j)-alpha));
        M(j) = (K21-beta)/((alpha-beta)*(Ka(j)-beta));
        N(j) = (K21-Ka(j))/((beta-Ka(j))*(alpha-Ka(j)));

        C(i,j) = (D0(i)*F*Ka(j)*1e3)/Vc*(L(j)*exp(-alpha*(i*dt))+...
            M(j)*exp(-beta*(i*dt))+N(j)*exp(-Ka(j)*(i*dt)));
    end
end

% plotting the values of the values of C(t,Ka), t and Ka in a 3D mesh
figure(1)
mesh (Ka,t,C); set(gca,'Ydir','reverse')
title ('Relação entre a concentração do compartimento central e K_a')
xlabel('Constante de absorcao k_a (1/h)')
ylabel('Tempo (h)');
zlabel('Concentracao (ng/mL)');

% b) Simulation using dC/dt and the Euler method
%initiation of the concentration vector
dt = 1/365; % using a smaller step time
t = 0:dt:12;

% initiation of the concentration vector

```

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```

C = zeros(length(t),length(Ka));
C(1,:) = 0;

d_C = zeros(length(t),length(Ka));

% definition of the oral dose vector
D0 = zeros(1,length(t));
D0(1) = 0;
D0(2:length(t)) = 40;

% initiation of the L, M and N vectors
L = zeros(1,length(Ka));
M = zeros(1,length(Ka));
N = zeros(1,length(Ka));

% using Euler method we calculate the values of C(t) with respect to
time
% and Ka in order to compare to the previous simulation
for i=1:length(t)-1
    for j= 1:length(Ka)
        L(j) = (K21-alpha)/((beta-alpha)*(Ka(j)-alpha));
        M(j) = (K21-beta)/((alpha-beta)*(Ka(j)-beta));
        N(j) = (K21-Ka(j))/((beta-Ka(j))*(alpha-Ka(j)));

        d_C(i,j)=((D0(i)*F*Ka(j)*1e3)/Vc)*(L(j)*(-alpha)*exp(-
alpha*i*dt)+...
        M(j)*(-beta)*exp(-beta*i*dt)+ N(j)*(-Ka(j))*exp(-
Ka(j)*i*dt));
        C(i+1,j)=C(i,j)+d_C(i,j)*dt;

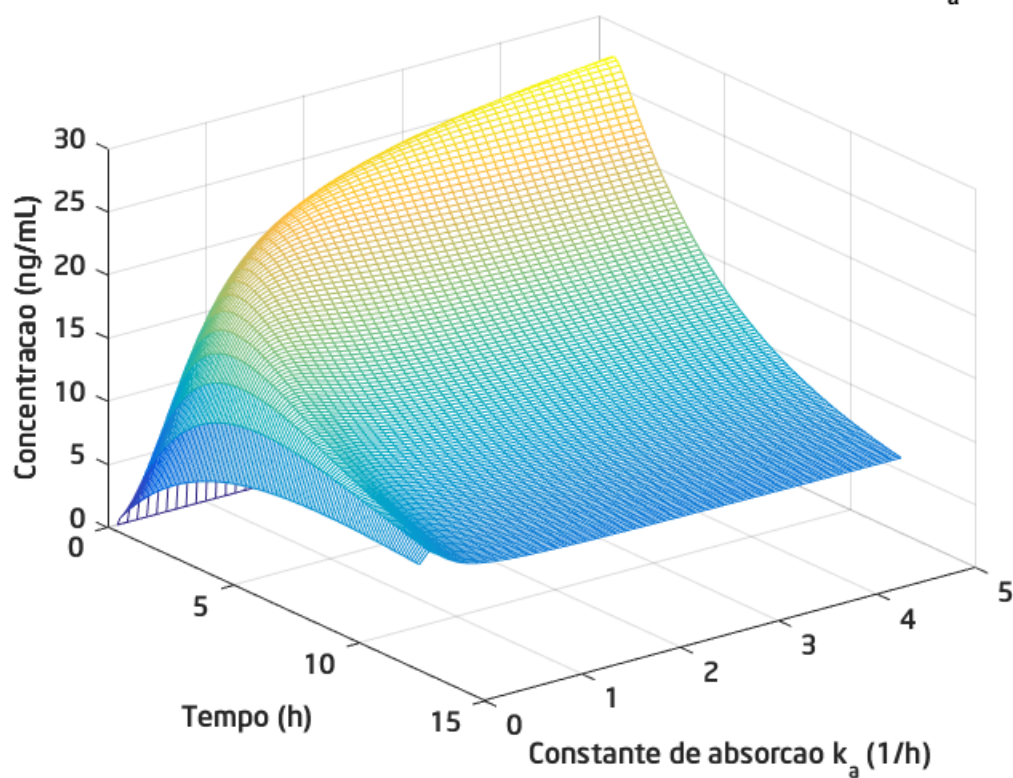
    end
end

% plotting the values of the values of C(t,Ka), t and Ka in a 3D mesh
figure (2)
mesh (Ka,t,C); set(gca,'Ydir','reverse')
title ('Relação entre a concentração do compartimento central e K_a
(usando Euler)')
xlabel('Constante de absorçao k_a (1/h)')
ylabel('Tempo (h)');
zlabel('Concentração (ng/mL)');

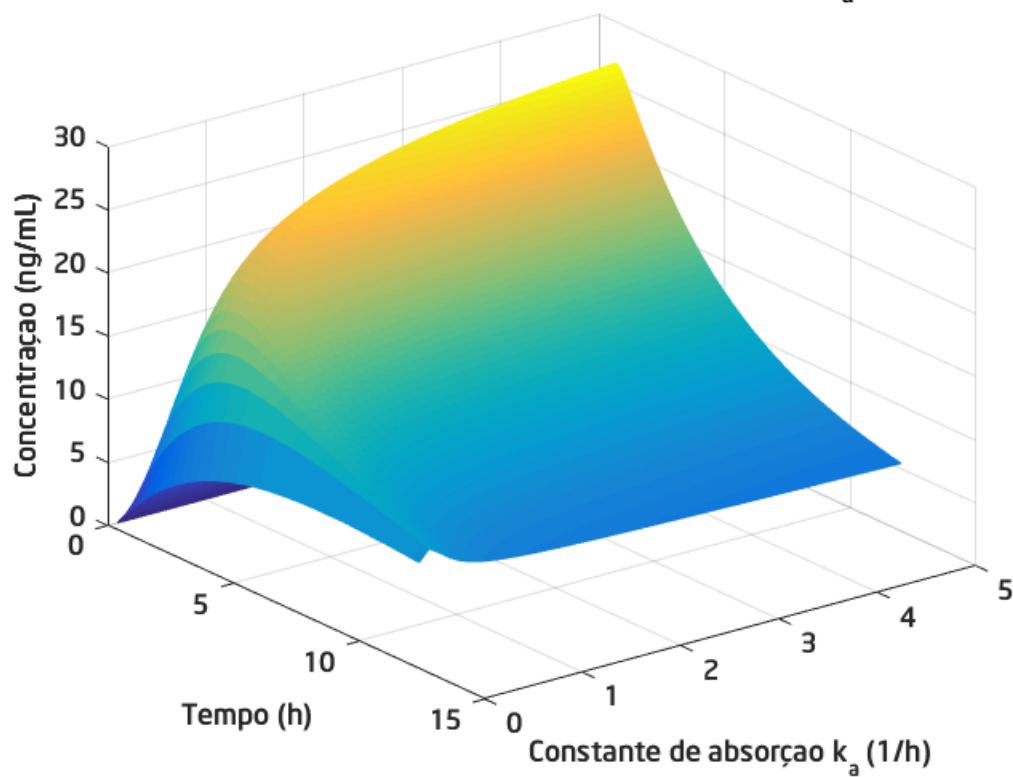
```

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Relação entre a concentração do compartimento central e  $K_a$



Relação entre a concentração do compartimento central e  $K_a$  (usando Euler)



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## Studie 2 - Changes in C with K10

This study aims to simulate the changes in the concentration of the drug, in time, with changing values of K10 (elimination rate), while fixing the absorption rate (Ka) and the oral dose (D0)

```
% setting initial variables
Ka = 2.6;
K10 = 0.01:0.01:1.5;

alpha = zeros(1,length(K10));
beta = zeros(1,length(K10));

% a) simulation using C(t)
dt = 0.1;
t = 0:dt:12;
C = zeros(length(t),length(K10));

% Definition of the oral dose vector
D0 = zeros(1,length(t));
D0(1) = 0;
D0(2:length(t)) = 40;

% initiation of the L, M and N vectors
L = zeros(1,length(t));
M = zeros(1,length(t));
N = zeros(1,length(t));

% calculation, using a for loop, of the concentration values with
fixed
% oral dose and absorption rate
for i=1:length(t)
    for j= 1:length(K10)

        [alpha_1, alpha_2] = f_r(-1,K10(j)+K21+K12,-K10(j)*K21);
        alpha(j) = max(alpha_1,alpha_2);

        beta(j) = K10(j)+K21+K12-alpha(j);

        L(i,j) = (K21-alpha(j))/((beta(j)-alpha(j))*(Ka-alpha(j)));
        M(i,j) = (K21-beta(j))/((alpha(j)-beta(j))*(Ka-beta(j)));
        N(i,j) = (K21-Ka)/((beta(j)-Ka)*(alpha(j)-Ka));

        C(i,j) = (D0(i)*F*Ka*1e3)/Vc*(L(i,j)*exp(-alpha(j)*(i*dt))+...
            M(i,j)*exp(-beta(j)*(i*dt))+N(i,j)*exp(-Ka*(i*dt)));
    end
end

% plotting the values of the values of C(t,K10), t and K10 in a 3D
mesh
figure(3)
mesh (K10,t,C)
set(gca, 'Ydir', 'reverse')
```

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```

title ('Relação entre a concentração do compartimento central e
      K_{10}')
xlabel('Constante de eliminação k_{10} (1/h)')
ylabel('Tempo (h)');
zlabel('Concentração (ng/mL)');

% b) simulation using dC(t)/t and Euler method
dt = 1/365;
t = 0:dt:12;

% initiation of the concentration vector
C = zeros(length(t),length(K10));
C(1,:) = 0;
d_C = zeros(length(t),length(K10));

% Definition of the oral dose vector
D0 = zeros(1,length(t));
D0(1) = 0;
D0(2:length(t)) = 40;

% initiation of the L, M and N vectors
L = zeros(1,length(K10));
M = zeros(1,length(K10));
N = zeros(1,length(K10));

% using Euler method we calculate the values of C(t) with respect to
time
% and K10 in order to compare to the previous simulation
for i=1:length(t)-1
    for j= 1:length(K10)

        [alpha_1, alpha_2] = f_r(-1,K10(j)+K21+K12,-K10(j)*K21);
        alpha(j) = max(alpha_1,alpha_2);

        beta(j) = K10(j)+K21+K12-alpha(j);

        L(j) = (K21-alpha(j))/((beta(j)-alpha(j))*(Ka-alpha(j)));
        M(j) = (K21-beta(j))/((alpha(j)-beta(j))*(Ka-beta(j)));
        N(j) = (K21-Ka)/((beta(j)-Ka)*(alpha(j)-Ka));

        d_C(i,j)=((D0(i)*F*Ka*1e3)/Vc)*(L(j)*(-alpha(j))*exp(-
alpha(j)*i*dt)+...
        M(j)*(-beta(j))*exp(-beta(j)*i*dt)+ N(j)*(-Ka)*exp(-
Ka*i*dt));
        C(i+1,j)=C(i,j)+d_C(i,j)*dt;
    end
end

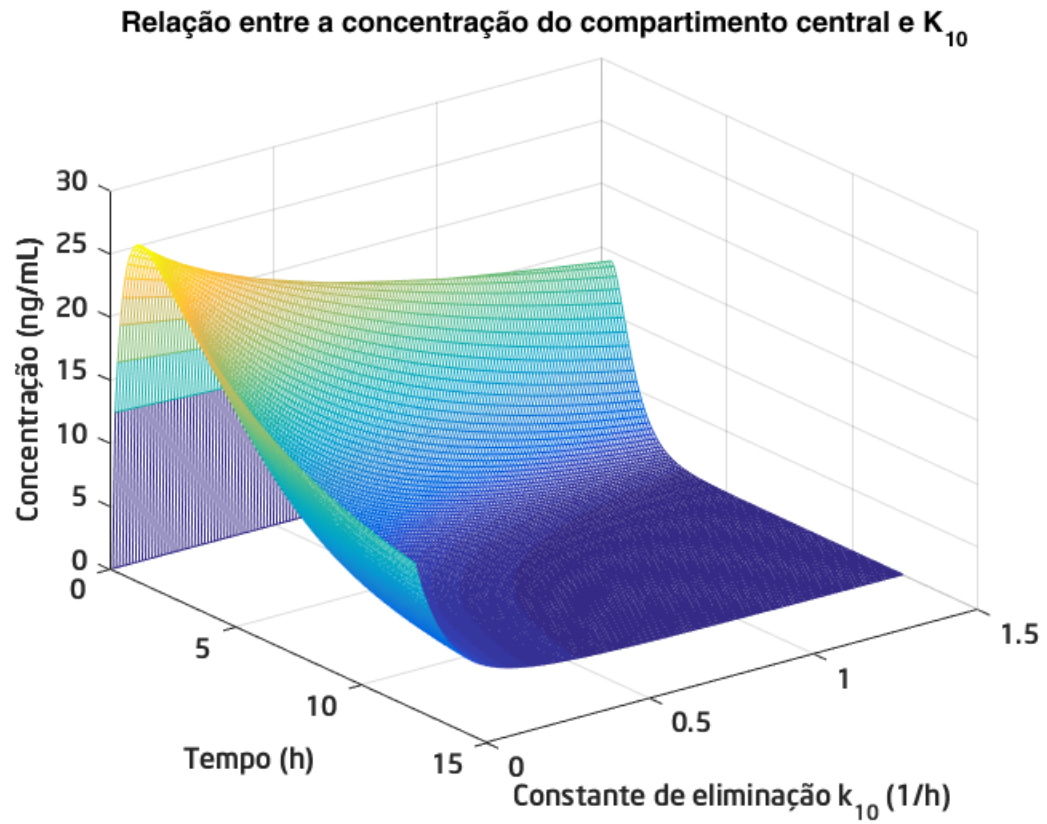
% plotting the values of the values of C(t,K10), t and K10 in a 3D
mesh
figure(4)
mesh (K10,t,C)
set(gca,'Ydir','reverse')

```

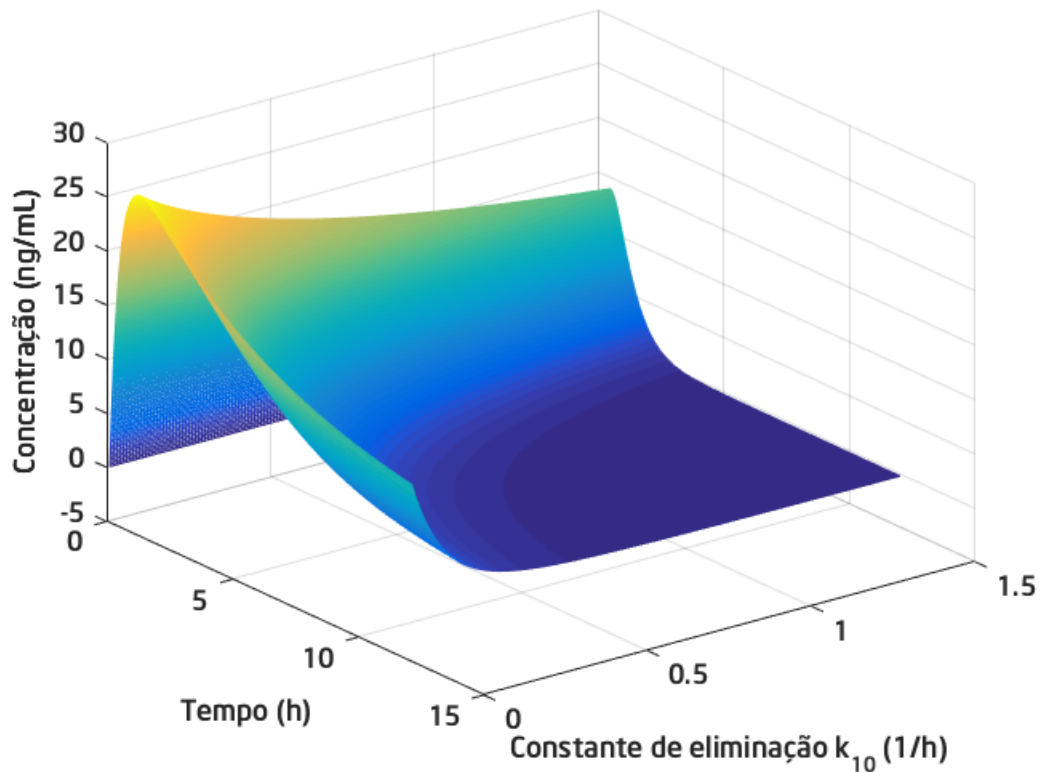
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```
title ('Relação entre a concentração do compartimento central e  $K_{10}$   
(usando Euler)')  
xlabel('Constante de eliminação  $k_{10}$  (1/h)')  
ylabel('Tempo (h)');  
zlabel('Concentração (ng/mL)');
```



Relação entre a concentração do compartimento central e  $K_{10}$  (usando Euler)



## Studie 3 - Changes in C with D0

This study aims to simulate the changes in the concentration of the drug, in time, with changing values of D0 (oral dose), while fixing the absorption rate ( $K_a$ ) and the elimination rate ( $K_{10}$ )

```
% setting initial values
Ka = 2.6;
K10 = CL/Vc;

% Definition of the hybrid constants using the function f_r
[alpha_1, alpha_2] = f_r(-1,K10+K21+K12,-K10*K21);
alpha = max(alpha_1,alpha_2);

beta = K10+K21+K12-alpha;

% a) simulation using C(t)
dt = 0.1;
t = 0:dt:12;
C = zeros(length(t),length(Ka));

% Definition of the oral dose vector
d_0 = 0:1:50;
D0 = zeros(length(d_0),length(t));
D0(:,1) = 0;

% initiation of the L, M and N vectors
```



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```

L = zeros(1,length(t));
M = zeros(1,length(t));
N = zeros(1,length(t));

% calculation, using a for loop, of the concentration values with
fixed
% absorption and elimination rates
for i=1:length(t)
    for j= 1:length(d_0)

        D0(j,2:length(t)) = d_0(j);

        L(i,j) = (K21-alpha)/((beta-alpha)*(Ka-alpha));
        M(i,j) = (K21-beta)/((alpha-beta)*(Ka-beta));
        N(i,j) = (K21-Ka)/((beta-Ka)*(alpha-Ka));

        C(i,j) = (D0(j,i)*F*Ka*1e3)/Vc*(L(i,j)*exp(-alpha*(i*dt))+...
            M(i,j)*exp(-beta*(i*dt))+N(i,j)*exp(-Ka*(i*dt)));
    end
end

% plotting the values of the values of C(t,D0), t and D0 in a 3D mesh
figure(5)
mesh (d_0,t,C)
set(gca,'Ydir','reverse')
title ('Relação entre a concentração do compartimento central e D_0')
xlabel('Dose D_0 (mg)')
ylabel('Tempo (h)');
zlabel('Concentração (ng/mL)');

% b) simulation using dC(t)/t and Euler method
dt = 1/365;
t = 0:dt:12;

d_0 = 0:1:50;
D0 = zeros(length(t),length(d_0));
D0(1,:) = 0;

C = zeros(length(t),length(d_0));
C(1,:) = 0;

L = (K21-alpha)/((beta-alpha)*(Ka-alpha));
M = (K21-beta)/((alpha-beta)*(Ka-beta));
N = (K21-Ka)/((beta-Ka)*(alpha-Ka));

% calculation of the values of C(t) using Euler's method and fixing
% elimination and absorption rate
for i=1:length(t)-1
    for j= 1:length(d_0)

        D0(2:length(t),j) = d_0(j);

        d_C(i,j)=((D0(i,j)*F*Ka*1e3)/Vc)*(L*(-alpha)*exp(-
alpha*i*dt)...

```

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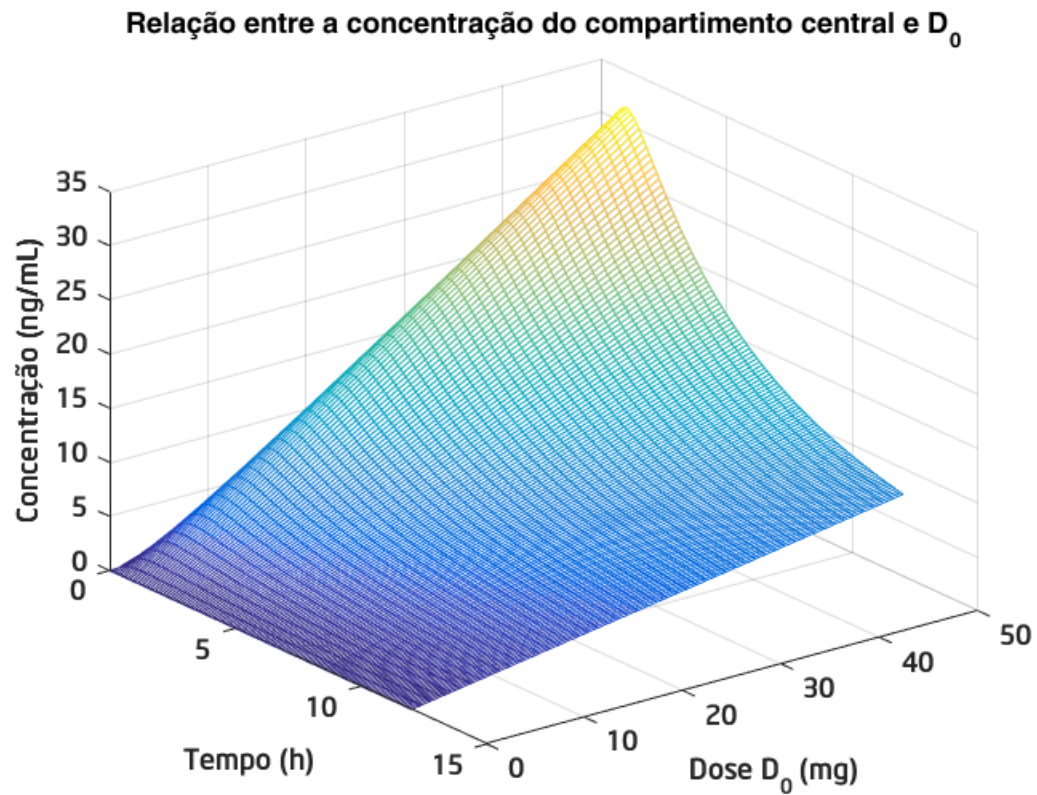
```

        +M*(-beta)*exp(-beta*i*dt)+ N*(-Ka)*exp(-Ka*i*dt));
        C(i+1,j)=C(i,j)+d_C(i,j)*dt;

    end
end

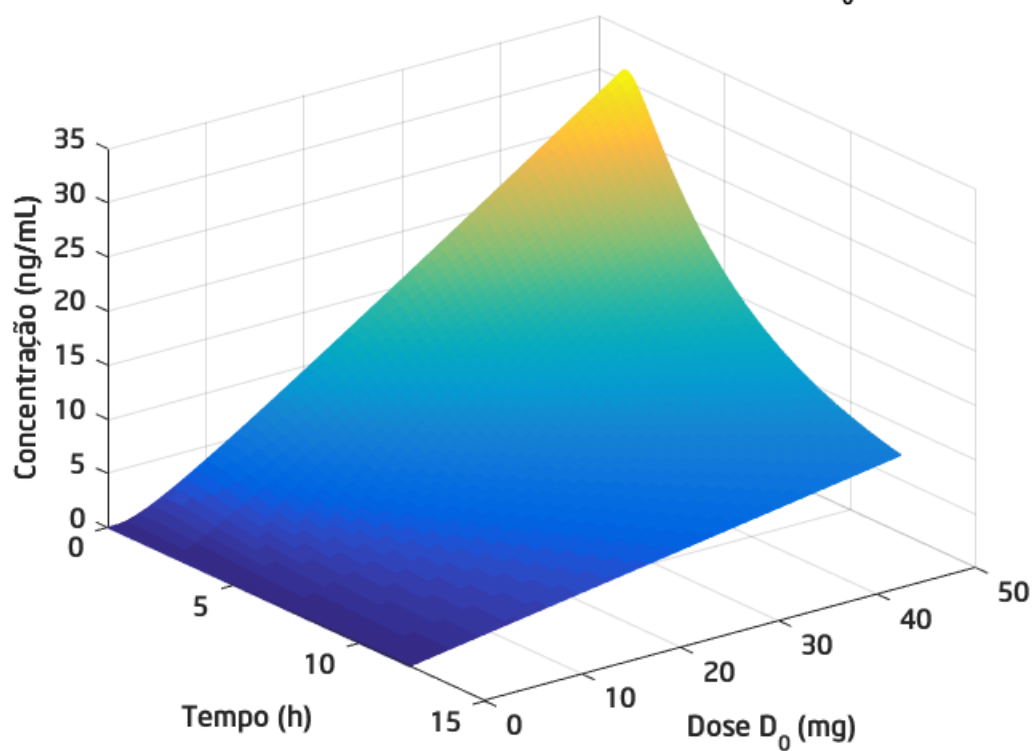
% plotting the values of the values of C(t,D0), t and D0 in a 3D mesh
figure(6)
mesh (d_0,t,C)
set(gca,'Ydir','reverse')
title ('Relação entre a concentração do compartimento central e D_0
(usando Euler)')
xlabel('Dose D_0 (mg)')
ylabel('Tempo (h)');
zlabel('Concentração (ng/mL)');

```



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**Relação entre a concentração do compartimento central e  $D_0$  (usando Euler)**



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