

Imports

```
In [7]: import numpy as np
import matplotlib.pyplot as plt
from scipy.integrate import solve_ivp
from SALib.sample import saltelli
from SALib.analyze import sobol
import numpy as np
```

Create ODE system and plot the number of cells over time for T_1 , T_2 , E_1 , and E_2 .

```
In [5]: def ode_system(t, state, g1,g2,a11,a12,a21,p1,d1,d2,e1,e2,r1,r2,r3,s1,s2,i12,i21,K1,
T1,T2,E1,E2 = state

    dT1dt = g1*T1*(1-T1/K1) - a11*E1*T1 - a12*E2*T1 - i12*T1*T2
    dT2dt = g2*T2*(1-T2/K2) - a21*E1*T2 - i21*T1*T2
    dE1dt = p1 - d1*E1 - e1*(T1+T2)*E1 + ((r1*(T1+T2))/(s1+T1+T2))*E1
    dE2dt = -d2*E2 - e2*T1*E2 + ((r2*T1)/(s2+T1))*E2 + r3*E1*(T1+T2)
    return [dT1dt, dT2dt, dE1dt, dE2dt]

g1 = 0.514
g2 = 0.35 * g1
a11 = 1.1e-7
a12 = 1.1e-10
a21 = a11
p1 = 1.3e4
d1 = 4.12e-2
d2 = 2.0e-2
e1 = 3.42e-10
e2 = e1
r1 = 1.24e-1
r2 = 1.24e-3
r3 = 1.1e-7
s1 = 2.02e7
s2 = s1
i12 = 1.1e-9
i21 = 1.5*i12
K1 = 5e8
K2 = K1

p = (g1,g2,a11,a12,a21,p1,d1,d2,e1,e2,r1,r2,r3,s1,s2,i12,i21,K1,K2)
initial = [8.0e7,2.0e7,1.1e7,0]

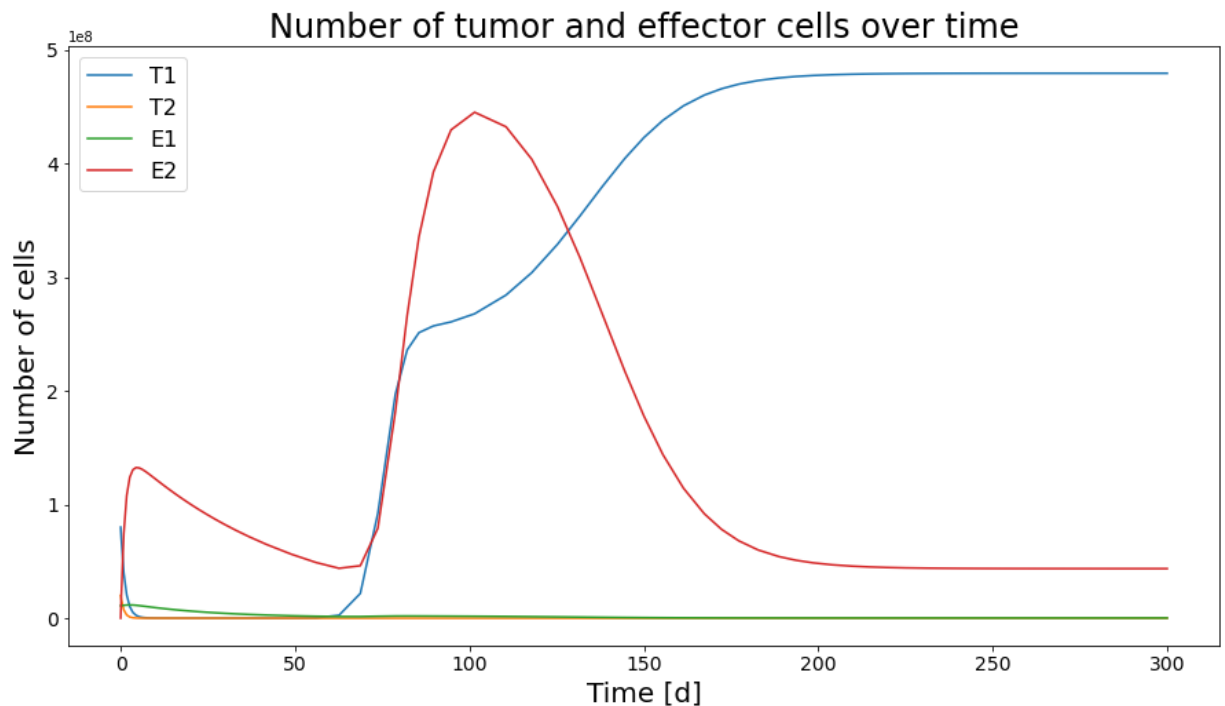
t_span = (0.0, 300.0)
t = np.arange(0.0, 300.0, 0.01)

result_solve_ivp = solve_ivp(ode_system, t_span, initial, args=p)

labels = ['T1', 'T2', 'E1', 'E2']
fig = plt.figure(figsize=(15,8))
for i in range(result_solve_ivp.y.shape[0]):
    plt.plot(result_solve_ivp.t, result_solve_ivp.y[i], label=labels[i])

plt.xlabel('Time [d]', fontsize=20) # the horizontal axis represents the time
plt.ylabel('Number of cells', fontsize=20)
plt.xticks(size=14)
```

```
plt.yticks(size=14)
plt.title('Number of tumor and effector cells over time', fontsize = 24)
plt.legend(fontsize=16) # show how the colors correspond to the components of X
fig.savefig('Output_ODE_test.jpg')
plt.show()
```



Make the same plots for different E_1 initial values and extract T_1 values for the time $t = 250$.

In [48]:

```
def ode_system(t, state, g1,g2,a11,a12,a21,p1,d1,d2,e1,e2,r1,r2,r3,s1,s2,i12,i21,K1,
               T1,T2,E1,E2 = state

    dT1dt = g1*T1*(1-T1/K1) - a11*E1*T1 - a12*E2*T1 - i12*T1*T2
    dT2dt = g2*T2*(1-T2/K2) - a21*E1*T2 - i21*T1*T2
    dE1dt = p1 - d1*E1 - e1*(T1+T2)*E1 + ((r1*(T1+T2))/(s1+T1+T2))*E1
    dE2dt = -d2*E2 - e2*T1*E2 + ((r2*T1)/(s2+T1))*E2 + r3*E1*(T1+T2)
    return [dT1dt, dT2dt, dE1dt, dE2dt]

g1 = 0.514
g2 = 0.35 * g1
a11 = 1.1e-7
a12 = 1.1e-10
a21 = a11
p1 = 1.3e4
d1 = 4.12e-2
d2 = 2.0e-2
e1 = 3.42e-10
e2 = e1
r1 = 1.24e-1
r2 = 1.24e-3
r3 = 1.1e-7
s1 = 2.02e7
s2 = s1
i12 = 1.1e-9
i21 = 1.5*i12
```

```

K1 = 5e8
K2 = K1

values_at_t250 = list()

p = (g1,g2,a11,a12,a21,p1,d1,d2,e1,e2,r1,r2,r3,s1,s2,i12,i21,K1,K2)
E1_list = [0.5e7, 0.6e7, 0.7e7, 0.8e7, 0.9e7, 1e7, 1.1e7, 1.2e7, 1.3e7, 1.4e7, 1.5e7]
for i in range(11):
    E1 = E1_list[i]
    initial = [8.0e7, 2.0e7, E1, 0]

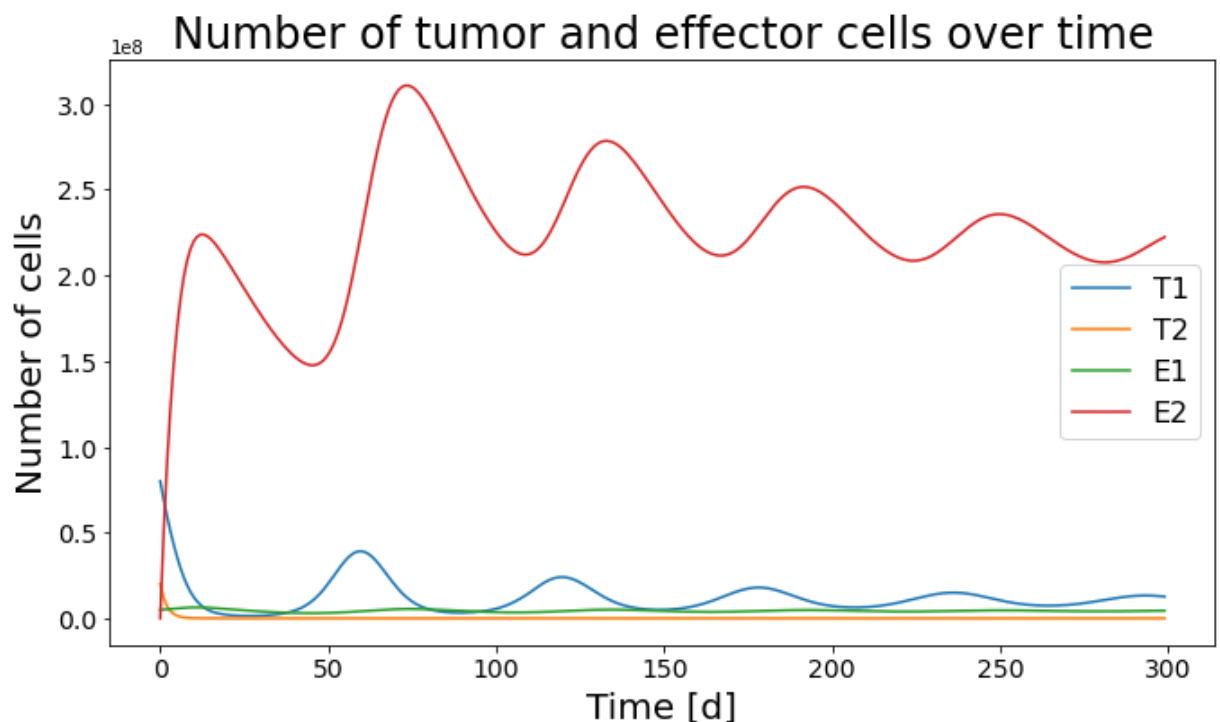
    t_span = (0, 300.0)
    t = np.arange(0, 300.0, 1)

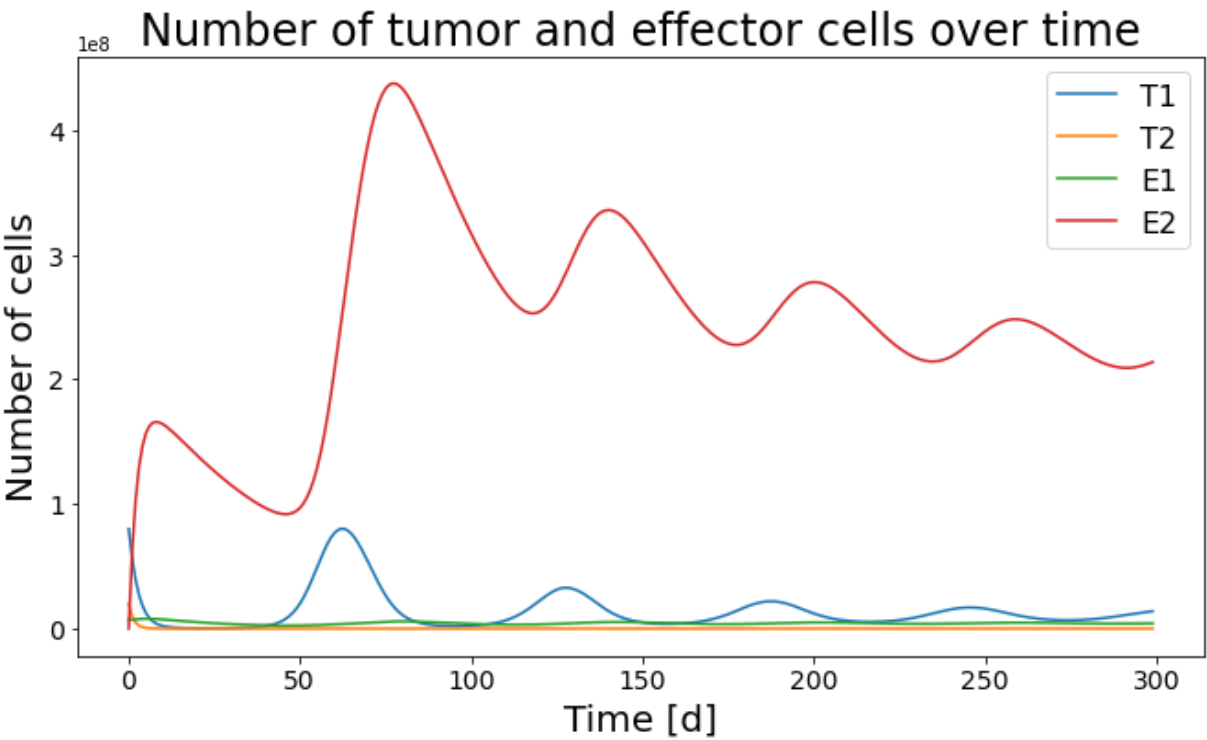
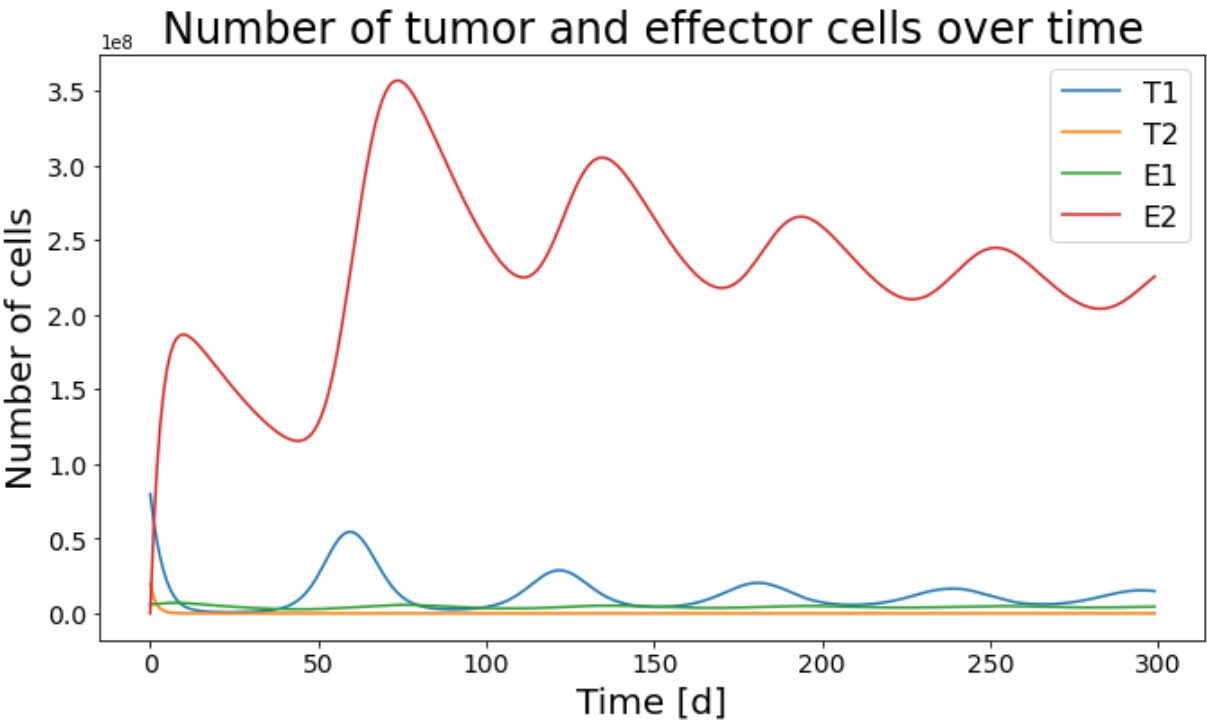
    result_solve_ivp = solve_ivp(ode_system, t_span, initial, args=p, t_eval=t)

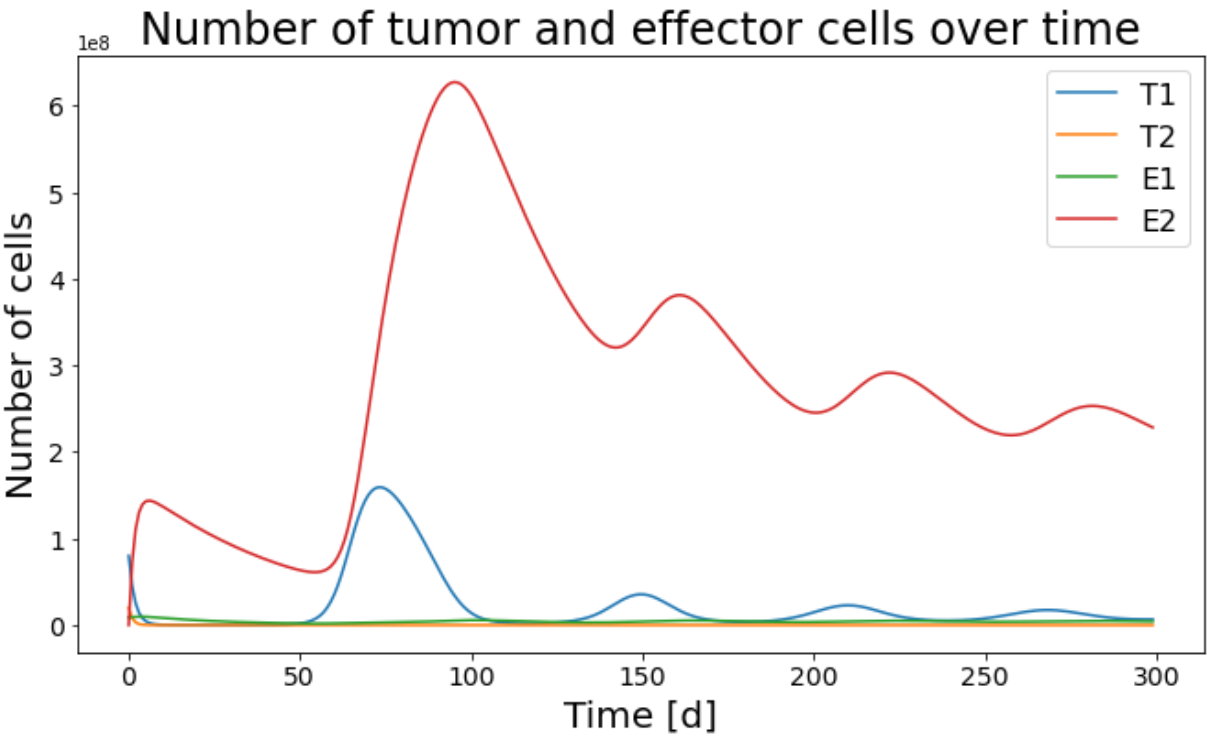
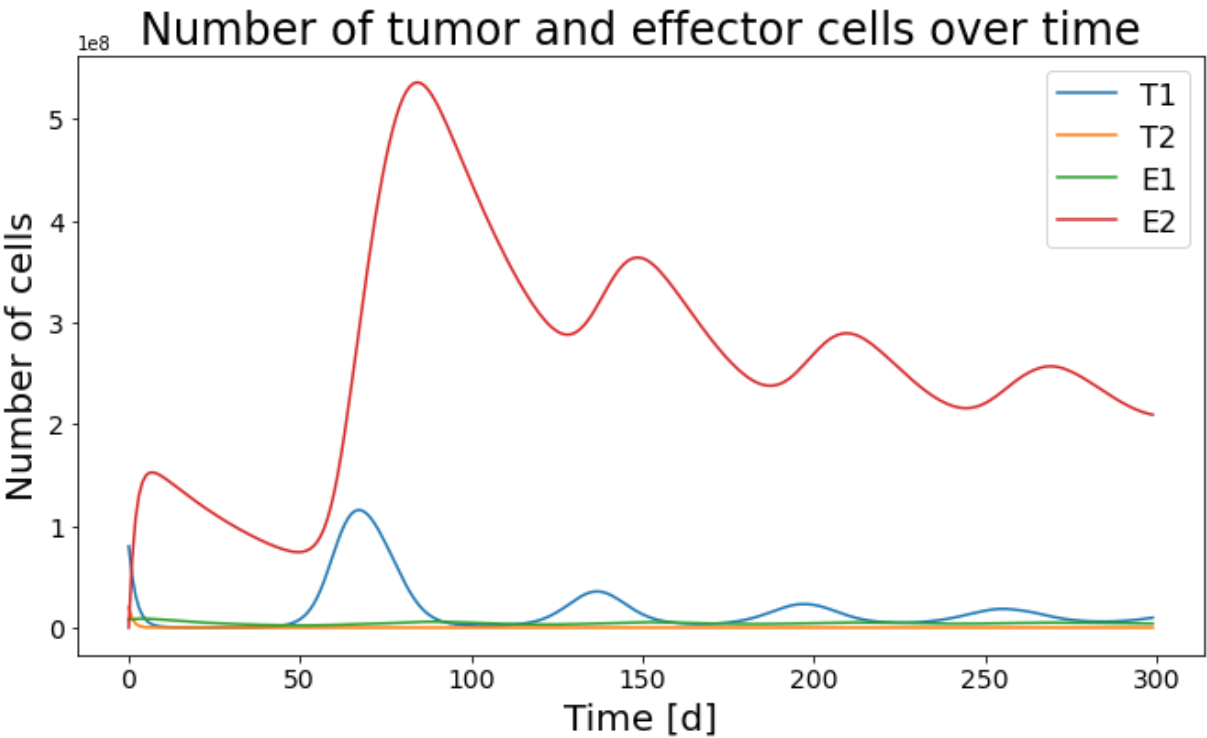
    labels = ['T1', 'T2', 'E1', 'E2']
    fig = plt.figure(figsize=(11,6))
    for i in range(result_solve_ivp.y.shape[0]):
        plt.plot(result_solve_ivp.t, result_solve_ivp.y[i], label=labels[i])
        values_at_t250.append(result_solve_ivp.y[i][249])

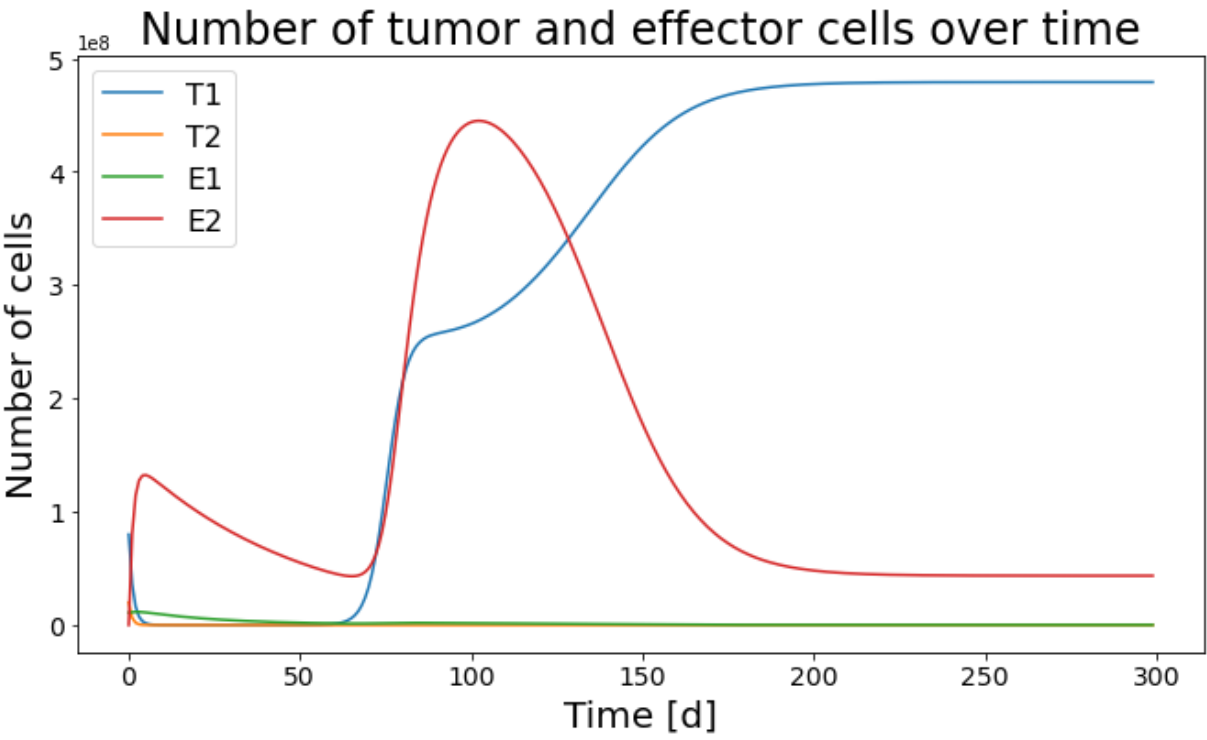
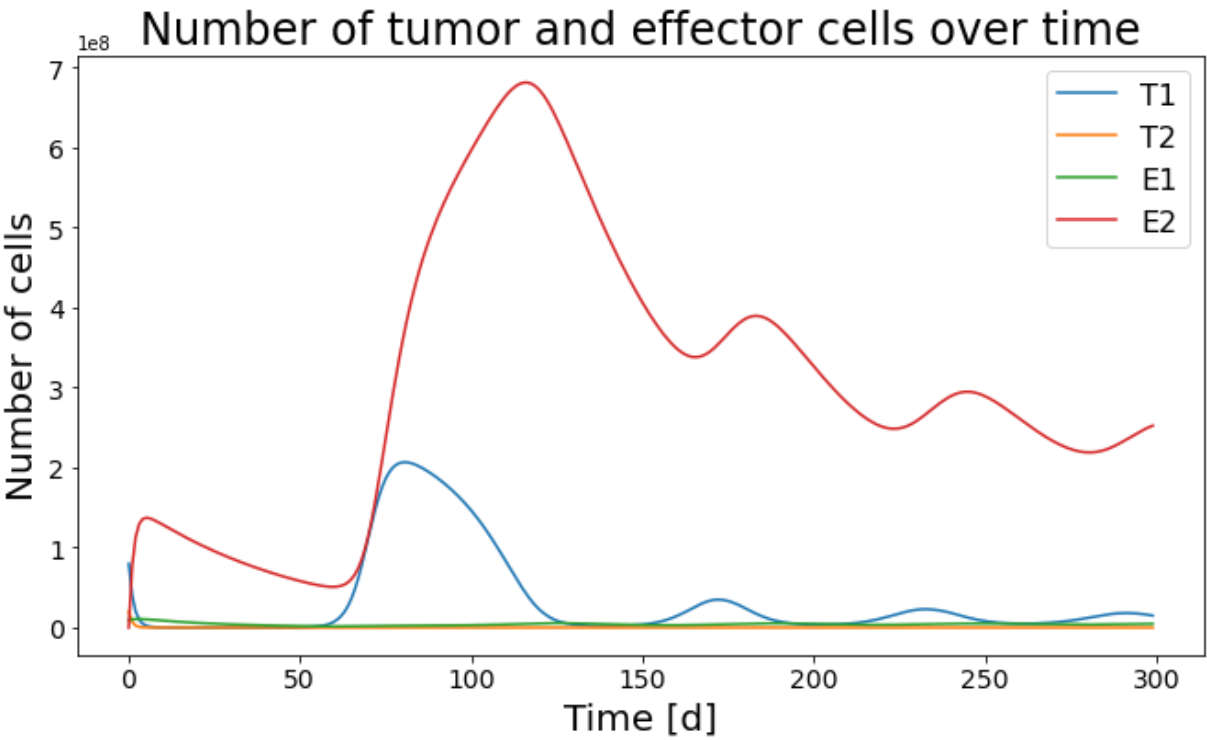
    plt.xlabel('Time [d]', fontsize=20) # the horizontal axis represents the time
    plt.ylabel('Number of cells', fontsize=20)
    plt.xticks(size=14)
    plt.yticks(size=14)
    plt.title('Number of tumor and effector cells over time', fontsize = 24)
    plt.legend(fontsize=16) # show how the colors correspond to the components of X
    fig.savefig('Output_ODE_test.jpg')
    plt.show()

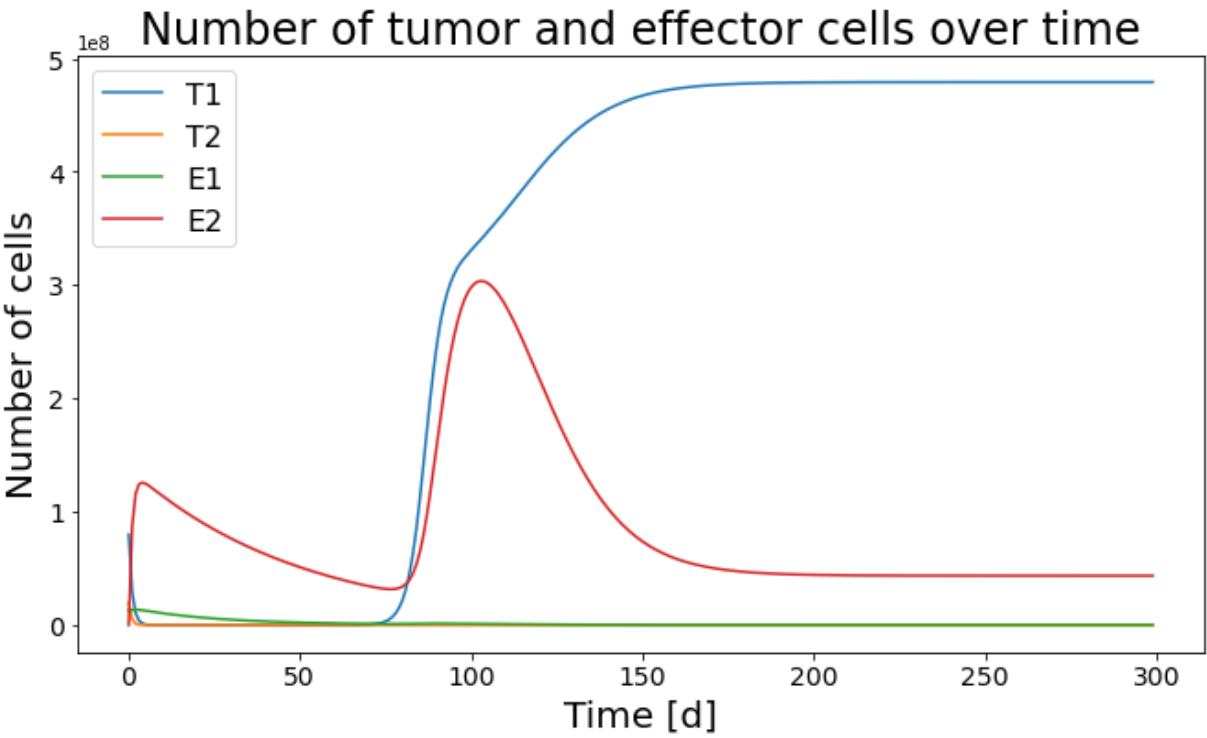
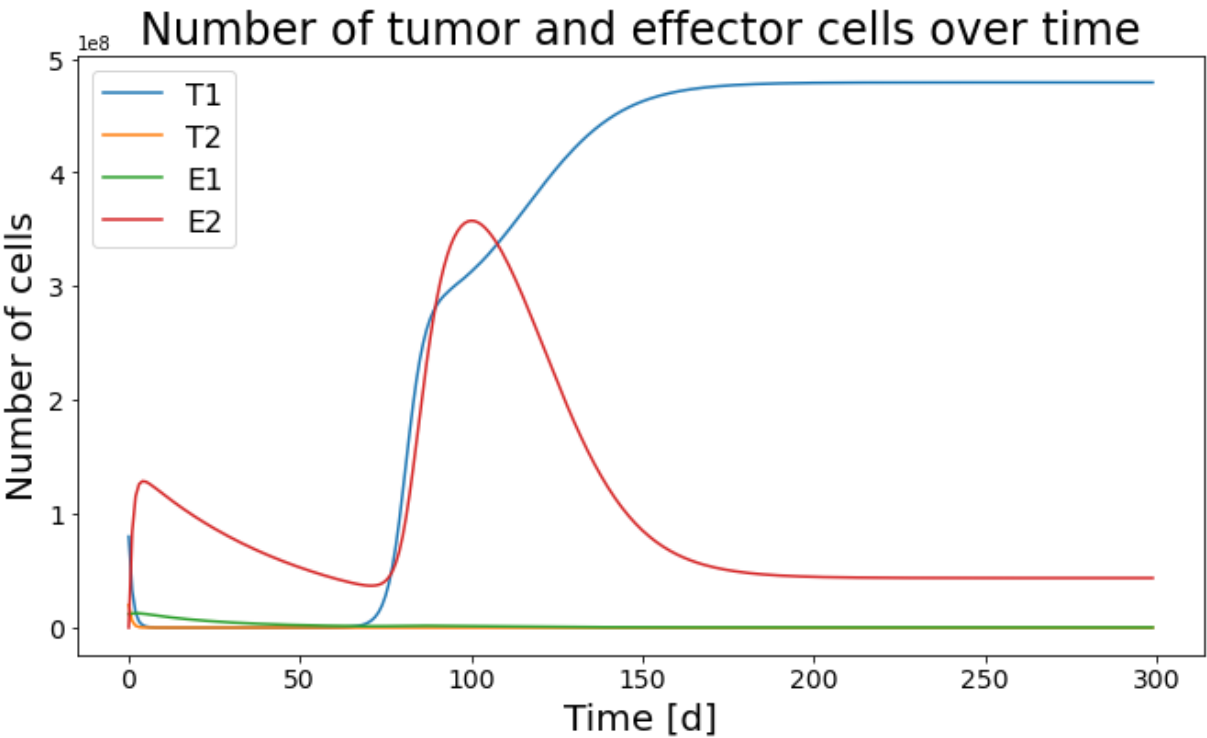
```

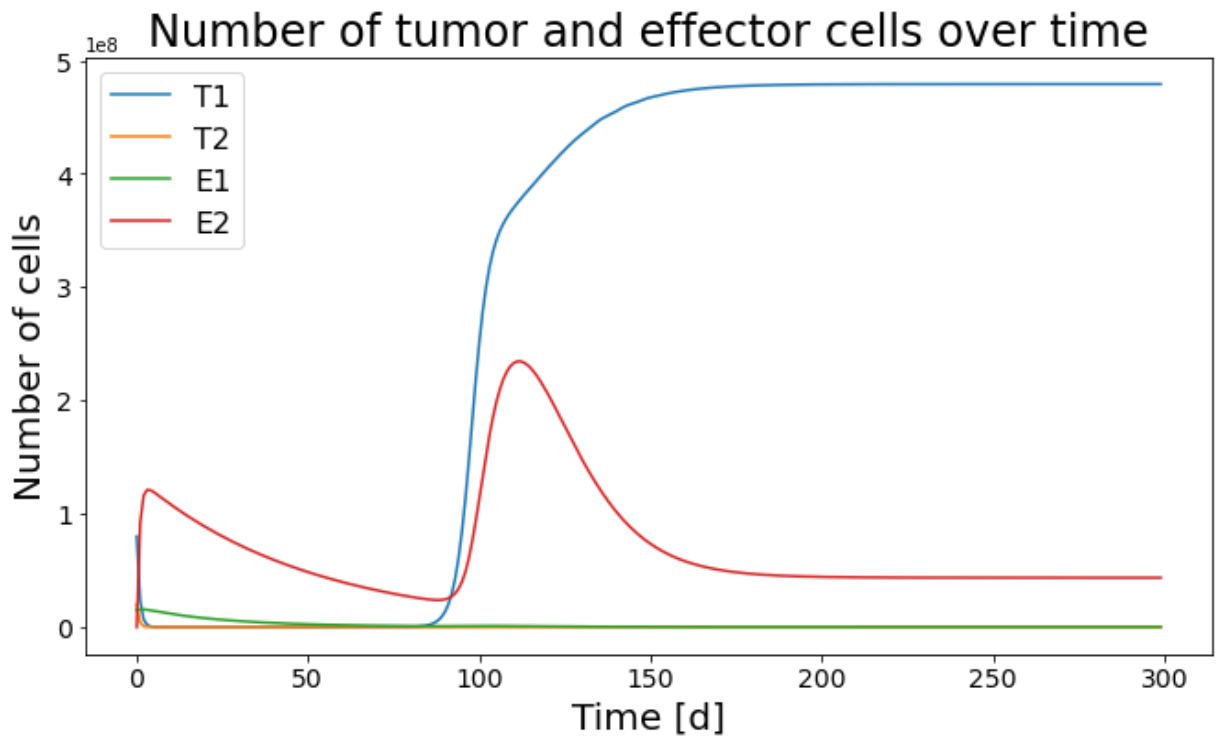
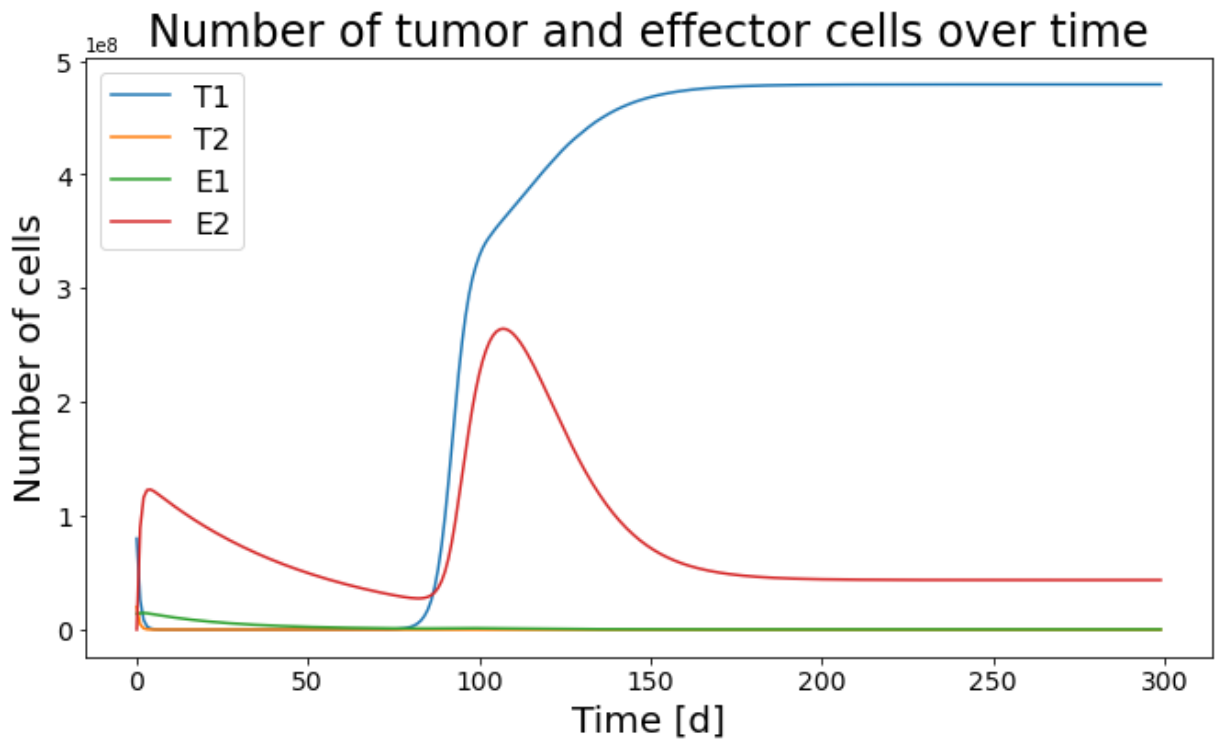












```
In [49]: values_at_t250 = [values_at_t250[i] for i in range(0, len(values_at_t250), 4)]
```

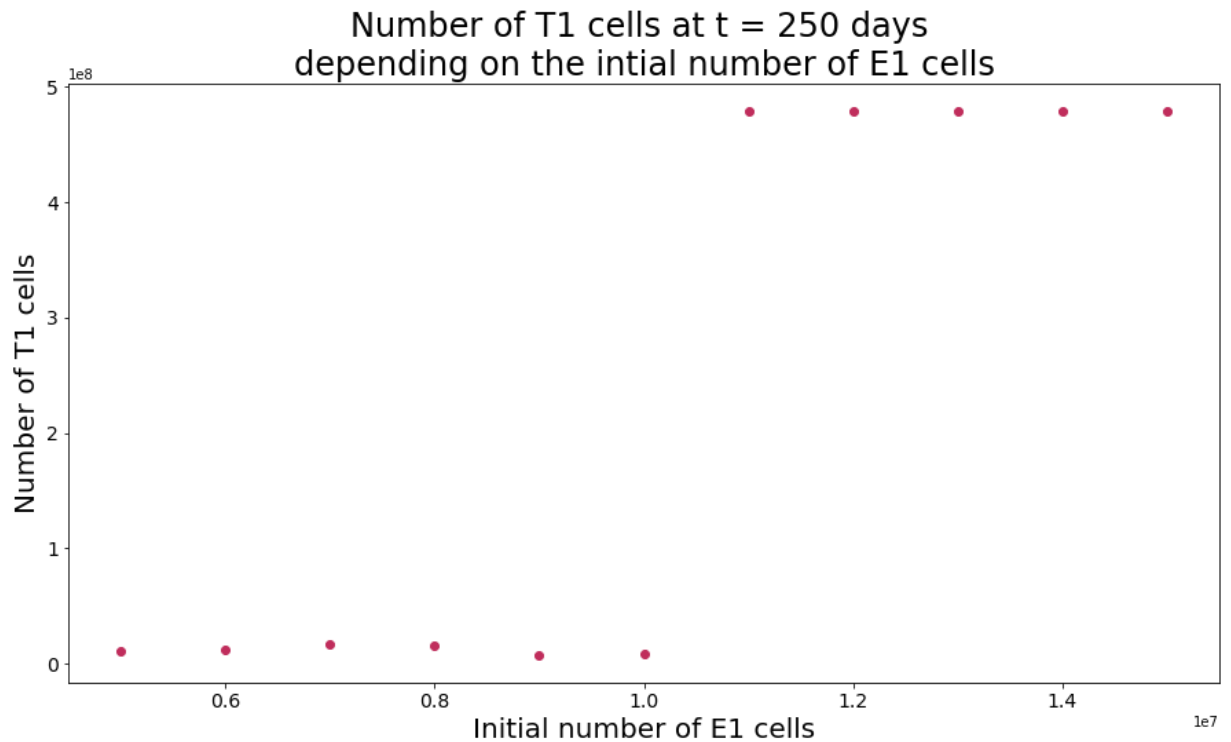
Plot the number of tumor cells against the number of initial E_1 cells.

```
In [55]: fig = plt.figure(figsize=(15,8))
plt.scatter(E1_list, values_at_t250, color='#c02d5c')

plt.xlabel('Initial number of E1 cells', fontsize=20) # the horizontal axis represen
plt.ylabel('Number of T1 cells', fontsize=20)
plt.xticks(size=14)
plt.yticks(size=14)
```



```
plt.title('Number of T1 cells at t = 250 days \ndepending on the intial number of E1
# show how the colors correspond to the components of X
fig.savefig('Sensitivity_E1.jpg')
plt.show()
```



Extract values for the number of tumor cells for two different initial E_1 values over time and plot phase diagram and number of tumor cells against time.

In [79]:

```
def ode_system(t, state, g1,g2,a11,a12,a21,p1,d1,d2,e1,e2,r1,r2,r3,s1,s2,i12,i21,K1,
    T1,T2,E1,E2 = state

    dT1dt = g1*T1*(1-T1/K1) - a11*E1*T1 - a12*E2*T1 - i12*T1*T2
    dT2dt = g2*T2*(1-T2/K2) - a21*E1*T2 - i21*T1*T2
    dE1dt = p1 - d1*E1 - e1*(T1+T2)*E1 + ((r1*(T1+T2))/(s1+T1+T2))*E1
    dE2dt = -d2*E2 - e2*T1*E2 + ((r2*T1)/(s2+T1))*E2 + r3*E1*(T1+T2)
    return [dT1dt, dT2dt, dE1dt, dE2dt]

g1 = 0.514
g2 = 0.35 * g1
a11 = 1.1e-7
a12 = 1.1e-10
a21 = a11
p1 = 1.3e4
d1 = 4.12e-2
d2 = 2.0e-2
e1 = 3.42e-10
e2 = e1
r1 = 1.24e-1
r2 = 1.24e-3
r3 = 1.1e-7
s1 = 2.02e7
s2 = s1
i12 = 1.1e-9
```

```

i21 = 1.5*i12
K1 = 5e8
K2 = K1

values = dict()

p = (g1,g2,a11,a12,a21,p1,d1,d2,e1,e2,r1,r2,r3,s1,s2,i12,i21,K1,K2)
E1_list = [1e7,1.2e7]
for i in range(len(E1_list)):
    E1 = E1_list[i]
    initial = [8.0e7,2.0e7,E1,0]

    t_span = (0, 300.0)
    t = np.arange(0, 300.0, 1)

    result_solve_ivp = solve_ivp(ode_system, t_span, initial, args=p, t_eval=t)

    labels = ['T1', 'T2', 'E1', 'E2']
    results = list()
    for i in range(result_solve_ivp.y.shape[0]):
        results.append(result_solve_ivp.y[i])
    values[E1] = results

```

In [67]:

```

#print(values[10000000][0])
tumor_cells = list()
E1_cells = list()
for i in range(len(values[10000000][0])):
    val = values[10000000][0][i] + values[10000000][1][i]
    tumor_cells.append(val)
    E1_cells.append(values[10000000][2][i])

tumor_cells_2 = list()
E1_cells_2 = list()
for i in range(len(values[12000000][0])):
    val = values[12000000][0][i] + values[12000000][1][i]
    tumor_cells_2.append(val)
    E1_cells_2.append(values[12000000][2][i])

```

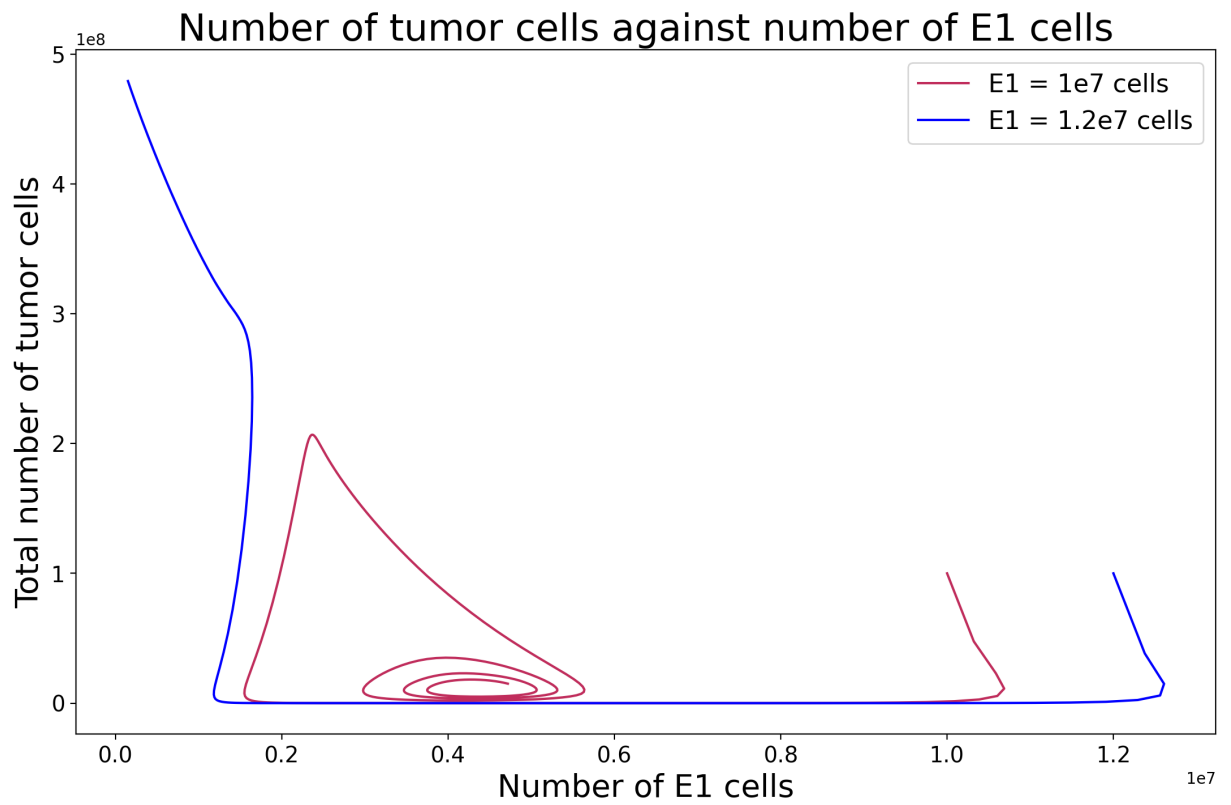
In [90]:

```

fig = plt.figure(figsize=(13,8), dpi=200)
plt.plot(E1_cells, tumor_cells, color='#c02d5c')
plt.plot(E1_cells_2, tumor_cells_2, color='blue')

labels=['E1 = 1e7 cells', 'E1 = 1.2e7 cells']
plt.xlabel('Number of E1 cells', fontsize=20) # the horizontal axis represents the t
plt.ylabel('Total number of tumor cells', fontsize=20)
plt.xticks(size=14)
plt.yticks(size=14)
plt.title('Number of tumor cells against number of E1 cells', fontsize = 24)
# show how the colors correspond to the components of X
plt.legend(labels, fontsize = 16)
fig.savefig('Phase_diagram.jpg')
plt.show()

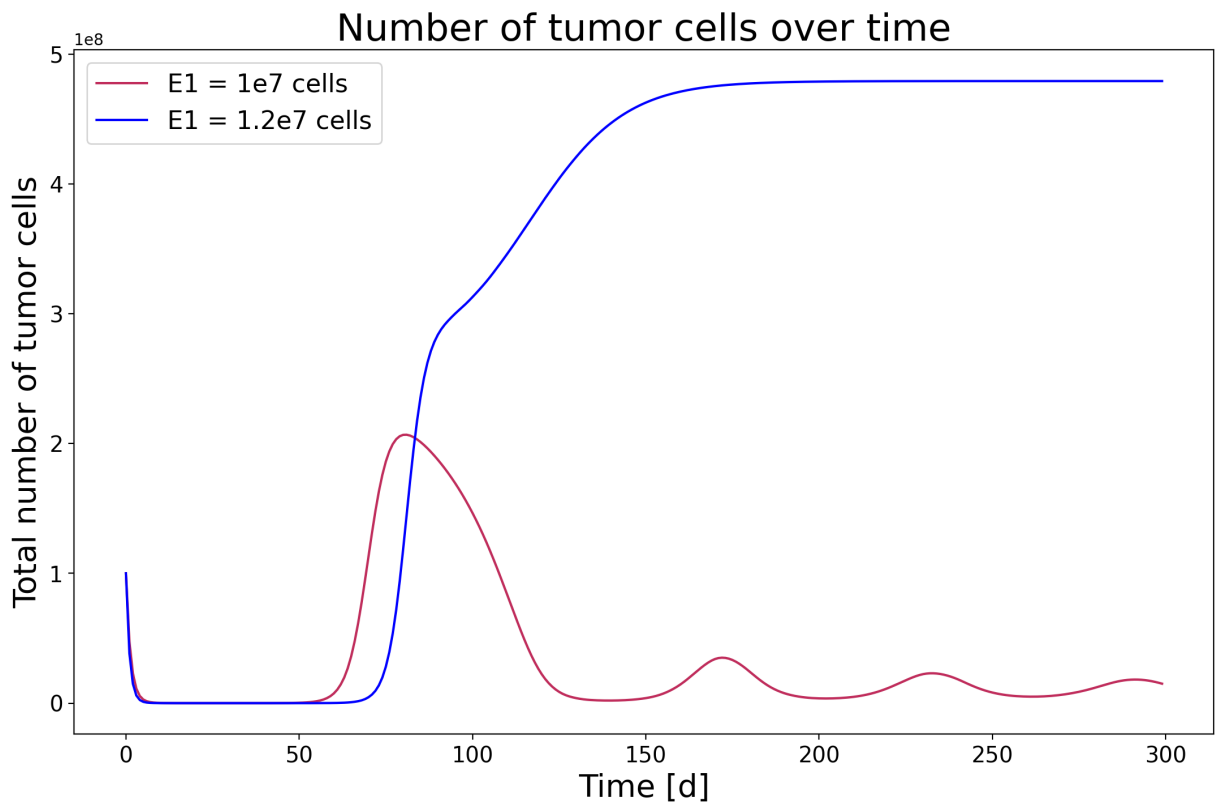
```



In [89]:

```
fig = plt.figure(figsize=(13,8), dpi=200)
plt.plot(t, tumor_cells, color='#c02d5c')
plt.plot(t, tumor_cells_2, color='blue')

plt.xlabel('Time [d]', fontsize=20) # the horizontal axis represents the time
plt.ylabel('Total number of tumor cells', fontsize=20)
plt.xticks(size=14)
plt.yticks(size=14)
plt.title('Number of tumor cells over time', fontsize = 24)
labels=['E1 = 1e7 cells', 'E1 = 1.2e7 cells']
plt.legend(labels, fontsize = 16)
fig.savefig('Tumor_dynamics.jpg')
plt.show()
```



Sensitivity analysis with Sobol's method using the SALib package

In [102...

```
def ode_system(t, state, g1, g2, a11, a12, a21, p1, d1, d2, e1, e2, r1, r2, r3, s1, s2, i12, i21, K1, K2, T1, T2, E1, E2) = state

    dT1dt = g1*T1*(1-T1/K1) - a11*E1*T1 - a12*E2*T1 - i12*T1*T2
    dT2dt = g2*T2*(1-T2/K2) - a21*E1*T2 - i21*T1*T2
    dE1dt = p1 - d1*E1 - e1*(T1+T2)*E1 + ((r1*(T1+T2))/(s1+T1+T2))*E1
    dE2dt = -d2*E2 - e2*T1*E2 + ((r2*T1)/(s2+T1))*E2 + r3*E1*(T1+T2)
    return [dT1dt, dT2dt, dE1dt, dE2dt]

g10 = 0.514
g20 = 0.35 * g10
a110 = 1.1e-7
a120 = 1.1e-10
a210 = a110
p10 = 1.3e4
d10 = 4.12e-2
d20 = 2.0e-2
e10 = 3.42e-10
e20 = e10
r10 = 1.24e-1
r20 = 1.24e-3
r30 = 1.1e-7
s10 = 2.02e7
s20 = s1
i120 = 1.1e-9
i210 = 1.5*i120
K10 = 5e8
K20 = K10
T10 = 8.0e7
T20 = 2.0e7
E10 = 1.1e7
E20 = 0
```

```

t_span = (0.0, 300.0)
t = np.arange(0.0, 300.0, 1)

result_solve_ivp = solve_ivp(ode_system, t_span, initial, args=p)

#definition of the problem settings
#the parameters as and the initial parameters for T1, T2, E1, and E2 are varied
problem = {
    'num_vars': 23,
    'names': ['g1', 'g2', 'a11', 'a12', 'a21', 'p1', 'd1', 'd2', 'e1', 'e2', 'r1', 'r2', 'r3', 's1', 's2', 's3', 'T1', 'T2', 'E1', 'E2'],
    'bounds': [[0.8*g10, 1.2*g10], [0.8*g20, 1.2*g20], [0.8*a110, 1.2*a110], [0.8*a120, 1.2*a120], [0.8*a210, 1.2*a210], [0.8*p10, 1.2*p10], [0.8*d10, 1.2*d10], [0.8*d20, 1.2*d20], [0.8*e10, 1.2*e10], [0.8*e20, 1.2*e20], [0.8*r10, 1.2*r10], [0.8*r20, 1.2*r20], [0.8*r30, 1.2*r30], [0.8*s10, 1.2*s10], [0.8*s20, 1.2*s20], [0.8*s30, 1.2*s30], [0.8*i120, 1.2*i120], [0.8*i210, 1.2*i210], [0.8*K10, 1.2*K10], [0.8*K20, 1.2*K20], [0.8*T20, 1.2*T20], [0.8*E10, 1.2*E10], [0, E10]]
}

#sampling with n = 10, leading to 480 samples
param_values = saltelli.sample(problem, 10)

#evaluation of the model
for i in range(len(param_values)):
    vals = param_values[i][:19]
    initial = param_values[i][19:]
    sol = solve_ivp(ode_system, t_span, initial, args=vals, t_eval=t)
    if i == 0:
        Y = sol.y
        #Y = sol.y.reshape((sol.y.shape[0]*sol.y.shape[1],1))
    else:
        #Y = np.append(Y, sol.y.reshape((sol.y.shape[0]*sol.y.shape[1],1)), axis=1)
        Y = np.append(Y, sol.y, axis=0)
print(Y.shape)
np.savetxt('test.out', Y, delimiter=',', fmt='%0.18f')

```

(1920, 300)

In [103...

```

#reading of the output file
values = np.loadtxt("test.out", delimiter=',', dtype=float)

```

In [104...

```

#sobel analysis for the problem
S_indices = [sobel.analyze(problem, Y) for Y in values.T]

```

In [105...

```

S_indices[250]

```

Out[105...

```

{'S1': array([ 0.02716781,  0.03724329,  0.68603832, -0.0108566 ,  0.02716781,
               0.03735469,  0.66113939,  0.14234826,  0.02716781,  0.0356917 ,
               0.53884975, -0.02050896,  0.02716781,  0.03738773,  0.69411509,
               0.01289318,  0.02716781,  0.03705073,  0.66797168,  0.15937505,
               0.02716781,  0.03574569,  0.56959616]),
 'S1_conf': array([0.28246723, 0.28228893, 0.4001919 , 0.16771533, 0.28246723,
                  0.28158532, 0.35682081, 0.14606378, 0.28246723, 0.28248444,
                  0.4040731 , 0.08436769, 0.28246723, 0.28221236, 0.39757994,
                  0.02322156, 0.28246723, 0.2823092 , 0.39876685, 0.24148875,
                  0.28246723, 0.28282834, 0.4076909 ]),
 'ST': array([1.39339353, 1.39152681, 1.66569817, 0.15472811, 1.39339353,
              1.38977886, 1.57912166, 0.22341332, 1.39339353, 1.38877079,
              1.5528489 , 0.19359589, 1.39339353, 1.38959036, 1.62418098,

```

```

0.00244128, 1.39339353, 1.39150177, 1.66896435, 0.17585036,
1.39339353, 1.39076777, 1.61627606]),
'ST_conf': array([0.35224733, 0.35234667, 0.17488881, 0.20148442, 0.35224733,
0.35156502, 0.21090305, 0.20420268, 0.35224733, 0.35134082,
0.17890132, 0.22677189, 0.35224733, 0.35211269, 0.17171705,
0.00275712, 0.35224733, 0.35231695, 0.17232569, 0.23716687,
0.35224733, 0.35227364, 0.18552178]),
'S2': array([[ nan, -0.29269115, -0.62840731, 1.73251232, -0.28276076,
-0.29099692, -0.53218296, 1.85318684, -0.28276076, -0.29125726,
-0.5837529 , 1.81497555, -0.28276076, -0.2920058 , -0.6501755 ,
1.88168104, -0.28276076, -0.29267954, -0.62239189, 1.57386473,
-0.28276076, -0.29008439, -0.49668357],
[ nan, nan, -0.73765196, -0.12765428, 0.43074142,
0.41321208, -0.71184934, -0.29255893, 0.43074142, 0.41489648,
-0.55630051, -0.10555761, 0.43074142, 0.41283557, -0.74655724,
-0.15256801, 0.43074142, 0.4136288 , -0.72395238, -0.31555408,
0.43074142, 0.41497791, -0.5943315 ],
[ nan, nan, nan, -0.77952017, -0.22448088,
-0.24172146, -1.34993836, -0.94562402, -0.22448088, -0.24003312,
-1.19473304, -0.75803021, -0.22448088, -0.24208435, -1.38418485,
-0.8056642 , -0.22448088, -0.24129404, -1.36148638, -0.966436 ,
-0.22448088, -0.23996292, -1.23336682],
[ nan, nan, nan, nan, 0.06200287,
0.06110934, -0.0268389 , -0.3244523 , 0.06200287, 0.06318648,
0.11722745, -0.15993682, 0.06200287, 0.0619492 , -0.00481126,
-0.18559052, 0.06200287, 0.06207987, 0.01705616, -0.19031917,
0.06200287, 0.06216235, 0.02666293],
[ nan, nan, nan, nan, nan,
-0.1166808 , -0.91595362, 1.38712838, -0.10130993, -0.11157578,
-0.64917098, 1.77642132, -0.10130993, -0.11635792, -0.91831104,
1.73122132, -0.10130993, -0.1157812 , -0.89478769, 1.52448669,
-0.10130993, -0.11433324, -0.77811498],
[ nan, nan, nan, nan, nan,
nan, -0.71196073, -0.29267032, 0.43063003, 0.41478509,
-0.55641191, -0.10566901, 0.43063003, 0.41272418, -0.74666864,
-0.1526794 , 0.43063003, 0.41351741, -0.72406377, -0.31566547,
0.43063003, 0.41486651, -0.5944429 ],
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The Sobol indices at the time $t = 250$ show the influences of the input variables and the initial values for T_1 , T_2 , E_1 , and E_2 on the values of the ODEs at that time. The 'ST' indices show the total influence of each input variable, taking first-order and higher-order interactions into account. The highest influence on the output values seem to have the third variable a_{11} , which stands for the elimination of tumor cells of type 1 by effector cells type 1, the 15th variable s_2 , the carrying capacity of tumor cell type 2, and the initial number of E_2 cells which all have values above 1.6. The smallest influences have the elimination rate of T_1 cells by E_2 cells and the influence that T_2 cells have on T_1 cells (i_{12}).

In []: