Constrained Optimization
Optimal Drug Injection for Cancer Treatment (4h)

Objective

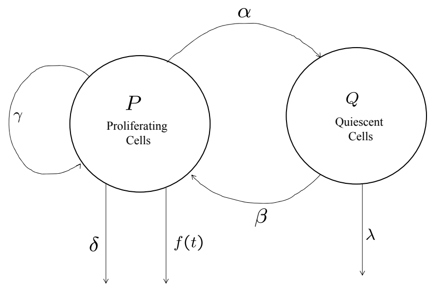
Solve an example of constrained optimal control problem. Learn how to define cost functions that are related to dynamic systems modelled by Ordinary Differential Equations. Use a non-linear constrained optimizer (FMINCON).

Problem Statement

The basic dilemma in cancer treatment by chemotherapy is to inject enough drug to reduce the population of proliferating cells while preserving the health of the patient. This is because drug also affects the healthy cells performance.

There are many models that intend to describe these effects. The following is one of the simplest one (see also the right Figure for a schematic view of the population model) :

$$\dot{P}(t) = [\gamma - \delta - \alpha - u(t)]P(t) + \beta Q(t) \quad (1)$$
$$\dot{Q}(t) = \alpha P(t) - (\lambda + \beta)Q(t) \quad (2)$$



Schematic view of the population model for cell-cycle specific chemotherapy

where :
- P : the number of proliferating cells
- Q : the of Quiescent (healthy) cells
- γ : the proliferating cells growth rate
- δ : the proliferating cells natural death rate
- α : the transition rate from proliferating state to the quiescent state
- β : the transition rate from quiescent to proliferating state
- λ : the cells differentiation rate (mature bone-marrow cells leaving the bone marrow to enter blood stream)
- $u(t)$ is the drug control variable that acts on the proliferating cells.

Note that if too much drug is injected P decreases too fast and leaves Q without any positive term. This mechanism leads to the negative side effect described above. To avoid that, the following optimization problem is defined for the treatment of duration T :

$$\min_{u(\cdot)} \Big[P(T) + \mu \cdot \int_0^T u(\tau)d\tau\Big]$$
$$\text{under the constraints } u(t) \in [0,1] \text{ and } P(t) + Q(t) \geq \rho \text{ for all } t \in [0,T] \quad (3)$$

where $P(T)$ is the number of proliferating cells at the end of the treatment and ρ is a lower bound on $P + Q$ as the condition $(\forall t) P(t) + Q(t) \geq \rho$ guarantees that the patient is not too diminished by the treatment.

The aim of this project is to provide a solution to this constrained optimization problem.

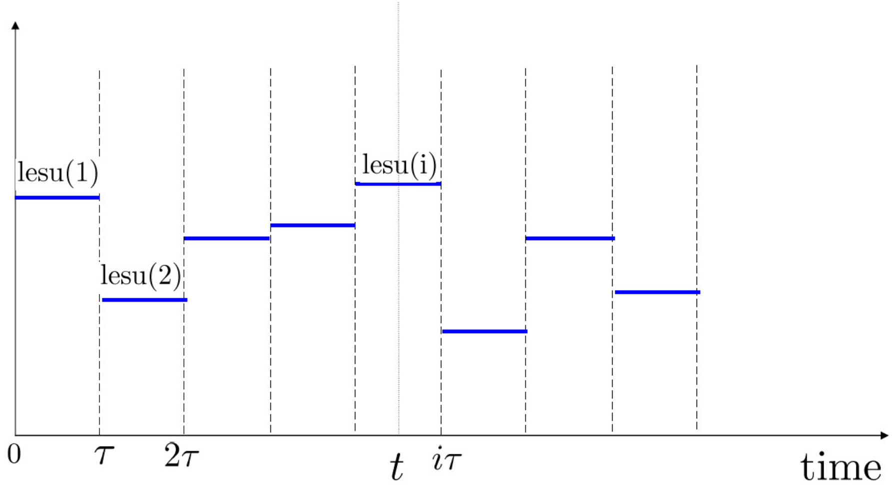
In this project, the numerical values proposed by [1] are used :

$$\gamma = 1.46 \ ; \ \alpha = 5.63 \ ; \ \lambda = 0.16 \ ; \ \delta = 0 \ ; \ \beta = 0.48 \ ; \ T = 30 \ ; \ \rho = 0.35 \ ; \ \mu = 10^{-3}$$

Questions

In order to do this project, you have to respect the following steps.

1. Create a main Matlab script, in which all the model coefficients α, β, etc are declared globally, [*Hint* : use the keyword ***global***].
2. Write a function that **selects** a control value $u(t) = lesu(i)$ where i is such that $t \in [(i-1)\frac{T}{N}, i\frac{T}{N}[$ from *lesu* which is a vector of N successive control actions defining a piecewise constant control (see the figure below).

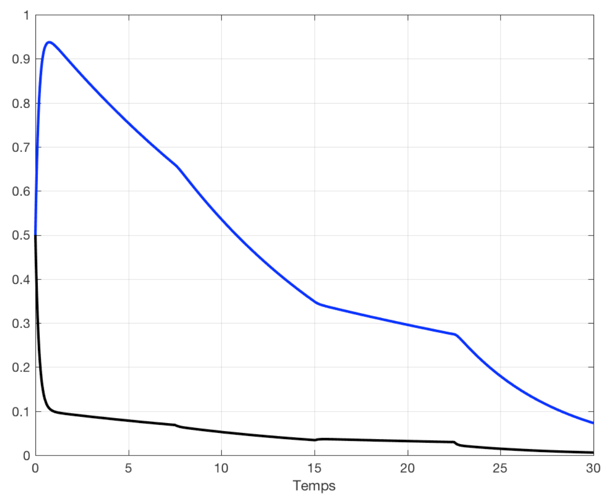


To verify for a vector *lesu=[0.5 ;0.8 ;0.3 ;1.9 ;0.54]*, the function u *=udet(T/3,lesu)* must gives a value of $u = 0.8$. Note that there are several ways to code this function .

3. Write a function that implements the ordinary differential equation (1)-(2) for use with the Matlab ODE solvers according to the following syntaxe :

xdot=my_ode(t,x,lesu)

where t is the simulation time, x is the state vector with P and Q as state variables, and *lesu* is the control sequence. **To verify** for the same vector *lesu=[0.5 ;0.8 ;0.3 ;1.9 ;0.54]*, the following code *[tt,xx]=ode45(@my_ode,[0 T],[P0 Q0],[ ],lesu) ;* will give the following figure.



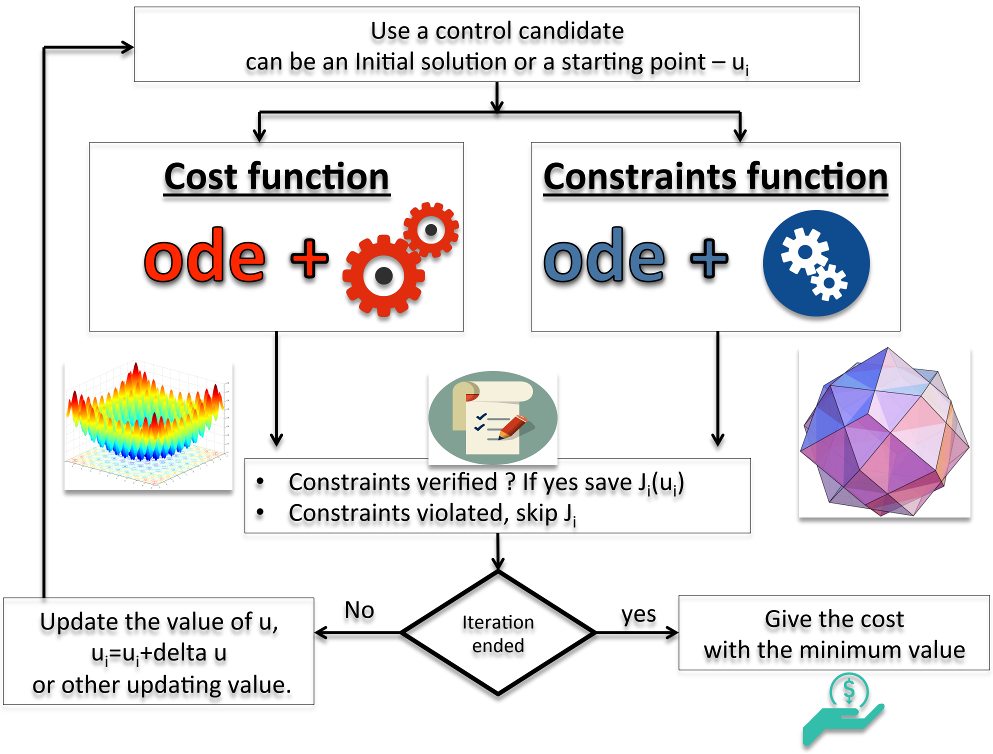
4. Using the above function, write a function that implements the cost function of the equation (3) for use with the Matlab optimizer fmincon, namely

J=cost(lesu)

[Hint : here again, the initial state x_0 must be fed as a global variable as well as the treatment duration T, etc.]

5. Write a function that compute the constraints defined in the optimization problem (3) according to the syntaxe required by FMINCON. Please read the documentation of this function by using the doc function. Note that you have to declare the equality and inequality constraints.

6. Compute the optimal Drug injection strategies for $P(0) = Q(0) = 0.5$ and the following different values of $N \in \{2, 5, 10\}$ and starting from the *initial quess lesu=(0,0,. . .,0)*. For each case, plot the resulting optimal solution (evolution of P, Q, $P + Q$ and u). Refer to the figure belwo to understand the algorithm of FMINCON



7. Repeat the preceding question using randomly generated initial guesses for *lesu*.

8. Repeat the preceding question using successively $\mu = 0.01$ and $\mu = 0.1$. Explain the results.

9. Give all the observations you find relevant concerning your experimentation.

References

[1] K. R. Fister and J. C. Panetta. *Optimal control applied to cell-cycle specific cancer chemotherapy. SIAM Journal on Applied Mathematics, 60 (3) :1059-1072, 2002.*