Optimal Drug Concentrations
Course Project Details

Project: Develop a numerical software package that will return the optimal drug concentration and two of the effect values when the third effect value and the effect weights are given. This is a three stage project. Let d_1 and d_2 denote the two drug concentrations. Let e_1, e_2, e_3 denote the effect values and a_1, a_2, a_3 denote the effect weights. For the given effect value e_3^* you must numerically solve the effect equation for d_2 given the drug concentration for d_1. Now suppose you take n possible values for the concentration d_1, d_1^j for $j = 1, \ldots, n$, then you will numerically obtain n concentrations of d_2, d_2^j for $j = 1, \ldots, n$, that will produce the desired effect e_3^*. Using the n points $(d_1^j, d_2^j), j = 1, \ldots, n$, the second task is to generate a cubic spline, P_3, that interpolates these points for effect e_3^*. Now you have a polynomial P_3 that will return all possible values of d_2 given d_1 such that effect e_3^* is achieved. Using these potential combinations of the two drugs, minimize the function

$$a_1 e_1 - a_2 e_2 + a_3 e_3^*.$$

The desired effects are e_1: sedation (measures time to wake up of patient), e_2: pain suppression (measures time to when patient begins to feel pain), and e_3: muscle response (measures time to when patients muscles respond properly to normal stimulation). The drug whose concentration is represented by d_1 is Remifentanil which has a range of concentrations from 0-40 nanograms/ml. The drug whose concentration is represented by d_2 is Propofol which has a range of concentrations from 0-8 micrograms/ml.

The equations describing the desired effects have the general form

$$e_i(d_1, d_2) = \frac{\left(\frac{d_1}{C_{1,i}} + \frac{d_2}{C_{2,i}} + \alpha_i \frac{d_1 d_2}{C_{1,i} C_{2,i}}\right)^{\beta_i}}{\left(\frac{d_1}{C_{1,i}} + \frac{d_2}{C_{2,i}} + \alpha_i \frac{d_1 d_2}{C_{1,i} C_{2,i}}\right)^{\beta_i} + 1} \tag{1}$$

where the values for $C_{1,i}, C_{2,i}, \alpha_i$, and β_i are given in the table.

i	$C_{1,i}$	$C_{2,i}$	α_i	β_i
1	33.1	2.2	3.65	4.99
2	8.84	4.16	8.2	8.34
3	21.3	4.57	14.7	6

Notes: The difference of scale in measurements is taken into consideration in the effect equations and is therefore irrelevant for your analysis (e.g. use the value 10 for 10 nanograms/ml). You may assume that smaller effect values produce better effect results for i=1,3 and higher values are better for $i = 2$ (thus the negation in the equation to be minimized). Therefore, your project is to minimize the weighted effect equation:

$$\text{minimize} \quad a_1 e_1 - a_2 e_2 + a_3 e_3 \tag{2}$$

where $a_1 + a_2 + a_3 = 1$ and e_1, e_2 are computed using the d_2 values obtained from the cubic spline $P_3(d_1)$.

A POSSIBLE OUTLINE

Your function should take the inputs e_3^*, a_1, a_2, a_3.

Sample values (d_1^k, d_2^k), for say $k = 1, \ldots, 11$ where d_2^k is the solution to the equation $e_3^* = e_3(d_1^k, x)$.

Create a free cubic spline that interpolates $\left\{(d_1^k, d_2^k)\right\}_{k=1}^{11}$.

Write a function $func(e_3^*, d_1)$ that is the cubic spline returning values d_2 for any $d_1 \in [0, 40]$. Use your code for false postion or the secant method on the function $e_3(d_1, x) - e_3^*$ to solve the function.

Now you want to minimize the equation

$$a_1 e_1 \left(d_1, func(e_3^*, d_1)\right) - a_2 e_2 \left(d_1, func(e_3^*, d_1)\right) + a_3 e_3^*.$$

There is a MatLab function **fminsearch** that you might use to find the minimizer $\bar{d_1}$ to the above equation and then $\bar{d_2} = func(e_3^*, \bar{d_1})$.

Now return the values $\bar{d_1}, \bar{d_2}, \bar{e_1} = e_1(\bar{d_1}, \bar{d_2})$, and $\bar{e_2} = e_2(\bar{d_1}, \bar{d_2})$. These values will tell us the the drug concentration that satisfies e_3^* and the effects $\bar{e_1}$, $\bar{e_2}$ which minimize our objective function. Minimizing the objective function will give us a combination that minimizes e_1 (time to wake up) and mazimizes $\bar{e_1}$ (time to feeling pain).

If you have the time and desire, modify your software so that we can fix any desired effect e_i^* and obtain a drug combination that will produce the best effects of the two remaining effects. This is not necessary, but it would be a very nice addition to the project and should be relatively easy to do (as it should only require you to change some indices).