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

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

where the values for \( C_{1,i}, C_{2,i}, \alpha_i, \) and \( \beta_i \) are given in the table.

<table>
<thead>
<tr>
<th></th>
<th>( C_{1,i} )</th>
<th>( C_{2,i} )</th>
<th>( \alpha_i )</th>
<th>( \beta_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>2.2</td>
<td>3.65</td>
<td>4.99</td>
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<tr>
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<td>8.84</td>
<td>4.16</td>
<td>8.2</td>
<td>8.34</td>
</tr>
<tr>
<td>3</td>
<td>21.3</td>
<td>4.57</td>
<td>14.7</td>
<td>6</td>
</tr>
</tbody>
</table>

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:

\[
\text{minimize } a_1 e_1 - a_2 e_2 + a_3 e_3^n
\]

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 $(d^k_1, d^k_2)$, for say $k = 1, \ldots, 11$ where $d^k_2$ is the solution to the equation $e^*_3 = e_3(d^k_1, x)$.

Create a free cubic spline that interpolates $\{(d^k_1, d^k_2)\}_{k=1}^{11}$.

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 position 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

$$a_1 e_1(d_1, func(e^*_3, d_1)) - a_2 e_2(d_1, func(e^*_3, d_1)) + a_3 e^*_3.$$

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 maximizes $\bar{e}_1$ (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).