Numerical Analysis of Theophylline Pharmacokinetics Using Cubic Spline Interpolation, Extrapolation, and Newton's Root-Finding Method

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I Introduction

We are interested in exploring how numerical computation methods can be used to improve drug performance and reduce the risk of over-prescribing medication. Giving patients more pills than they need is not only inefficient and costly, but can also lead to misuse or long-term storage of unnecessary medication. By analyzing dosage patterns and identifying when a certain drug's minimum effective concentration fall to certain threshold, we can help eliminate unnecessary doses and improve treatment.

For readers unfamiliar with this area, it's helpful to understand that we are working with pharmacokinetic data. Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolized, and eliminated from the body.

We are using a pharmacokinetics dataset of the anti-asthmatic drug theophylline. Theophylline is a medication that is primarily used as a bronchodilator. It's is prescribed to treat chronic respiratory diseases such as asthma and emphysema. Theophylline's purpose is to help relax and open the airways in the lungs.

An oral dose of theophylline was administered to each of the twelve patients. The data provides details about serum concentration over a time of approximately 25 hours. Additionally, the dataset includes each patient's body measurements. The dataset in CSV format was borrowed from Johar M. Ashfaque through the website Kaggle.com. However, Boeckmann, Sheiner, and Beal (1994) reported the data from a study by Dr. Robert Upton. The data is experimental.

Analysis of the data for each of the twelve patients can help us understand the trends of the drug effectiveness given weight, dosage, or both. Questions we hope to answer include:

- **We are interested in finding a trend between bodily comorbidity and drug concentration over time. Bodily comorbidity is an umbrella term for metabolic rate, diabetes, high blood pressure, and more. In order to test this, we can analyze if weight and dose show a trend in the rate at which theophylline concentration decreases over time. If there is a clear trend, it implies weight and dose are the leading factors; however, if there is not a clear trend, it implies that other factors such as bodily comorbidity play a larger role and should be tested.**
- **At what approximate time does concentration reach a certain threshold of 0.5mg/L for each of the twelve patients? The MEC (minimum effective concentration for theophylline) is 0.5mg/L.**
- **Does dosage level increase the effectiveness of theophylline?**

II Methods

To make the dataset cooperative to analysis, we used `pandas` to extract and sort the `Time` and `conc` values by subject. We then used `NumPy` to convert these pandas Series into NumPy arrays, making them compatible with mathematical modeling tools such as cubic spline interpolation and Newton's method.

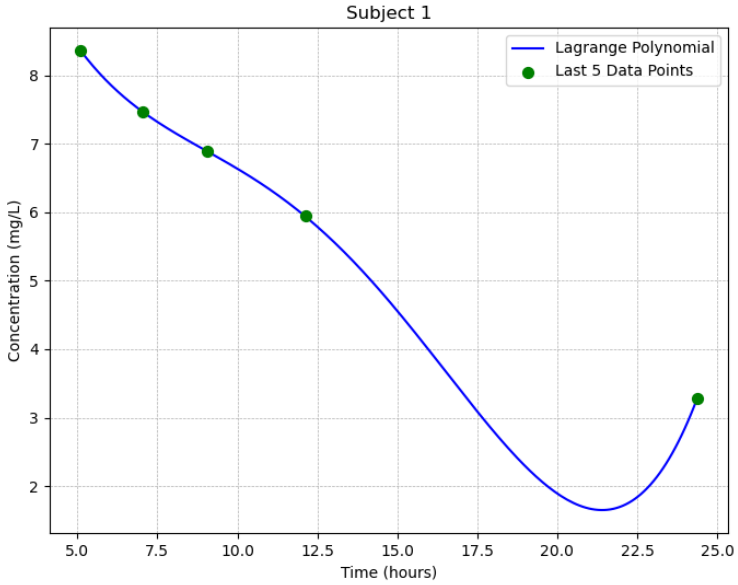
As part of our data analysis process, we constructed cubic spline interpolations of the time/concentration trend for each of the twelve patients using the last four available data points. We used four data points to avoid Runge's phenomenon, which can increase oscillation from overfitting. Additionally, we chose the last four points because they are the closest to the MEC, and evaluating less data points helps reduce time complexity. We enabled extrapolation as a parameter in the spline function call in order to simulate the drug's behavior beyond the given recorded twenty-five hour range. We made the new range thirty-eight hours. This allowed us to estimate the full elimination polynomial of theophylline since none of the observed concentration data drop below the MEC of 0.5 mg/L.

Previously, in our first approach, we attempted to use Lagrange interpolation to plot our subject polynomials; however, this approach still invoked Runge's phenomenon, even when not all data points were used. Lagrange interpolation also did not allow us to extrapolate past our given data.

The interpolated curves were visualized using `Matplotlib`, with each graph displaying the original data points, interpolated data points, smooth spline interpolation, and a dotted line representing the MEC threshold.

To estimate when the theophylline concentration fell below the MEC, we applied Newton's method to the spline function closest to the MEC threshold. Newton's method is designed to find the root of a function at which $f(x) = 0$. Because the MEC threshold we are approximating is 0.5 mg/L, we had to adjust our Newton's method formula. The new function we are finding the root of is: $f(x) = 0.5$.

II.I First Approach



The graph above depicts the aggressive oscillation at approximately twenty-one hours. This oscillation is caused by interpolation at the end points, and depicts Runge's phenomenon. The polynomial does not extend beyond the given data points; therefore, we can not approximate the threshold.

II.II Relevant Code Implementation

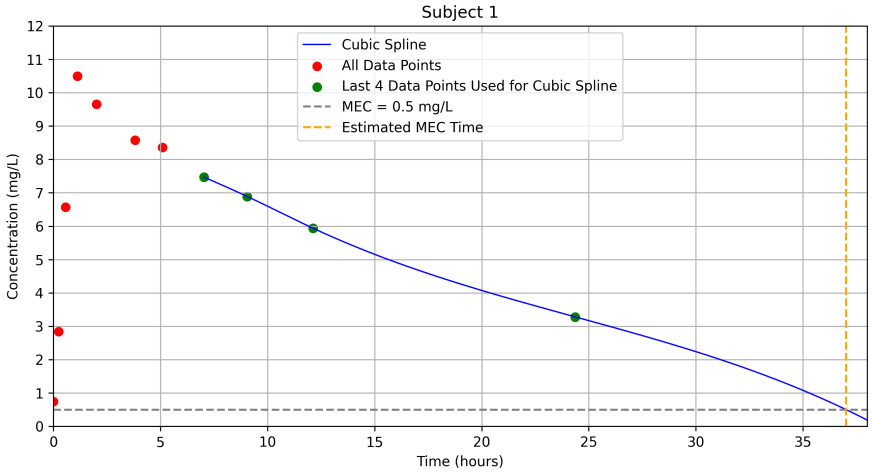
```
# Process each subject. Data frame is in increasing time order.
for subject in subject_ids:

    # Create cubic spline. Extrapolate past the given data points.
    cs = CubicSpline(x_subset, y_subset, bc_type='natural',
        extrapolate=True)

    # Construct sub-spline poly for Newton's method.
    x = sp.Symbol('x')
    subspline_equ = a * (x - subspline)**3+ b * (x - subspline)**2
        + c * (x - subspline)+ d

    # Apply Newton's method.
    root = newtonsMethodWithTarget(subspline_equ, x_points[len(
        x_points)-1], n=10, target=0.5)

    # Evaluate full spline for plotting.
    x_fine = np.linspace(x_subset[0],38, 200)
    y_fine = cs(x_fine)
```

Full Source Code: The complete implementation and plotting scripts: `https://github.com/davismann/Numerical-Analysis-Theoph.git`

III Results

Through analysis of our results, we accurately found the approximate time at which each patient's serum concentration reached the MEC of 0.5 mg/L. Additionally, the polynomials constructed for each patient allowed us to dissect the critical trends in drug elimination. Below are each patient's polynomial graph and a table including each patient's weight, dose, and the corresponding times at which their concentration reached the MEC threshold.

III.I Sample Subject Graph



The graph above represents a smooth polynomial of subject one's concentration/time using cubic spline interpolation. There is no aggressive oscillation in the overall polynomial because cubic spline ensures that each piecewise polynomial's second and first derivatives match at the connecting points.

All Subject Graphs: The complete set of subject graphs: `https://github.com/davismann/Numerical-Analysis-Theoph/tree/main/Subject-Outputs`

III.II Subject Table

Subject	Weight (kg)	Dose (mg)	Estimated MEC Time (hours)
5	54.6	5.86	31.582
10	58.2	5.5	32.250
12	60.5	5.3	28.154
7	64.6	4.95	27.844
11	65.0	4.92	27.353
3	70.5	4.53	28.047
8	70.5	4.53	33.942
2	72.4	4.4	30.774
4	72.7	4.4	28.541
1	79.6	4.02	37.016
6	80.0	4.0	27.073
9	86.4	3.1	31.770

III.III Evaluation of Results

Prior to running a numerical analysis on our data, we dissected that as time increases concentration decreases, and that an increase in dose invokes an increase in concentration (higher peak concentration than lower doses). After analysis of our subject output graphs and subject table, we have all the relevant information to answer these questions:

- **Does an increase in body weight cause the concentration level of theophylline in the serum to decrease at a slower rate?**

  There is an inconsistent trend between body weight and the decrease in the concentration of theophylline. For example, Subject 1 (79.6 kg) reached MEC at 37.016 hours, while Subject 4 (72.7 kg) reached it at 28.54 hours, despite receiving a larger dose. However, Subject 7 (64.6 kg) had a longer duration of 27.844 hours before reaching the MEC, while Subject 11 (65.0 kg) had a shorter duration of 27.353 hours, despite having near-exact doses. This indicates that body weight may influence serum concentration decline. However, it is not the leading factor. This indicates that body comorbidity variables are more important than subject's weight.

- **Does dosage level increase the effectiveness of theophylline?**

  Yes, sometimes subjects who received higher doses of theophylline had a higher time at MEC. For instance, Subject 10 (5.5 mg dose) reached MEC at 32.250 hours, and Subject 12 (5.3 mg dose) at 28.154 hours, despite having almost the exact weight. In contrast, Subject 3 (70.5 kg), who received 4.53 mg, reached MEC sooner at 28.047 hours, than Subject 8 (70.5 kg) who received the same dose yet reached the MEC later at

33.942 hours. These trend supports the conclusion that higher dosages can sometimes increase the duration of the drug's effectiveness; however, metabolic rate plays a vital role.

IV Conclusion

Since we concluded that there is no definitive evidence to suggest that weight and dosage are always proportional to the effectiveness of theophylline, we assume that bodily comorbidity variables are the leading factor. Some trends from the graphs suggest that weight and dosage can play a role in the effectiveness; however, factors like metabolism rate, blood pressure, age, and other health conditions can alter these findings. On the contrary, we did find a simple way to effectively find the time when the MEC falls to 0.5 mg/L using cubic spline extrapolation, interpolation, and a modified Newton's root-finding method. This information could help medical personnel effectively distribute the right amount of pills, given the current dosage plan.

We can extend this research by gathering other criteria from the patients, such as metabolic rate, age, and liver function, to better understand the trends from the table. In the future, we can apply this numerical approach to a field of research that involves drug use for the effectiveness of weight loss. A dataset of a pharmaceutical drug such as Semaglutide could give us insight into whether starting weight and age play a role in the weight-loss process. Additionally, if subjects are prescribed drugs used in the past, previous MEC time approximations using numerical computation methods can be used to accurately predict the time their blood concentration hits the MEC value, and the prescription amount.

Sources

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