MA 131-Project

Pharmaceuticals play a major role in society today. A recent study conducted at the Mayo Clinic suggests that nearly 70% of Americans are on least one prescription drug. Many of these drugs are administered orally and absorbed into the blood stream through the digestive system. The effectiveness of most of these drugs depends on the concentration of the drug in the blood plasma. If the concentration of the drug in the blood is too low (below the *minimum effective concentration for desired response* or MEC), a patient will not benefit from the therapeutic effects of the drug. If the concentration becomes too high (above the *minimum effective concentration for adverse response*) the drug may have a toxic effect on the patient, causing sickness or even death. One of the challenges of choosing an appropriate dosage for patients is to administer enough drug to be therapeutic but not so much as to be toxic.

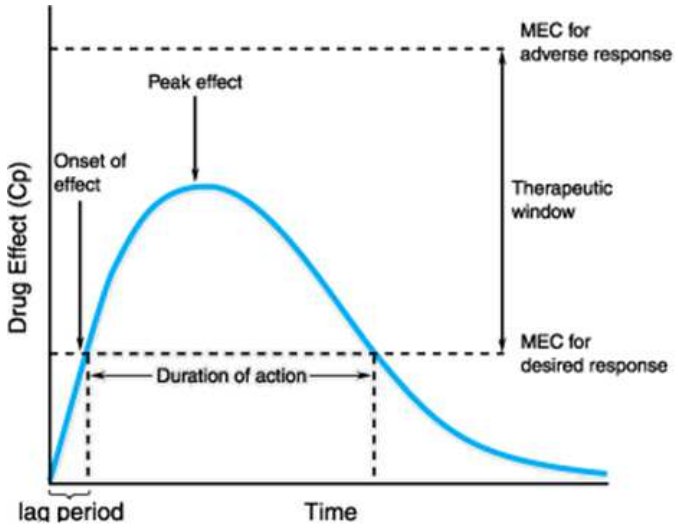

Figure 1: Temporal characteristics of drug effect and relationship to the therapeutic window.

For a drug that is administered orally (in tablet form), we can model the blood plasma concentration over time $C(t)$ of the drug using the formula

$$C(t) = \frac{D * F * k_a}{V_d(k_a - \lambda)}\left(e^{-\lambda t} - e^{-k_a t}\right)$$

where

- D is the dosage of the drug in g, mg, or μg
- F is the *bioavailability* of the drug
- V_d is the *volume of distribution* of the drug
- k_a is the constant of absorption (related to the rate at which the drug is absorbed into the plasma)
- λ is the constant of clearance (related to the rate at which the drug is cleared from the plasma)

Your group has been asked to analyze the drug *acetaminophen*. Acetaminophen is an over-the-counter pain reliever and fever reducer. Attached you will find a data set showing the clinical concentrations of the drug over an 12 hour time window for an average patient. The patient was initially administered a 1g dose, and we estimate the bioavailability of acetaminophen to be 0.9. The therapeutic window for acetaminophen is 5-20 mg/L.

Project Requirements

1. Do some background research on your drug. Include an introductory section in your paper giving the reader a summary of your research (2-3 paragraphs).
2. Use your data to estimate the parameters λ, k_a, and V_d.
3. With the parameters you found in (2) estimate:
    a. the time to onset
    b. time to peak concentration
    c. peak concentration
    d. intensity
    e. duration of effect
    f. the time it takes for the patient to clear the drug from their system.

    (Do not use the data for this: use the model.)
4. Determine how sensitive your solutions in (3) are to:
    a. absorption rate
    b. clearance rate
    c. volume of distribution.

    That is, how do outcomes like time to onset, time to peak concentration, peak concentration, intensity, duration of effect, and time to clear the drug form the system change if the parameters change? (It's been observed clinically that λ and k_a may vary by up to 25%, and V_d may vary by as much as 30% from patient to patient).

    A good way to start analyzing sensitivity of your model to a parameter is to see how much an output value changes when you change the parameter. For instance, if you change a parameter by 1%, by what percent does the output change?
5. Determine how sensitive your solutions in (3) are to dosage and bioavailability? According to the manufacturer, acetaminophen has a bioavailability in the range of 0.85 to 0.95 and comes in doses of 325mg, 500mg, and 1000mg.
6. Recommend a dosing regimen to keep the patient safely within the therapeutic window. Justify your plan using your answers from parts (2) through (5)

Project Deadlines

There are two components to your final project solution.

1. A 10-minute formal presentation. (See "Guidelines" for details).
2. A formal written report.

Presentations will take place on Monday, December 8 and Tuesday, December 9 during class. The formal written report is due by Saturday, December 13 before 1:00pm.

Project Guidelines

You must work in groups of 2 or 3 students. You should turn in one written report for your group, and your oral presentation will be done as a group. Every student should have some part in the oral presentation, and the presentation should be done with Power Point.

The main purpose of a paper in mathematics is to explain a series of calculations, so that the reader can clearly understand what math is being done and why. Explaining your math is the heart and soul of your paper. A good paper will often alternate between an equation and a paragraph explaining exactly what is being done and the purpose of this calculation. Your written report should be done in Microsoft Word, using equation editor, or some other comparable word processor with mathematics capabilities. It must be broken into sections (beginning with section titles in large bold letters), including an **introduction**, a **conclusion**, and **references**. You should use the introduction to briefly summarize the problem in your own words and set the stage for your paper. In the conclusion you should summarize your results and tie things together. Your textbook should be listed as a reference, as should any other sources (books or web sites) you consult.

One other requirement for the written report is that is must begin with a **one-page summary**. This should be an abstract, a brief overview of your entire project, including a very short problem description (shorter than in the introduction), the main methodologies used, and a brief statement of the main results you achieved. Think of this as possibly the only part of your report that a senior manager might read. It needs to clearly and succinctly summarize what you have done.

No rough draft is required, but I strongly encourage all groups to schedule a meeting with me to discuss the project and presentation.

Some Writing Suggestions

Write in the first person, and use the active voice whenever reasonable. For example, rather than, “It was discovered that…”, write “We discovered…”.

Show your equations and figures clearly. Label all tables and figures, and be sure to explain them in the text. If a figure or table isn’t explained in the text, then it should not be included in the paper. Plots should clearly label both the x and y axes.

The paper should be more than just a list of answers to homework-style questions – it should tell the story of your project. It is not necessary, nor even desirable, to list the number of the question you are answering. Instead, collect your answers and tell your story with them. Also, feel free to let your personality shine through; it’s great to insert humor or invent characters to support your problem scenario.

Spelling and grammar count – proofread carefully!

The introduction and conclusion should *not* be judgments about the problem – refrain from saying, for example, "In conclusion, this was a worthwhile project. I learned a lot." Your introduction should set the stage for your paper – sort of an overview of the problem. Your conclusion should tie together the paper and highlight the major result(s).

Some Presentation Suggestions

Have fun making your slides, but beware of getting so fancy that it detracts from your content. Very plain slides with no moving words are perfectly acceptable.

You will probably not have time during your presentation to discuss every aspect of your problem. Do be sure, though, that you appropriately introduce your problem.

Make sure you can access your presentation in two different ways (for example, from your X drive and on a flash drive). I have seen several groups in the past have trouble with corrupted disks. You are responsible for having your presentation in working order at the time you are scheduled to present.

Contributions, References, Plagiarism, & Integrity

Each team must submit a page, signed by all team members, either stating that all team members contributed equally to the project or offering an explanation and relative efforts if contributions were not equal. All papers must contain a "References" section in the APA style that lists our textbook: Our text was the original source of most of the techniques that you will use in this project. If you get any other help on this project from other books, web sites, other student work/papers, or even if you talk to other classmates outside of your team, you need to include these in your reference section, acknowledging that not everything in your paper was your own original idea. It is very important that there is no file sharing, of Word documents, Matlab commands, or any other electronic files of any kind: That is considered cheating. You and your team must type in everything yourselves, into Word, into Matlab, and any other tools that you may use. You may talk to your classmates outside of your team about the general ideas of the project, but you may not copy the specifics: We expect all teams to create their own unique functions.