CASE STUDY 3: KINETICS

MODELING AND SIMULATION

OCTOBER 20, 2008

Overview

Please choose one of the following three cases. The first case involves a new HIV drug called maraviroc. The second case involves chemical clock reactions. The third case is quite open and involves you creating your own case study.

Each case expects you to do something a little different. For example, in the *Maraviroc* case you are asked to create a model that matches experimental data obtained during three Phase I clinical studies. You are then asked to use your model to make predictions about the behavior of maraviroc under different dosing and frequency schedules. In the *Clock* case you are asked to develop and implement a model for clock reaction kinetics of your choice. We expect you to calibrate your model using published data or perhaps perform your own experiments.In the *Create Your Own* case you are asked to study a physical system that can be described by systems of ordinary differential equations.

While each case has more or less guidance about what you should *do*, there are certain expectations that are common to each. You are expected to formulate and implement a model using MATLAB. You are expected to work with a teammate. You are expected to prepare several deliverables including:

Butcher paper version of question and model Prepare a poster draft using butcher paper of your question and proposed model. This is due no later than the beginning of class on *Friday 24 October*.

Butcher paper version of entire poster Prepare a poster draft using butcher paper of your entire poster. This is due no later than the beginning of class on *Friday 31 October*.

Printed version of entire poster Prepare a final draft of your poster using the poster printer. This is due no later than the beginning of class on *Friday 7 November*.

Pharmacokinetics

People have been using pharmacological agents (drugs) for medical purposes since the dawn of time. In the beginning drug effects were determined empirically. Only more recently, with advances in biological understanding and analytical tools, has it been possible to study the mechanisms of action of drugs. In the quest for this understanding, two related fields of study have emerged - pharmacokinetics and pharmacodynamics. Pharmacokinetics is concerned with the effect of the body on a drug - specifically the distribution and time course of a drug in the body. Pharmacodynamics is concerned with the effect of a drug on the body - focusing on the given concentration and site of action (e.g. systemic, specific organ, etc.). To understand the movement and effects of drugs, both pharmacokinetics and pharmacodynamics employ models which range in scale (molecular level to organism level) and complexity. These models are used clinically to chose dosing regimines, understand differences between patient populations, and to draw conclusions regarding efficacy.

Figure 1: Françoise Barré-Sinoussi and Luc Montagnier share part of the 2008 Nobel Prize in Physiology or Medicine for their discovery of human immunodeficiency virus.

HIV and Maraviroc

Infection with the human immunodeficiency virus (HIV), which can lead to acquired immunodeficiency syndrome (AIDS), is a global pandemic. As of 2007, roughly 33 million people living were with HIV and 2.1 million people died from AIDS [1]. The virus acts by infecting and destroying cells of the immune system, decreasing infected individuals' ability to fight infection. Though there is no cure for HIV infection, massive research efforts over the past few decades have identified numerous drugs which can dramatically slow the progression of AIDS. Many of these work by blocking viral replication and drugs are often given in combination. Unfortunately, one of the characteristics of HIV is that it is able to rapidly mutate and become resistant to existing drugs.

[1] UNAIDS AIDS Epidemic Update December 2007

More recently drugs that aim to block the entry of HIV into cells have been more intensively studied. HIV infects $CD4^+$ white blood cells (those white blood cells expressing a molecule called CD4 on their surface) by binding to CD4 in order to enter the cell. In addition to using CD4 to enter cells, some strains of HIV bind simultaneously to another molecule called a co-receptor. CCR5 is a common co-receptor and in August 2007 the US Food and Drug Administration (FDA) approved the first HIV entry drug, maraviroc (also known as selzentry). This drug has been shown to lower the count of viral genetic material in $CD4^+$ cells and may hold great promise for HIV+ individuals who have shown resistance to other drugs (the population for which it has been

approved by the FDA).

In early studies, different doses (in mg) of maraviroc were administered orally and the concentration of drug in the plasma was monitored over time [2]. In this case study you will create a model of maraviroc pharmacokinetics and calibrate it using data obtained in the clinical trials. In these trials, maraviroc was given either once or twice per day. Since clinical trials are enormously expensive to run, we would like you to use your model to explore the effects of different dosing schemes on maraviroc pharmacokinetics.

[2] Assessment of the pharmacokinetics, safety and tolerability of maraviroc, a novel CCR5 antagonist, in healthy volunteers, *Abel et al.* BJCP 65 Suppl. 1 5-18 (2008). A copy can be found on the course website.

Clock Reactions

According to the Wikipedia:

> "A chemical clock is a complex mixture of reacting chemical compounds in which the concentration of one component shows an abrupt change accompanied by a visible color effect. The onset of the color change may be used to tell time.[3]"

Examples include the Belousov-Zhabotinsky reaction, the Briggs-Rauscher reaction, the Bray-Liebhafsky reaction and the (ubiquitous) iodine clock reaction.

Choose one of these reactions and develop a model that describes its kinetics, most likely using a system of first-order differential equations. Write an implementation of your model using MATLAB and `ode45`.

A successful model will have a small number of free parameters so that it can be calibrated with a small dataset and then used to make predictions that can be tested with a larger dataset. You should be able to find useful data on the Internet, but it is also possible that we can arrange an opportunity for you to perform your own experiments.

You can read about chemical kinetics at `en.wikipedia.org/wiki/Chemical_kinetics`, but the single most important piece of information you will need is The Rate Law, which you can read about at `en.wikipedia.org/wiki/Rate_law`.

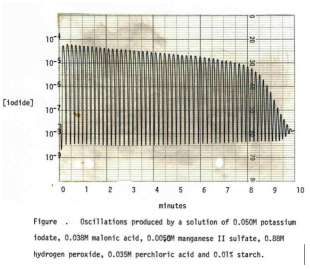

Figure 2: Clock reaction data from `en.wikipedia.org/wiki/Briggs-Rauscher_reaction`.

[3] `en.wikipedia.org/wiki/Clock_reaction`

Create Your Own Case Study

If neither of the previous options suits you, you have the option of creating your own case study.

You can study any kind of physical system that interests you, with the restriction (for now) that the primary model you use should be based on a system of first-order differential equations. For now, second-order systems are off limits, so that eliminates most mechanical systems. But it includes many thermal, chemical and biological systems.

Here are some ideas to help you get started:

- You could study the pharmacokinetics of a different drug. For example, you could work on a variation of the model of alcohol metabolism from the paper we gave you.
- You might be interested in Tylenol, which is one of the most toxic drugs available over the counter; according to the Wikipedia, "acetaminophen toxicity is the most common cause of acute liver failure in the United States.[4]"
- Or you might be interested in how Naloxone[5] works as a treatment for opiate overdose.
- You might be interested in enzyme processes like the one in Dignostic 5 (producing glucose from corn meal). You could work on an improved model of this reaction, or model an alternative process like cellulosic ethanol production[6].
- One of the puzzles of planetary cartography is that the surface of Venus appears to be too young. One possible explanation is that the surface of the planet melts periodically. You could investigate this hypothesis and see if you can build a model of Venus's geophysics[7] that explains periodic resurfacing events.

If you don't like any of these suggestions, you are free to propose your own. You might find it challenging to think of a physical system that can be modeled, usefully, by a system of first order differential equations. You might want to run an idea past us before you put too much time into it!

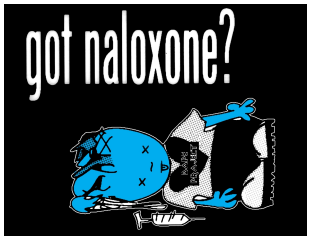

Figure 3: From "Overdose Prevention and Survival" at www.harmreduction.org.

[4] en.wikipedia.org/wiki/Tylenol

[5] en.wikipedia.org/wiki/Naloxone

[6] en.wikipedia.org/wiki/Cellulosic_ethanol

[7] Or is it called Cytherophysics?