

Two-Compartment Pharmacokinetic Models

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Editor: This paper is based on a project completed at the Harvey Mudd College Workshop, June 16-20, 1992. See the related article by Shampine on p. 10.

Introduction. Pharmacokinetics is the study of the movement of drugs through the human system, from their introduction by ingestion, injection, or other means, to elimination through excretion or metabolism. It makes heavy use of compartment models as found in many differential equations textbooks. Since almost all students take medications from time to time, pharmacokinetics models are something they can easily relate to.

For convenience many drugs are taken orally in the form of tablets. With some exceptions, these tablets are designed to swell and disintegrate rapidly, causing the medication to dissolve quickly in the gastrointestinal tract. From there, the medication passes into the bloodstream, which delivers it to the sites at which it has therapeutic effect. Typically, the drug is removed from the bloodstream by filtration through the kidneys or by metabolism in the liver.

A Compartment Model. I will discuss a simple two-compartment model that gives a good approximation to this process. The first compartment will be the GI tract and the second compartment will be the bloodstream. I will illustrate it with two drugs commonly used in combination for allergies and colds.

In the model, we will assume that the medication is taken as a tablet four times daily. Furthermore, the tablet dissolves uniformly over half an hour following ingestion. These conditions are typical

for tablets designed for immediate release (as opposed to sustained release).

There are a wide variety of over-the-counter products for relief of stuffed and runny noses. These typically contain both a decongestant and an antihistamine. Phenylpropanolamine hydrochloride (PPA) is commonly used as the decongestant, and chlorpheniramine maleate (CPM) is commonly used as the antihistamine. For an immediate release formulation, the usual dose frequency is every six hours. These two drugs are somewhat different in the rate at which they move from the GI tract to the bloodstream and are very different in the rate at which they are cleared from the blood.

PPA has a half-life of about one half hour in the GI tract and a half-life of about five hours in the bloodstream, whereas CPM has a half-life of about one hour in the GI tract and about thirty hours in the bloodstream. When we solve the differential equations, we should not be surprised by the different behavior exhibited by the two drugs.

The Model ODEs. Let us take one hour as the unit of time. We are interested in the shape of the solutions, not actual magnitudes, so let us think simply of a unit dose. We will need a uniform pulse of width $1/2$ and height 2, repeated every six hours, to represent the input of the drug. Call this function $f(t)$. The rate constants k are given by the formula $k = (\ln 2) / (\text{half-life})$. With the faster

moving PPA component, the rate constants are:

From the GI tract to the blood:

$$(\ln 2) / (1/2) = 1.386$$

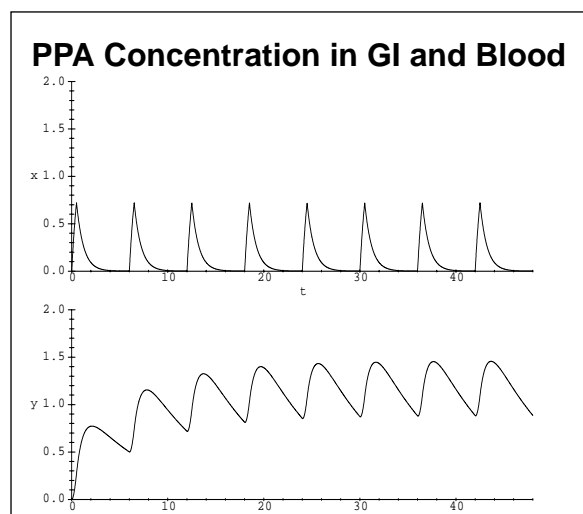
For elimination from the blood:

$$(\ln 2) / 5 = 0.1386$$

Letting x represent the amount of PPA dissolved in the GI tract and y represent the amount of PPA in the blood, we have the following system of differential equations:

$$\begin{aligned} x' &= -1.386x + f(t), & x(0) &= 0 \\ y' &= 1.386x - 0.1386y, & y(0) &= 0 \end{aligned}$$

Analysis of Model. Using **ODETOOLKIT 2.0**, developed at Harvey Mudd College, I solved the system numerically, obtaining the results in Figure 1. Within a single day, blood levels rise reasonably close to steady-state. By the end of the second day, steady state has been achieved for all practical purposes. Note, however, that steady state does not mean near-constant blood levels. The elimination rate is too large for that.



For the slower moving CPM component, the story is different. The rate constants are:

From the GI tract to the blood:

$$(\ln 2) / 1 = 0.6931$$

For elimination from the blood:

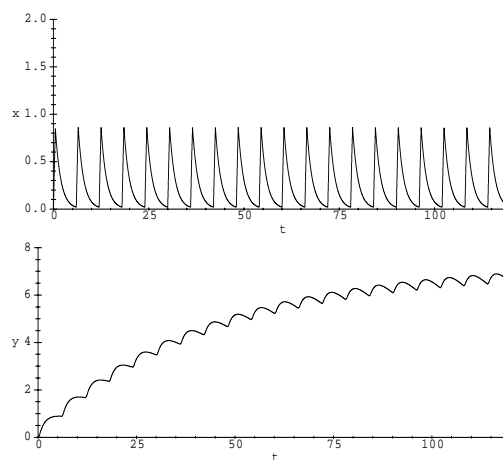
$$(\ln 2) / 30 = 0.0231$$

The equations for CPM in the GI tract and the blood are:

$$\begin{aligned} x' &= -0.6931x + f(t), & x(0) &= 0 \\ y' &= 0.6931x - 0.0231y, & y(0) &= 0 \end{aligned}$$

The solution to these equations is shown in Figure 2. Steady state is eventually approached, but only after about five days. (For those students made drowsy by antihistamines, you may notice a progressive worsening in classroom attention span when they are on this medication.) With CPM, blood levels become nearly constant at steady state.

CPM Concentration in GI and Blood



Model Modifications. An important variation on this example is to modify the release pattern for PPA. This can smooth out the blood levels of PPA and also make it possible for the patient to take fewer doses per day. One way this is done is to make a tablet or capsule built up of small beads of drug in resins of various dissolution rates. SmithKline Beecham's well-known **Contac** (for

“continuous action”) is a good example. Its two ingredients are in fact PPA and CPM, and the recommended dosing interval is 12 hours rather than 6 hours. An interesting series of exercises can be built by assuming different, nonuniform sustained-release patterns.

Another interesting set of exercises can be built around lithium, which is used for treatment of manic-depressive illness. Its half-life in the GI tract is approximately 1/2 hour, and its half-life in the blood is approximately 24 hours. Lithium (carbonate, chloride, etc.) is usually given in immediate release form, with a 12 hour dosing interval. As opposed to most drugs, lithium has a low ratio of toxic to therapeutic levels. Because of the long half-life, there will be an accumulation over several days as the blood levels build to steady state. Some care must be taken that the blood levels do not ultimately rise above the threshold of toxicity.

For a patient with active manic-depressive disorder, the physician might prescribe an initial loading dose to bring blood levels more rapidly to steady state. How large a loading dose can be given without causing the blood levels ever to rise above the steady state (peak) levels? Elderly patients often have impaired renal function, leading to longer medication half-life. If a patient has a half-life of 36 hours for lithium in the blood but all else remains the same, how much larger do the steady state levels become? What happens if the half-life is 48 hours?

Generalizations. Pharmacokinetics goes far beyond the simple two-compartment models we have dealt with here. Depending on the drug, different organs of the body may store substantial fractions of the total volume. In fact, in many investigations, the GI tract is bypassed

by injecting the drug directly into the blood, and still there may be as many as four compartments involved. With high concentrations and/or clearance by metabolism, the differential equations may become nonlinear.

There is considerable literature on these topics; I did a Medline search from 1986 to the present for abstracts containing both of the words “lithium” and “pharmacokinetic(s)” and found 66 different journal articles. Consider what I have presented here to be just a scratch on the surface of a very deep subject!

References:

- Godfrey, Keith, **Compartmental Models and Their Application**. London, New York: Academic Press, 1983.
- Welling, Peter G., **Pharmacokinetics: Processes and Mathematics**. Washington: American Chemical Society, 1986. □

Teaching ODEs With Computer Experiments

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Robert Borrelli

The 5-day workshop at Harvey Mudd College had 36 participants from June 16 thru the 20th, 1992. The workshop was supported by a grant from the Undergraduate Faculty Enhancement Program through the NSF Division of Undergraduate Education. The main speakers were Robert Borrelli and Courtney Coleman; a number of short talks by the participants gave added perspective to the workshop.