ADMINISTRATION OF DRUGS

6.337 Mathematical Modelling

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ADMINISTRATION OF DRUGS

Single compartment model: Consider the simple compartment model where a drug is administered directly into the blood. In reality, the drug is spread into the tissues by means of the blood, but for simplicity we assume that it dissipates in the blood, and that this is where it is used up (hence single compartment).

Problem: A drug is administered intravenously, and is distributed throughout the body in a short period of time by means of the blood. The drug is used up entirely, i.e. there are no residues that would normally need to be taken into consideration.

The amount of drug in the system decreases with time, and there is no need for repeating the dosage. The drug is therefore assumed to be effective with just one dose given.

Experiments suggest that the rate of absorption is directly proportional to the amount present. There is a limitation to this because if a person is in immediate need of a drug, one cannot administer a large amount in hope that it will be absorbed quickly. Nevertheless this observation will help us in developing the model.

Assumptions: There is only one injection given, and the dose is of appropriate amount so there is no possibility of overdose, or the drug exceeding some

tolerance level. There are no side effects.

These assumptions are reasonable since at this point we are only interested in how fast the drug dissipates given some initial amount, and how much of the drug is left at some time t. One can calculate the amount of drug left in the body using this model, given some initial data about the administration and the time of the administration. The drug is totally absorbed, there are no residues. This again keeps the model simple, and easy to evaluate.

To establish a starting point in developing the model, we look at what happens when the drug is first administered. We inject some amount A, which will decrease with time. So we are looking at the change in A with time t. There will be a constant variable (k, dissipation constant) which will direct how quickly or how slowly the drug dissipates. It will have to be negative, since the amount of the drug decreases.

Model:

(1) $\frac{dA}{dt} = kA$

$\frac{dA}{dt}$ - change in the amount A of drug in time t

k - rate at which drug is used up (<0 since drug is being used up)

A - amount of drug

Solve:

The above equation is separable:

$\frac{1}{A}dA = kdt$ - gather like terms together

$\int \frac{1}{A}dA = \int kdt$ - integrate both sides

$\ln|A| = kt + C$ where C is a constant of integration

since we are only interested in A>0 (negative amount of drug makes no sense)

we replace ln|A| with ln(A):

$\ln(A) = kt + C$ take exponents of both sides and solve for A:

$e^{\ln(A)} = e^{kt} + e^{C}$

(2) $\therefore A(t) = De^{kt}$ where $D=e^{C}$

D can be interpreted as the initial amount of drug administered at some time t_0:

in this case (2) becomes:

$A(t_0) = A_0$ A at some initial time t_0

Substitute A_0 into equation (2):

$A_0 = De^{kt_0}$

Solve for D:

$$D = \frac{A_0}{e^{kt_0}}$$

or: $$D = A_0 e^{-kt_0}$$

Now substitute D back into equation (2):

(3) $$\therefore A(t) = A_0 e^{k(t-t_0)}$$ where $A_0 = A(t_0)$

Given some initial amount A_0, and a time interval, it is possible to find the variable k, which will allow us to predict further behavior of the drug being administered.

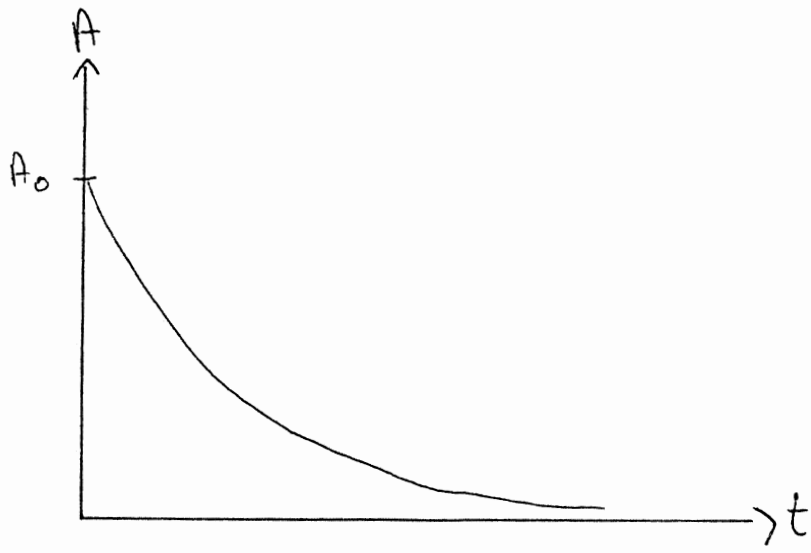
Solving for k:

Take logs of both sides of equation (3):

$$\ln(A) = k(t-t_0) + A_0$$

Solve for k:

(4) $$\therefore \quad k = \frac{\ln(A) - A_0}{t - t_0}$$



Amount in blood vs time

CONCENTRATION AND RESIDUE

Problem: Let's assume that the concentration of the drug is of particular importance. The drug can be in the form of a liquid, or taken with a liquid. Again the drug is administered directly into the blood stream. Let us assume it is governed by the Malthusian model, which is simple, but appropriate for this situation:

Model:

(5) $\frac{dC}{dt} = -kC$

$\frac{dC}{dt}$ - change in concentration C with time t

C - concentration of drug

k - elimination constant (>0)

Now consider multiple doses (non-continuous), i.e. there is a time interval in between doses when drugs are not administered). There is a possibility that the

drug may have a tolerance level beyond which undesirable side effects occur, or an effective level below which the drug has no beneficial effect. At that point it may be necessary to modify the dosage scheme, either modify the amount taken, or increase dosage interval.

With every subsequent dose given, the concentration is raised by a fixed amount C_0. But before the next dose is given, there is a residual R from the previous one, therefore the next dose is actually $R+C_0$.

Assumption: Each dose is exactly the same: same amount of drug, and same concentration. This allows us to treat C_0 as a constant, rather than a variable. Another assumption is that the drug is administered at regular time intervals t = 0, T, 2T, 3T...

Let C_n denote the concentration after the n^{th} dose, and R_n denote the residual just before the $(n+1)^{st}$ dose is given.

Calculating C_n and R_n:

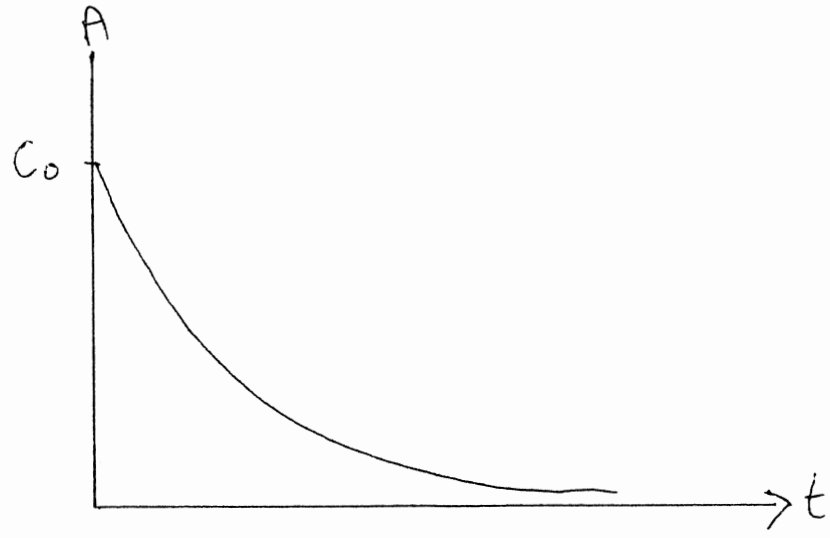
Original Model (equation 5): $\frac{dC}{dt} = -kC$

Solution (equation is separable as in (1), and we follow the same technique to find the solution):

$$C(t) = De^{-kt}$$

if we let $D = C(t_0)$ $C(t_0)$ - concentration at some initial time t

(6) $$\therefore \quad C(t) = De^{-k(t-t_0)}$$



Concentration in blood vs time

Calculating the concentrations and residuals in the subsequent doses:

First interval

$C_1=C_0$ The concentration of first dose is equal to the initial concentration

$C(t)=C_0e^{-kt}$ Concentration at some time t if only one dose is given

$R_1=C_0e^{-kt}$ Residual after the first dose is administered

Second interval

$C_2=R_1+C_0$ Concentration of second dose is equal to the first dose plus the residual from the first dose.

$C(t)=(R_1+C_0)e^{-k(t-T)}$ Concentration at some time t if only two doses are administered.

$R_2=(R_1+C_0)e^{-kT}$ Residual after the first and second dosages.

Third interval

$C_3=R_2+C_0$ Concentration of the third dose is equal to the first dose plus the residual from the second dose.

$C(t)=(R_2+C_0)e^{-k(t-2T)}$ Concentration at some time t if three doses are administered.

$R_3=(R_2+C_0)e^{-kT}$ Residual after the third dosage.

We can see a pattern developing in the equations for C(t) and R, which will allow us to develop the general equations $C(t)_n$ and R_n.

General equation for concentration:

$C_1 = C_0$

$C_2 = R_1 + C$

$= C_0 e^{-kT} + C_0$

$= C_0(1 + e^{-kT})$

$C_3 = R_2 + C_0$

$= C_0(1 + e^{-kT} + e^{-2kT})$

(5) $\therefore \quad \underline{C_n} = C_0(1 + e^{-kT} + e^{-2kT} + \ldots + e^{-(n-1)kT})$

General equation for residual:

$R_1 = C_0 e^{-kT}$

$R_2 = (C_0 e^{-kT} + C_0) e^{-kT}$

$= C_0(1 + e^{-kt}) e^{-kT}$

$R_3 = (C_0 + C_0 e^{-kT} + C_0 e^{-2kT})\, e^{-kT}$

(6) $\therefore \underline{R_n} = C_n e^{-kT}$

Problem: There is a possibility that the drug has a tolerance level beyond which undesirable side-effects occur. Assume that the tolerance level is known, (for example 2 ml of drug every two hours). The problem is to find the minimum dosage time interval which can be used safely, without side effects occurring.

S - safe tolerance level

C_0- concentration administered

To calculate this time interval T, we look at the limit of C_n as $n \to \infty$, specifically we do not want the limit to exceed the safe tolerance level:

$$\lim_{n \to \infty} C_n \leq S$$

To calculate the limit, we need to rewrite C_n. Since it is a geometric series, we can find its sum:

$$C_n = \frac{C_0(1-e^{-nkT})}{1-e^{-kT}}$$

Now take the limit:

$$\lim_{n \to \infty} C_n = \frac{C_0}{1-e^{-kT}} \leq S$$

Manipulate the equation in order to solve for T:

$$\frac{C_0}{S} \leq 1\text{-}e^{-kT}$$

$$\frac{C_0}{S} - 1 \leq -e^{-kT}$$

$$1 - \frac{C_0}{S} \geq -e^{-kT}$$

Now take logs of both sides to eliminate the exponential:

$$\ln(1 - \frac{C_0}{S}) \geq -kT$$

$$-\frac{1}{k} \ln(1 - \frac{C_0}{S}) \leq T$$

(7) $$\therefore \quad T_{min} = -\frac{1}{k} \ln(1 - \frac{C_0}{S})$$

So in order to calculate what is the minimum time between the intervals, we need to know what the concentration of the particular drug is, and what is its tolerance level. The concentration has to be a constant, otherwise this equation will not be valid.

Problem: We now consider a modified model, where the drug is administered intravenously, and continuously. This model takes into consideration not only the initial amount, but also an injection rate which we assume to be constant.
The model is basically the same as equation (1), except that we add an injection rate.

Model:

$\frac{dA}{dt} = kA + R$ R - intravenous injection rate (constant)

k - absorption rate

$k<0$, $R>0$

This model is a Malthusian model which incorporates a constant 'immigration rate'.

Solution:

Separate the above model equation:

$\frac{1}{kA+R}dA = dt$

$\int \frac{1}{kA+R}dA = \int dt$ integrate both sides

$\ln|kA + R| = kt + C$

$|kA + R| = e^{C}e^{kt} = D\,e^{kt}$ C is a constant of integration

$kA + R = Le^{kt}$ $L = \pm D \neq 0$

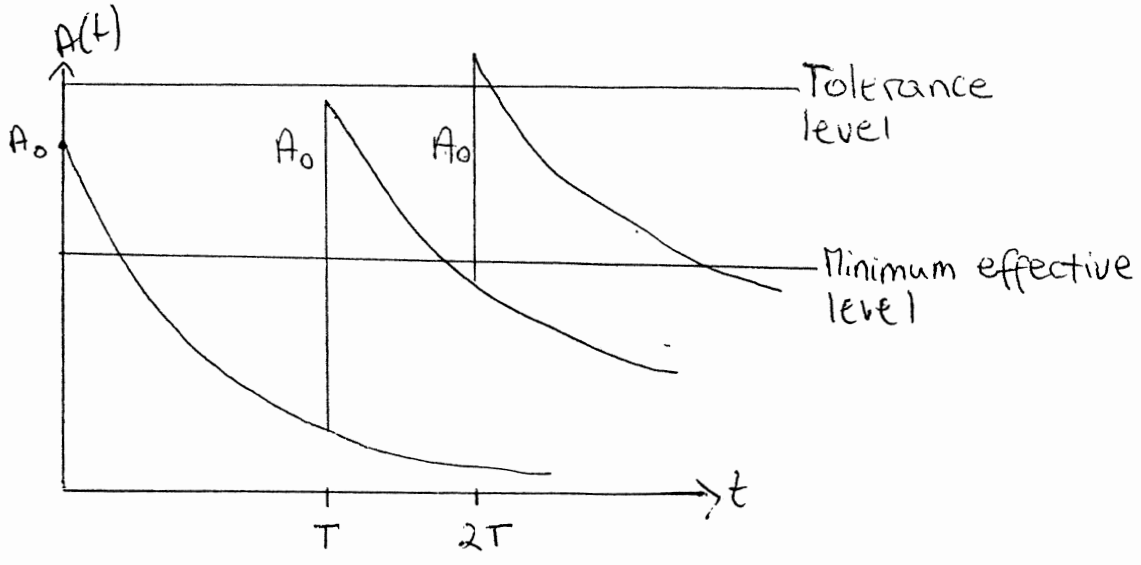
(8) $\therefore \quad A(t) = \frac{Le^{kt} - R}{k}$

or $A(t) = -\frac{R}{k} + \frac{L}{k} e^{kt}$

where $\frac{R}{k}$ is a positive constant

in $\frac{L}{k}$ $k<0$, so $\frac{L}{k}>0$ if $L<0$

$\frac{L}{k}<0$ if $L>0$



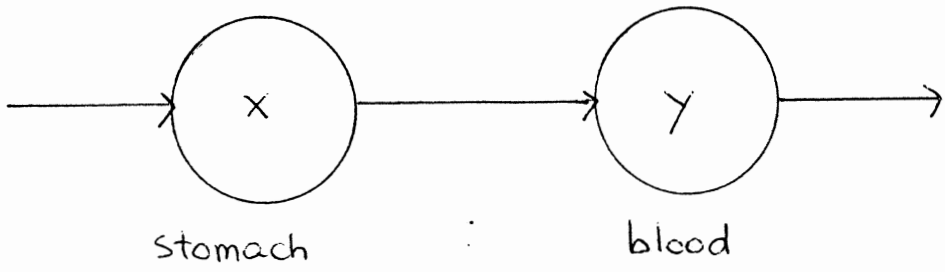
Repeated injections

Two compartment model: We now consider orally administered drugs such as tablets. The first compartment is the stomach. The drug is swallowed, after which it 'sits' in the stomach for some period of time. The amount of the drug decreases with time, eventually goes to zero. This suggest a Malthusian

decay model.

The second compartment is the blood. The amount of drug first increases in the blood, reaches a maximum (that's when the drug is at minimum in the stomach), and then decreases. The model for the blood compartment is more complicated because it involves two variables the stomach and the blood.

Let us illustrate this situation:



Model:

$\frac{dx}{dt} = -lx$ $\frac{dx}{dt}$ - rate of change of amount x in time t in the stomach

l - dissipation constant (>0)

x - amount of drug

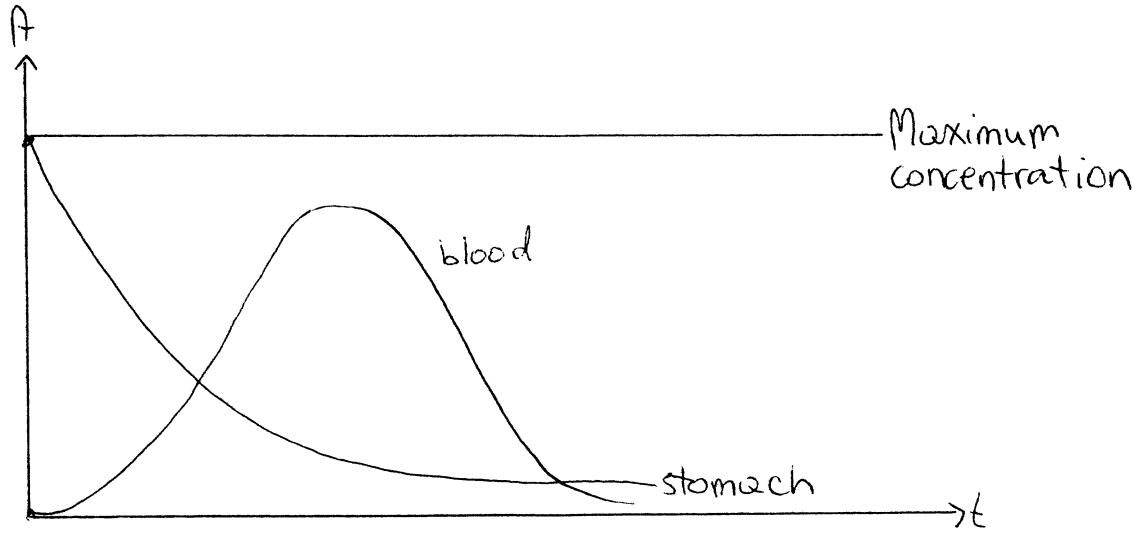
$\frac{dy}{dt} = lx - ky$ $\frac{dy}{dt}$ - rate of change of amount y in time t in the blood

k - dissipation constant (>0)

y - amount of drug

This is a system of differential equations in two unknowns.

Anticipated graph of the solution:



Case study: **Astracaine - local anesthetic (Articaine HCI)**

Articaine is a local anesthetic of the amide type. As with other local anesthetics, it prevents the generation and conduction of the nerve impulse by interfering with the large transient increase in the permeability of the membrane to sodium ions. It decreases the flow of blood in the area of injection.

Following intra oral injection of a 240 mg dose of articaine 4% with epinephrine 5 μg/mL in healthy volunteers, peak plasma levels of 1.17 ± 0.14 μg/mL were reached at approximately 17 minutes. The elimination half-life was 25.28 ± 3.3 minutes.

Articaine is excreted mainly by the kidneys. 2 to 5% is excreted unchanged, 40 to 70% is excreted as articainic acid, and 4 to 15% as articainic acid glucuronide.

A warning is issued that the lowest dose that results in effective anesthesia should be used to avoid serious undesirable side effects. The injection should be made slowly, with frequent aspirations before and during the injection.

The drug has serious side effects if it were to be administered during or following injections of other drugs such as chloroform, halothane, cyclopropane, or other such agents.

The duration of the anesthesia depends on the type of block and the amount injected.

Tolerance level varies with the status of the patient. Debilitated or elderly patients, acutely ill patients and children should be given reduced doses according

to their age and physical status.

Aspirin: (ASA)

This is probably the most common drug used today, and it comes in a number of varieties. When ASA is taken orally, it is rapidly absorbed from the stomach and proximal small intestine. The gastric mucosa is permeable to the non-ionized form of ASA, which passes through the stomach wall by a passive diffusion process. Absorption in the small intestine occurs at a significantly faster rate than in the stomach.

After an oral dose of 650 mg Aspirin, the plasma acetylsalicylate concentration in man usually reaches a level between 0.6 and 1.0 mg% in 20 minutes after ingestion and drops to 0.2 mg% within an hour. Within the same period of time, half or more of the ingested dose is hydrolyzed to salicylic acid by esterases in the gastrointestinal mucosa and the liver, the total plasma salicylate concentration reaching a peak between 1 or 2 hours after injection, averaging between 3 and 7 mg%.

Many factors influence the speed of absorption of ASA in a particular individual at a given time; tablet disintegration, solubility, particle size, gastric emptying time, **psychological state**, physical condition, and nature and quantity of gastric contents.

Distribution of salicylate throughout most body fluids and tissues proceeds at a rapid rate after absorption. Tissues containing high concentrations of the drug are

the kidney, liver, heart and lungs. Concentrations in the brain are usually low, and are minimal in feces, bile and sweat.

Excretion of salicylates occurs principally via the kidney. The full dose requires up to 48 hours for complete elimination.

ASA is used for the relief of pain, fever and inflammation of a variety of conditions such as influenza, common cold, low neck and back pain, headache, dysmenoohea, toothache, and a variety of other pains.

Patients taking ASA daily are at an increased risk of developing gastrointestinal bleeding following the ingestion of alcohol.

Adverse effects: Gastrointestinal: (the frequency and severity of these adverse effects are dose related) nausea, vomiting, diarrhea, heartburn.

Ear: tinnitus, vertigo, hearing loss

Miscellaneous: mental confusion, drowsiness, sweating, thirst.

Overdose: Symptoms: In mild over dosage these may include rapid and deep breathing, nausea, vomiting, flushing, sweating. Severe cases may show fever, hemorrhage, excitement, confusion, convulsions or coma and respiratory failure.

Dosage: Analgesic and Antipyretic: Adults: 1 to 2 tablets (325 to 650 mg) orally every 4 hours. Children under 12: 10 to 15 mg/kg every 6 hours, not to exceed daily dose of 2.4 g.

Anti-inflammatory: Adults: 3 tablets (975 mg) 4 to 6 times a day, up to 30 tablets daily, may be required for optimal anti-inflammatory effect. A blood level

between 15 and 30 mg/100mL is in the desirable therapeutic range.

Children: 60 to 125 mg/kg daily in 4 to 6 divided doses.

One might be interested what are the ingredients of a tablet, in this case Aspirin with stomach guard.

Regular strength: Each film-coated tablet contains: ASA 325 mg, calcium carbonate 160 mg, magnesium carbonate 34 mg and magnesium oxide 63 mg.

Non-medical ingredients: acacia, carnauba wax, cornstarch, croscarmellose sodium, FD&C #2, hydrogenated vegetable oil, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polysorbate 80, polyvinylpyrrolidone, propylene glycol, silicon dioxide, sodium lauryl sulfate, talc, titanium dioxide and triacetin. A very extensive list of ingredients.

References: All information on drugs was provided by the Canadian Pharmacists Association.