First Order Drug Elimination Kinetics

Introduction

Understanding the kinetics of drug elimination is paramount for the design of appropriate dosage regimens. For most drugs, some minimum concentration is needed to achieve a therapeutic benefit. However, toxic effects may occur if the concentration of the drug becomes too high. The challenge therefore is to design a dosage schedule which maintains the concentration above the minimum therapeutic concentration, but below the threshold for toxic effects. Furthermore, the schedule should also be convenient and feasible for the patient to follow. A final consideration is how long it takes to reach the therapeutic concentration. For certain drug therapies it is essential that it be obtained quickly. Designing these schedules therefore requires a quantitative description of drug concentration in patients as a function of time for different dosage regimens. The elimination of many drugs from the body follows ideal first order kinetics, meaning that their rate of elimination is proportional to their concentration. Thus, in this article I develop equations to describe the first order elimination of drugs from the body. I consider single discrete doses, periodic doses, as well as continuous administration.

Single discrete dose

Let $C(t)$ be the concentration of drug molecule in a patient at time t. Suppose that the drug is eliminated from the body through a first order process with the apparent rate constant k. Consider a single dose of m grams. The initial concentration (C_0) which results depends on the drug's volume of distribution (V_d) and bioavailability (F). The initial concentration in the body is:

$$C_0 = \frac{m}{V_d F}$$

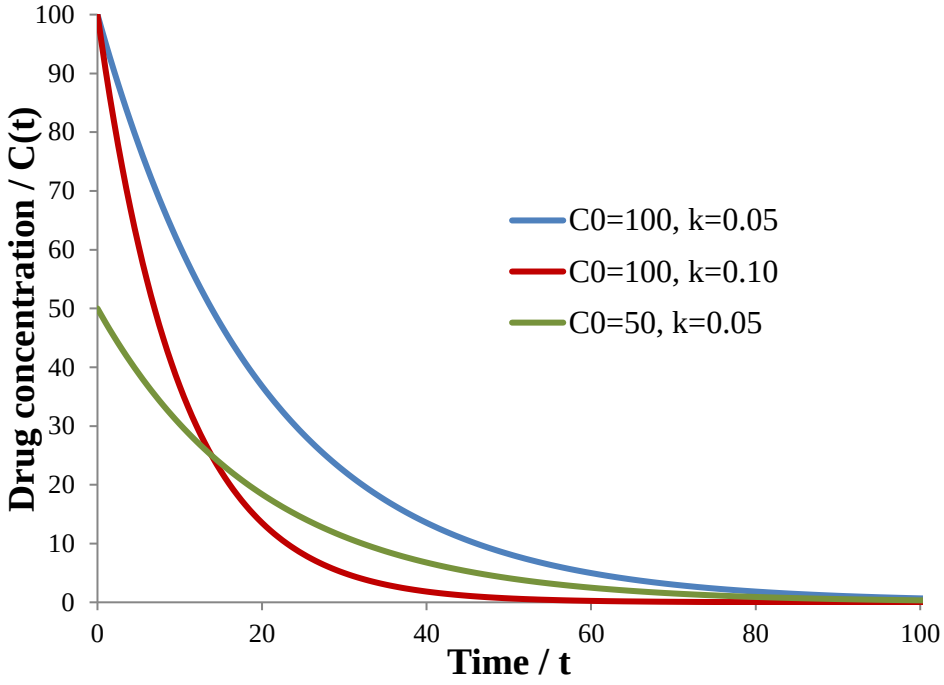
Since the dose increases $C(t)$ by the value of C_0, it is simplest to write the kinetic equations in terms of C_0 instead of m. Since drug elimination is assumed to follow a first order rate law:

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

Solving this differential equation gives:

$$C(t) = C_0 e^{-kt}$$

The concentration therefore follows an exponential decay as a function of time. A few examples given different values of C_0 and k are plotted below:



The drug concentration decreases according to an exponential decay. The steepness of the decay is determined by the first order rate constant (k), while the overall size of the curve is determined by the dosage size (C_0).

Periodic discrete doses

General equation

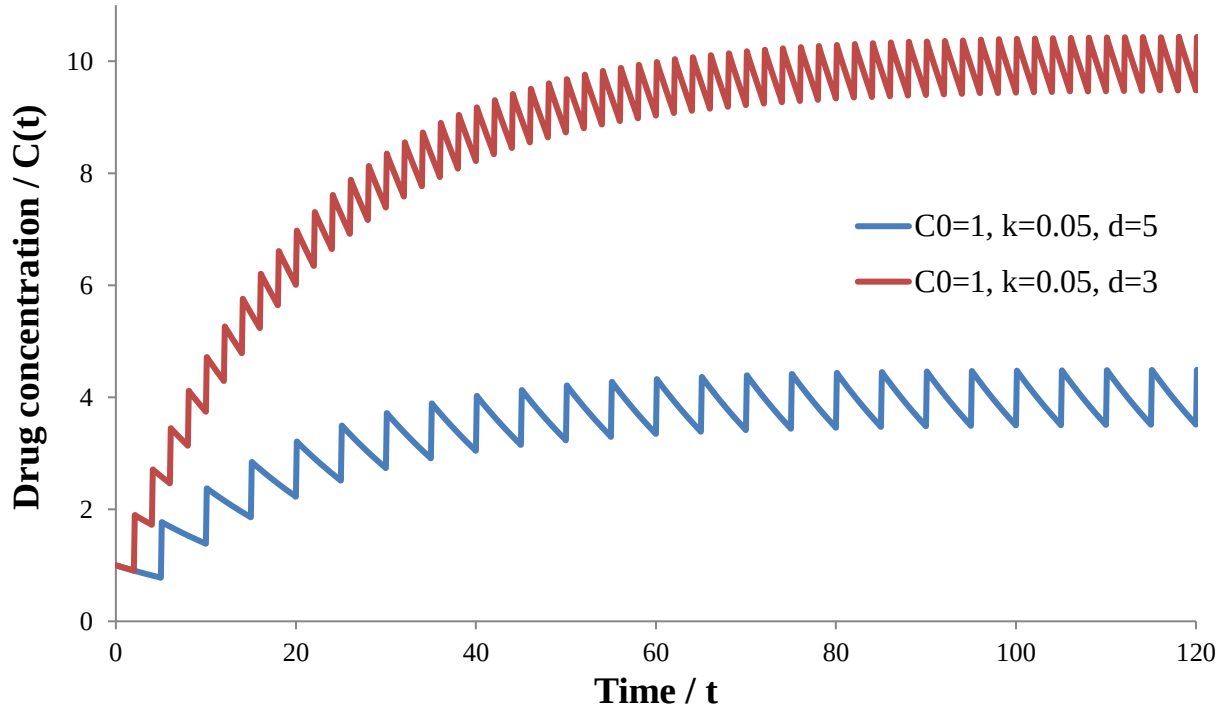
Since drug concentration decreases according to an exponential decay, the drug must be re-administered regularly to maintain it at a given level. Drugs doses are therefore often taken at regular intervals. For instance, a pill could be taken every 6 hours. The three important modifiable parameters are the dosage size (C_0), the time between each dose (d), and the first order rate constant for the elimination of the drug (k). Thus, discrete doses of the drug is administered at the times $= 0, d, 2d \ldots n$. The concentration immediately after each dose is administered is C_0 plus whatever concentration of drug was left from the previous dose(s). Thus, we could write this as a piecewise function, each time window described by an exponential decay with a different initial value:

$$C(t) = \begin{cases} C_0 e^{-kt} & t \le d \\ C_0(1 + e^{-dk})e^{-kt} & d < t \le 2d \\ C_0[(1 + e^{-dt})e^{-2kd} + 1]e^{-kt} & t > 2d \\ \vdots & \end{cases}$$

More conveniently, we can alternatively treat each drug dose as an independent elimination exponential decay. This allows the concentration function to be written as a growing sum of phase-shifted exponential terms:

$$C(t) = \begin{cases} C_0 e^{-kt} & t \le d \\ C_0 e^{-kt} + [C]_0 e^{-k(t-d)} & d < t \le 2d \\ C_0 e^{-kt} + C_0 e^{-k(t-d)} + C_0 e^{-k(t-2d)} & 2d < t \le 3d \\ \vdots & \\ C_0 \sum_{n=0}^{n} e^{-k(t-nd)} & nd < t \le (n+1)d \end{cases}$$

Where n is the number of additional doses that have been administered at time t. For instance, the first dose corresponds to $n = 0$, the second to $n = 1$, and so forth. A few examples of these dose regimens are plotted below:



The drug concentration increases after each dose and subsequently decreases by an exponential decay until the next dose is given. Over time a steady state is reached where the rate that drug is eliminated from the patient is equal to the rate at which it is administered.

Properties of the steady state

For any set of values of k, d, and C_0 we have seen that a steady state is eventually reached where the average rate of drug elimination (R_{out}) is equal to the average rate at which it is administered (R_{in}). This region of the curve is particularly important, as any drug given chronically on a consistent schedule will eventually enter this phase. I will therefore characterize this region fully, including calculating the concentration maximum (M), minimum (B), average (C_{avg}), and range (Δ) at steady state. Firstly, we can calculate the maximum by developing expressions for R_{in} and R_{out}.

Every d time units drug is administered, increasing the serum concentration by C_0. thus the average rate is:

$$R_{\text{in}} = \frac{C_0}{d}$$

To calculate the amount of drug eliminated over each d time units we must consider the exponential decay starting from the maximum concentration at steady state (M). Starting from a new dose at steady state, $C(t)$ is given by:

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

To find the average rate of drug elimination we can calculate the decrease in $C(t)$ from $t = 0$ to $t = d$ according to this exponential decay:

$$R_{\text{out}} = \frac{C(d) - C(0)}{d} = \frac{M}{d}(e^{-kd} - 1)$$

$$R_{in} = -R_{out} \rightarrow \frac{C_0}{d} = -\frac{M}{d}(e^{-kd} - 1)$$

$$M = \frac{C_0}{1 - \mathrm{e}^{-kd}}$$

Next, I will calculate the minimum concentration at steady state. The minimum concentration (B) occurs at the end of each dose interval, the time immediately before the administration of the next dose ($t = d$):

$$B = Me^{-kd} = \frac{C_0 e^{-kd}}{1 - e^{-kd}}$$

Another parameter of interest is the average drug concentration at steady state (C_{avg}). We can compute this by integrating the steady state exponential decay from when a new dose is given ($t = 0$) to when the next one is ($t = d$). Division of this area by the dosage time, d, gives the average:

$$C_{\text{avg}} = \frac{1}{d}\int_0^d Me^{-kt}\,dt = \frac{M(1 - e^{-kd})}{kd} = \frac{C_0}{1 - e^{-kd}}\frac{1 - e^{-kd}}{kd}$$

$$C_{\text{avg}} = \frac{C_0}{kd}$$

Thus, the drug concentration at steady state can be increased by increasing the dosage (increasing C_0), giving dosages more frequently (decreasing d), or decreasing the first order rate constant for the drug's elimination (decreasing k).

Lastly, we can calculate the range of drug concentrations spanned at steady-state (Δ):

$$\Delta = M - B = \frac{C_0}{1 - \mathrm{e}^{-kd}} - \frac{C_0 e^{-kd}}{1 - e^{-kd}} = \frac{C_0(1 - e^{-kd})}{1 - \mathrm{e}^{-kd}}$$

$$\Delta = M - B = C_0$$

Interesting, the range of drug concentrations spanned at steady state (Δ) is independent of dosage frequency (d) and the rate constant of drug elimination (k); it depends only on the dosage size (C_0). This result is expected when the nature of the steady state is considered: a steady state is reached when over each dosage interval the amount of drug eliminated is equal to the dosage size. Thus, the range of concentrations spanned at the steady state must simply be the dosage size.

Rate of steady state attainment

To follow the rate of steady state attainment, we can calculate the maximum concentration obtained upon administering the nth dose (m). The steady state is attained when $R_{\text{in}} = -R_{\text{out}}$. Before this point, there is a net gain from each dose as $R_{\text{in}} - R_{\text{out}} > 0$. Since the drug is eliminated from the body according to a first order rate law, the rate of increase of this maximum is proportional to the difference between the current maximum and the steady state maximum. Furthermore, this rate is proportional to the parameters k and d. This is because increasing either decreases C_{avg} and thus increases the rate at which steady state can be obtained. Thus:

$$\frac{dm}{dn} = kd(M - m)$$

$$\int \frac{1}{M - m} dm = \int (kd) dn$$

$$\therefore m(n) = Xe^{-kdn} + M$$

Where X is an unknown constant resulting from the integration.

$$m(0) = X + M = C_0 \rightarrow X = C_0 - M$$

$$\boxed{m(n) = (C_0 - M)e^{-kdn} + M}$$

Next, the minimum concentration during the nth dose (b) can be found. It is given by the concentration remaining after an exponential decay for d time units from the most recent maximum (m):

$$\boxed{b(n) = m(n)e^{-kd}}$$

To explicitly describe the rate at which the steady state can be obtained, we can consider the dosage number (n) at a given fraction (f) of the maximum concentration at steady-state is attained:

$$m(n_f) = ([C]_0 - M)e^{-kdn_f} + M \geq fM$$

$$\boxed{n_f = \left\lceil \frac{1}{kd} \ln\left(\frac{M - C_0}{(1 - f)M}\right) \right\rceil}$$

The brackets refer to the ceiling function, if n_f is not an integer, this function rounds the number to the nearest greater integer. This is necessary since the dosages are administered discretely. We must round up to get the dosage number for which $m(n_f) \geq fM$.

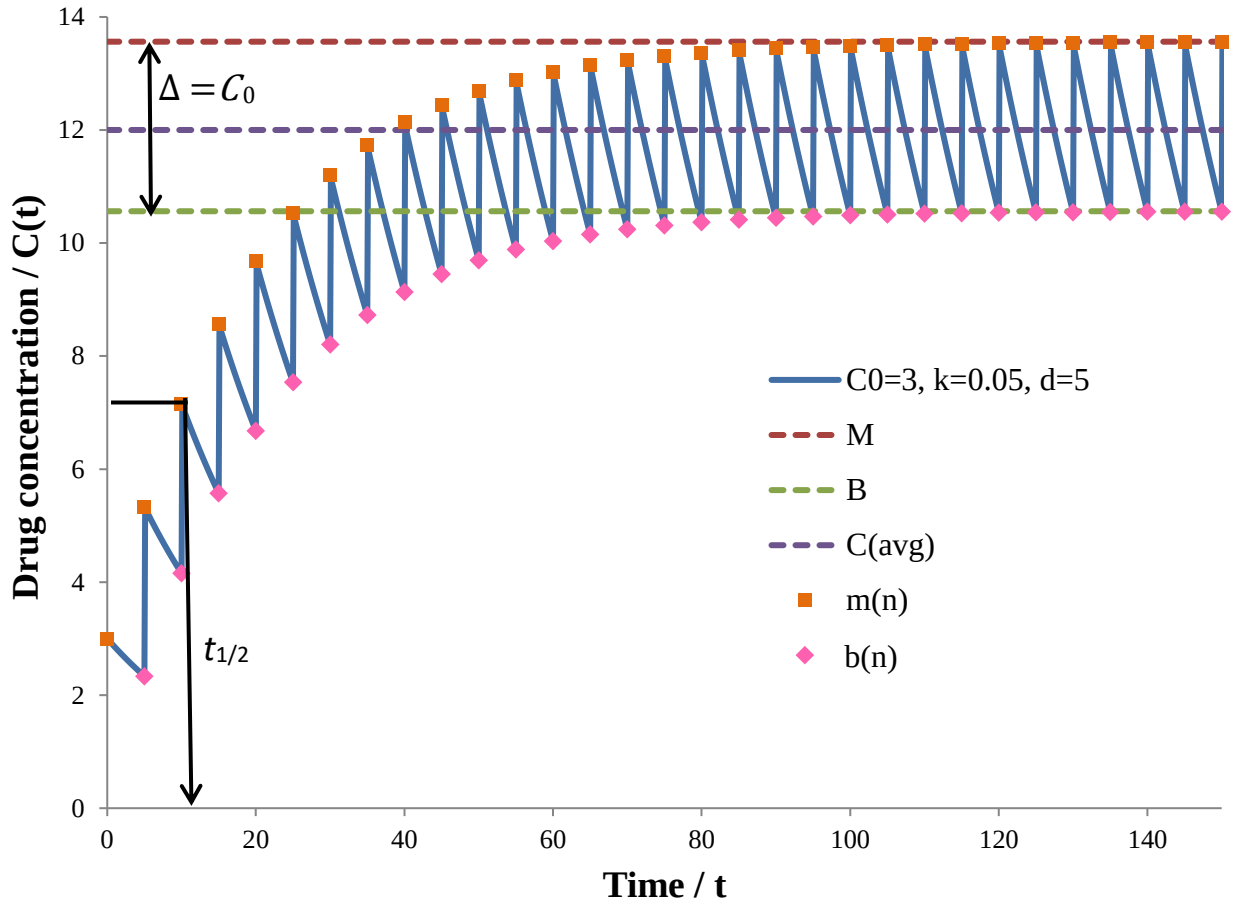
It is easy to calculate the time (t_f) corresponding to n_f:

$$t_f = n_f d$$

For instance, the time for the patient's drug concentration to reach at least half of the theoretical maximum ($t_{1/2}$) is:

$$t_{1/2} = d\left\lceil \frac{1}{kd} \ln\left(2\frac{M - C_0}{M}\right)\right\rceil$$

Another concentration-time profile for periodic discrete doses is shown below (blue line). To illustrate that these derived equations really do describe the properties of the curve, it is annotated with the parameters as calculated by my equations.



The equations accurately predict the concentration maximum (M), minimum (B), average (C_{avg}), and range (Δ) at steady state. Furthermore, the time to reach at least half of the maximum drug concentration ($t_{1/2}$) is correctly predicted. Lastly, the local maxima (m) and minima (b) as a function of dose number (n) are in excellent agreement with the actual values. While only one case is shown, extensive testing of these equations showed that they robustly predict the exact values for these features given any C_0, k, and d.

Continuous administration

Although discrete drug dosages are often convenient, continuous drug administration is also a commonly practiced. For instance, intravenous injection at a constant, slow flow rate. Note that a single injection of a drug, rather than continuous injection, should be modelled as a single discrete dose. In general, injection affords faster administration and higher bioavailability. If continuous, it also allows an exact concentration to be reached and maintained, rather than a range of concentrations as for periodic discrete doses. Suppose that a constant rate of drug administration (v) is maintained such that:

$$v = R_{in} = \frac{1}{V_d}\frac{dm}{dt}$$

Where m is the mass of drug administered and V_d is the volume of distribution as before. Note that for intravenous injection the bioavailability is maximum ($F = 1$). The rate of change of drug concentration is now determined by two terms, one for the continuous addition of drug and the other for its first order elimination from the body:

$$\frac{dC}{dt} = v - kC$$

Solving this differential equation gives:

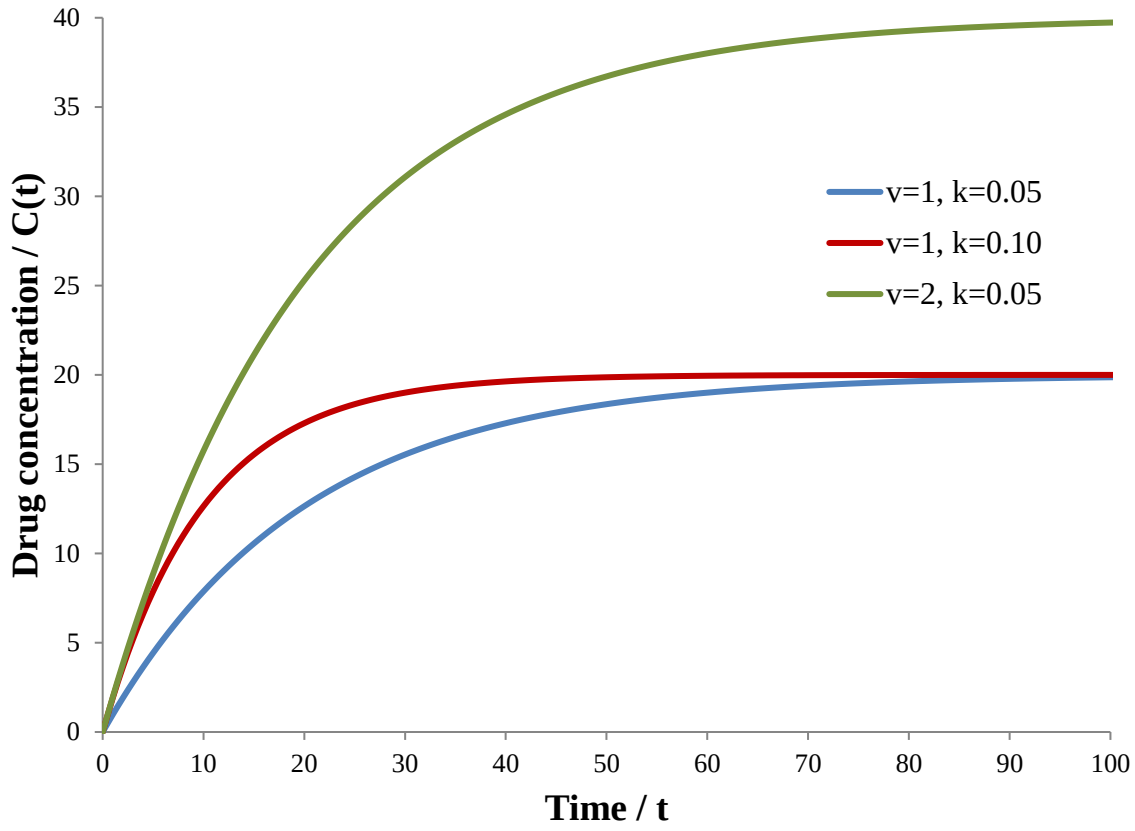
$$C(t) = Xe^{-kt} + \frac{v}{k}$$

Where X is an unknown constant resulting from integration.

$$C(0) = X + \frac{v}{k} = 0 \rightarrow X = -\frac{v}{k}$$

$$C(t) = \frac{v}{k}(1 - e^{-kt})$$

A few examples of this equation for different values of v and k are plotted below.



A steady state is eventually reached where the rate of drug into the patient (v) is equal to the rate it is eliminated. The maximum concentration of drug obtained (M) can be determined by the following limit:

$$M = \lim_{t \to \infty} \left[\frac{v}{k} (1 - e^{-kt}) \right]$$

$$M = \frac{v}{k}$$

As for periodic discrete doses, the steady state concentration can be increased by increasing the dosage (increasing v) or decreasing the first order rate constant for the drug's elimination (decreasing k)

We can monitor the system's approach to steady state by considering the concentration (C) as a fraction of the maximum (M):

$$f(t_f) = \frac{C(t_f)}{M} = 1 - e^{-kt_f}$$

The time t_f to attain a fraction f of the maximum is thus:

$$t_f = -\frac{\ln(1-f)}{k}$$

For instance, the time to reach half of the maximum concentration ($t_{1/2}$) is:

$$t_{1/2} = \frac{\ln 2}{k}$$

As expected, increasing the rate constant for drug elimination (k) decreases the time required to reach the steady state and decreases t_f.

Conclusion

Equations have been developed to model the drug concentration in patients as a function of time for drugs whose elimination follows first order kinetics. This was done for a variety of commonly used dosage regimens: single discrete doses, periodic discrete doses, and continuous administration. In addition to general equations for the concentration as a function of time, the properties of the steady state and the rate of steady state attainment were quantitatively described. These equations facilitate the precise and efficient design of dosage regimens for new drugs to achieve whatever properties are desired clinically.