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# A MODEL FOR DRUG CONCENTRATION*

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**Abstract.** A model, suitable for classroom use, is developed to describe the concentration of a drug in the body when the drug is administered repeatedly. The model shows that under certain conditions there are limiting values for the maximum and minimum concentrations of the drug in the system. Cases of random detoxification and enzymatic detoxification are discussed.

**1. The model.** In this note we show how a simple differential equations model can be used to predict the concentration of a drug in the body under certain circumstances. The results are generalizations of those presented by Rustagi [2]; the method of solution used was suggested in § 5 of [3].

We are interested in what happens to the concentration of a drug in the body when the drug is introduced into the body repeatedly. Will repeated application of the drug cause the concentration to become too large eventually? How should the time interval between applications be chosen so that the concentration does not become so large as to be dangerous or so small as to be ineffective?

We will answer these questions on the basis of the following assumptions: If $y(t)$ is the concentration of the drug at time $t$, we assume that (i) the rate of destruction of the drug depends only upon the amount of drug present, i.e., $y' = f(y)$. Appropriate forms for the function $f$ will be considered later, but it makes sense to assume that (ii) $f$ is a continuous, nonpositive, monotone decreasing function with $f(0) = 0$. At time $t = 0, T, 2T, \cdots$ a dose of the drug is administered in such a way that the concentration of the drug is increased by an amount $d$. We assume that (iii) the concentration is immediately increased throughout the body when the dose is administered.

Under these assumptions, there is a sequence of initial value problems which describes the situation. The important features of this sequence can be seen in the accompanying figure. Let $y_n(t)$ be the concentration of the drug on the interval $(n-1)T < t < nT$. When the drug is first introduced into the body at time $t = 0$, the concentration of the drug rises from 0 to $d$, so $y_1(0) = d$. Thereafter the concentration decreases according to the equation $y_1' = f(y_1)$ to a value $y_1(T)$ when a booster dose is given raising the concentration to $y_1(T) + d$. This value becomes the initial value of $y_2$: $y_2(T) = y_1(T) + d$. After this jolt, the concentration of the drug again decreases, this time according to $y_2' = f(y_2)$ until it reaches $y_2(2T)$ when another dose is given, raising the concentration to $y_2(2T) + d$. This becomes the initial condition for $y_3$: $y_3(2T) = y_2(2T) + d$. This process continues, giving a sequence of initial value problems, the general case being

$$y_{n+1}' = f(y_{n+1}), \qquad y_{n+1}(nT) = y_n(nT) + d \tag{1}$$

on the interval $nT < t < (n+1)T$.

The concentration of the drug immediately after the administration of the dose at time $nT$ is $y_n(nT) + d$. The concentration then decreases until it reaches its minimum value $y_{n+1}((n+1)T)$ just before a new dose is given. Since $y_n(nT) + d$

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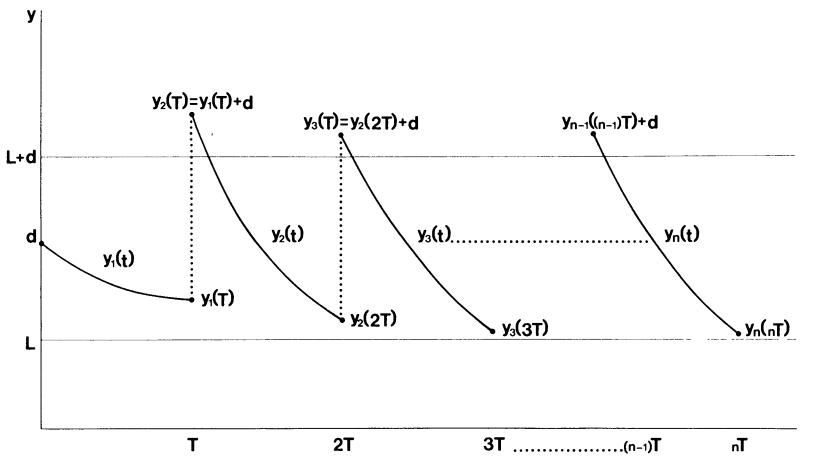


FIG. 1

and $y_{n+1}((n+1)T)$ give the maximum and minimum concentrations of the drug on the interval $nT<t<(n+1)T$, the questions raised at the beginning of this note can be answered by considering the sequence $\{y_n(nT)\}$.

In particular, if it could be shown that the sequence $\{y_n(nT)\}$ converges to a limit $L$, say, then we would know that the maximum concentration approaches $L+d$ and that the minimum approaches $L$. See Fig. 1.

**2. Analysis.** By separating the variables in (1) and integrating, we find

$$\int_{d+x_n}^{x_{n+1}} \frac{dx}{f(x)} = \int_{nT}^{(n+1)T} dt = T, \tag{2}$$

where we have introduced $x$ as a dummy variable of integration and set $x_n = y_n(nT)$ for convenience in notation.

Assume for the moment that $x_n = y_n(nT) \to L$. Then taking the limit $n \to \infty$ in (2) we obtain

$$\int_{L+d}^{L} \frac{dx}{f(x)} = T. \tag{3}$$

It will be shown below (Theorem 1) that if there is a number $L$ which satisfies equation (3), then $\{y_n(nT)\}$ does in fact converge to $L$. For the moment we use this result without proof to analyze two examples.

**3. Examples.** We will consider two explicit forms of the function $f$ which may be appropriate under certain circumstances. The first case is that in which the concentration of the drug is reduced by random action of the system on the drug. (Such is the case with penicillin, for example.) Under random action, the rate at which the drug is destroyed is proportional to the amount of the drug present, so $f(x) = -kx, k > 0$. We can calculate the limiting maximum and minimum

concentrations $L+d$ and $L$ by using equation (3)

$$-\int_{L+d}^{L} \frac{dx}{kx} = T \quad \text{or} \quad \ln\left[\frac{L+d}{L}\right] = kT.$$

This last equation can be solved for $L$ to obtain $L = d/(e^{kt}-1)$. The limiting maximum concentration is $L+d = d/(1-e^{-kT})$. This agrees with the result in [2] where the case of $f(x) = -kx$ was also discussed.

As another example, consider the case where the destruction of the drug is due to enzymatic action. In this case it is appropriate under some conditions to take $f(x) = -ax/(b+x)$, $a, b > 0$. This is the Michaelis–Menton equation which is derived in most texts on biological chemistry; see, for example, [1, pp. 225–229]. When the concentration of the drug is very small, the enzymatic case reduces to the case of random action, but when the concentration of the drug is large, as with repeated doses of an alcoholic beverage, the Michaelis–Menton equation provides a reasonable model. By putting $f(x) = -ax/(b+x)$ into (3), integrating, and solving for $L$, we find for the minimum and maximum concentrations

$$L = \frac{d}{e^{(aT-d)/b}-1}, \qquad aT-d>0,$$

and

$$d+L = \frac{d}{1-e^{(d-aT)/b}}, \qquad aT-d>0.$$

It is interesting to note that a solution exists in this case only if $d < aT$. If $d > aT$, then either the dosage is too large or the time interval too short (or both) for the concentration to be reduced sufficiently between applications of the drug for a limit to be established.

We note in passing that in both of these examples, the limiting concentration $L$ increases if $d$ increases and decreases if $T$ increases. These results, which are not surprising, are consequences of Theorem 2 below.

**4. Theorems.**

THEOREM 1. *If $f$ is a continuous, monotone decreasing, nonpositive function with $f(0) = 0$ which is such that the equation*

$$\int_{r+d}^{r} \frac{dx}{f(x)} = T \tag{4}$$

*has solution $r = L$, then the sequence $\{x_n\}$ defined by (2) with $x_1 = y_1(T)$ converges to $L$.*

*Proof.* Because of the monotonicity of $f$, the solution $L$ of equation (4) is unique. We will show that $\{x_n\}$ is a monotone bounded sequence. Suppose that $x_1 < L$. Then (with $g(x) = (1/f(x))$),

$$\int_{x_2}^{L} g(x)\,dx = \int_{x_2}^{x_1+d} g(x)\,dx + \int_{x_1+d}^{L+d} g(x)\,dx + \int_{L+d}^{L} g(x)\,dx = \int_{x_1+d}^{L+d} g(x)\,dx < 0.$$

Thus, $x_2 < L$. Since

$$\int_{x_1+d}^{x_2} g(x)\,dx = \int_{L+d}^{L} g(x)\,dx$$

and $x_1 < L$, the monotonicity of $f$ implies that $(x_1+d)-x_2 < (L+d)-L$. Thus $x_1 < x_2$. The same reasoning, coupled with mathematical induction, will show that if $x_1 < L$, then $x_n < x_{n+1}$ for $n = 1, 2, 3, \cdots$. The sequence $\{x_n\}$ is therefore monotone increasing and bounded above by $L$. A similar argument will show that if $x_1 > L$, then $\{x_n\}$ is a monotone decreasing sequence bounded below by $L$. Should it happen that $x_1 = L$, then $x_n = L$, all $n$. In each case the sequence converges to $L$ since the function

$$h(r) = \int_{r+d}^{r} g(x)\,dx$$

is continuous in $r$.

THEOREM 2. *For $f$ as in Theorem* 1, *equation* (4) *defines $r$ implicitly as a function of $d$ and $T$. This function is monotone increasing in $d$ ($T$ fixed) and monotone decreasing in $T$ ($d$ fixed).*

*Proof.* The first statement of the theorem follows from the monotonicity of $f$. The remainder follows since $\partial r/\partial d$ is positive and $\partial r/\partial T$ is negative.

*Project suggestions.* Students may wish to formulate and solve other problems described by first order equations. Some which come to mind are a growing population periodically decimated by disease, a cooling body whose temperature is periodically changed drastically.

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