A PROPERTY OF SECOND ORDER DIFFERENTIAL EQUATIONS WITH APPLICATION TO FORMAL KINETICS

JOHN Z. HEARON

From the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda

ABSTRACT It is shown that if $x(t)$ is the solution of a second order differential equation, with real negative characteristic roots (not necessarily distinct), which exhibits an extremum at $t = T$, then $T|x(T)|/|A| \leqq 1/e$ where A is the area under the $x(t)$ curve. This result is compared to a special case previously derived by M. Morales and applications of the theorem to formal kinetic problems are discussed.

Many years ago, Morales (1) proved, in a formal kinetic context, a little noted theorem. We have had occasion to broaden and apply this theorem and it seems of interest to point out the original version and compare it to the present one.

Consider the system

$$\dot{x}_1 = -k_1 x_1, \qquad x_1(0) = x_1^0 > 0 \qquad [1]$$

$$\dot{x}_2 = k_1 x_1 - k_2 x_2, \qquad x_2(0) = 0 \qquad [2]$$

where dots denote time derivations and k_1 and k_2 are positive and distinct. The well known solutions are

$$x_1 = x_1^0 e^{-k_1 t} \qquad [3]$$

$$x_2 = \frac{k_1 x_1^0}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t}). \qquad [4]$$

If the single maximum of x_2 (t) occurs at $t = T$, then from [2] and [3]

$$x_2(T) = k_1 \frac{x_1^0}{k_2} e^{-k_1 T}. \qquad [5]$$

But the integral $A = \int_0^\infty x_2(t)dt$ has, from [4], the value x_1^0/k_2, and since $k_1 T e^{-k_1 T}$ is not more than $1/e$, [5] can be put in the form

$$T x_2(T)/A \leqq 1/e. \qquad [6]$$

This is the theorem referred to (we have essentially paraphrased Morales' proof) and it states that the area of the rectangle $Tx_2(T)$ is not more than $1/e$ of the area under the curve $x_2(t)$.

Equation [4] describes the concentration of the intermediate X_2 in the scheme

$$X_1 \xrightarrow{k_1} X_2 \xrightarrow{k_2} X_3 \qquad [7]$$

under the initial conditions given in [1] and [2]. If one has data on such a supposed species (or corresponding information in any of a variety of analogues to the chemical kinetic situation) from which the maximum value, $x_2(T)$, and the area, A, can be estimated, then, if these estimates infringe the inequality [6] one must abandon the hypothesis that the model [7] gave rise to the data. On the other hand if [6] is obeyed the model [7] may or may not obtain and we include in what follows a more general model which exhibits the property [6].

Consider the function

$$x(t) = a_1e_1(t) + a_2e_2(t) \qquad [8]$$

where $e_i(t) = \exp(-\lambda_i t)$, the λ_i are positive and distinct, and the a_i are constants which later will be tacitly restricted. We proceed to show that the inequality [6] actually stems from the fact that the sign of function

$$\Phi(t) = x + \frac{\dot{x}}{\lambda_2} - \lambda_1 e_1 A \qquad [9]$$

where A is the integral $\int_0^\infty x(t)dt$, is strictly determined by the sign of $x(0)$. In fact for all $t \geqq 0$,

$$\begin{aligned} x(0) \geqq 0 \quad &\text{implies} \quad \Phi(t) \leqq 0 \\ x(0) \leqq 0 \quad &\text{implies} \quad \Phi(t) \geqq 0. \end{aligned} \qquad [10]$$

For, from [8] and its derivative

$$x + \frac{\dot{x}}{\lambda_2} = \lambda_1 e_1 a_1 \left[\frac{1}{\lambda_1} - \frac{1}{\lambda_2}\right]. \qquad [11]$$

But

$$A = \frac{a_1}{\lambda_1} + \frac{a_2}{\lambda_2}$$

$$x(0) = a_1 + a_2$$

and hence

$$x + \frac{\dot{x}}{\lambda_2} = \lambda_1 e_1 \left(A - \frac{x(0)}{\lambda_2}\right) \qquad [12]$$

from which the stated properties of $\Phi(t)$ follow at once.

If, in [12] we set $x(0) = \dot{x}(T) = 0$, a generalization of [5] is obtained and if $A > 0$ the corresponding generalization of [6] follows. In fact if $x(0) \geqq 0$ and $A > 0$ then for any t such that $\dot{x}(t) \geqq 0$ we have

$$tx(t)/A \leqq 1/e. \qquad [13]$$

In general if $\dot{x}(T) = 0$ (and for λ_i real as assumed, there is just one such T) it follows from [12] that

$$T\,|x(T)|/|A| \leqq 1/e \tag{14}$$

and this is a property of a solution of a linear second order differential equation with constant coefficients and negative characteristic roots provided that solution exhibits an extremum.

Equation [12] holds if the subscripts 1 and 2 are interchanged, as is clear from its derivation, and it also holds if $\lambda_1 = \lambda_2 = \lambda > 0$. For then we must take $x(t)$ to be

$$x(t) = ae^{-\lambda t} + bte^{-\lambda t}$$

from which

$$x + \frac{\dot{x}}{\lambda} = \frac{b}{\lambda^2}\lambda e^{-\lambda t}$$

$$x(0) = a$$

$$A = \frac{a}{\lambda} + \frac{b}{\lambda^2}$$

and thus

$$x + \frac{\dot{x}}{\lambda} = \lambda e^{-\lambda t}[A - x(0)/\lambda],$$

the inequality [14] following as before

Obviously equality in [14] cannot hold if $x(0) \neq 0$, since $|A - x(0)/\lambda_i| = |A|$ if and only if $x(0) = 0$. However, given $x(0) = 0$, equality obtains in [14] if $\lambda_i T = 1$, for one of the λ's in case they are distinct, or if $\lambda T = 1$, in case $\lambda_1 = \lambda_2 = \lambda$. But in the distinct case[1] this value of T will not satisfy $\dot{x}(T) = 0$.

We can summarize the only case of real interest in chemical kinetics as follows:—

The non-negative solution[2] of a linear second order differential equation with real negative characteristic roots obeys

$$Tx(T)/A \leqq 1/e$$

where $\dot{x}(T) = 0$, with equality if and only if $x(0) = \lambda_1 - \lambda_2 = 0$.

The above theorem applies to the concentration of either X_1 or X_2 (whichever exhibits a maximum) in the scheme

$$X_4 \leftarrow X_1 \leftrightarrows X_2 \rightarrow X_3.$$

[1] The fact that given $x(0) = 0$ equality holds in [14] when $\lambda_1 = \lambda_2$ suggests a means of distinguishing between overdamping and critical damping in any second order system. The damped case, quite different, is considered briefly at the end of this paper and in Note II.

[2] It has been shown (3) that necessary conditions for non-negative solutions of $\dot{x}_i = a_{i1}x_1 + a_{i2}x_2$, $x_i(0) \geqq 0$, $i = 1, 2$, are $a_{ii} \leqq 0$, $a_{ij} \geqq 0$, $i \neq j$, and it can be shown that these are sufficient and always satisfied in linear kinetic cases. In general for a second order equation it is necessary and sufficient, if $x(0) \geqq 0$, $\dot{x}(0) \geqq 0$, for the companion matrix of the characteristic polynomial to be similar to a matrix $[a_{ij}]$ with $a_{ii} \leqq 0$, $a_{ij} \geqq 0$, $i \neq j$.

It was for the purpose (2) of excluding, on the basis of experimental data, such a model that the above theorem was derived. In the case[3] under discussion (2), data were available on $x_3\ (t)$ which obeys $\dot{x}_3 = kx_2$. The area A, under the x_2 curve, is given by direct integration as $A = [x_3(\infty) - x_3(0)]/k$, where $x_3(\infty)$ is the final yield of x_3, a well defined observable quantity. The maximum value of $x_2(t)$ is given by $x_2(T) = \dot{x}_3(T)/k$, where $\dot{x}_3(T)$ is the slope of $x_3(t)$ at the inflection point exhibited when $\dot{x}_2(t) = 0$. Thus

$$T\dot{x}_3(T)/[x_3(\infty) - x_3(0)] = Tx_2(T)/A$$

and observations on the slope of $x_3(t)$ at the inflection point, the time $t = T$ at which it occurs, and the asymptotic value of $x_3(t)$ permit a test of the inequality which is a necessary condition for the model to apply. It should be pointed out that in practice, T, $x(T)$, and A (whether directly estimated or indirectly as in the above example) are afflicted with error; thus the test, which can only exclude a given hypothesis, must be used with care when $Tx(T)/A$ is not very different from $1/e$. The problem of applying the test in a statistically rigorous manner does not appear to be a simple one. However, in many cases $Tx(T)/A$ will exceed $1/e$ to such an extent that, in view of the errors of observation involved, rejection of the model appears to be quite safe.

It is worth noting, from [1] and [2], that $\dot{x}_1 + \dot{x}_2 = -k_2x_2$, and integration of both sides of this relation leads at once to $k_2A = x_1^0$. Now the same is true of the equations

$$\dot{x}_1 = -k_1x_1 + k_{-1}x_2, \qquad x_1(0) = x_1^0$$
$$\dot{x}_2 = k_1x_1 - (k_{-1} + k_2)x_2, \qquad x_2(0) = 0 \qquad [15]$$

which describe X_1 and X_2 in the scheme $X_1 \leftrightarrows X_2 \rightarrow X_3$. Thus the area under the $x_2(t)$ curve is x_1^0/k_2 independent of the value of k_{-1}; in particular it is the same whether or not the conversion of X_1 to X_2 is reversible. It was this observation which prompted the present investigation. In fact for the scheme

$$X_1 \leftrightarrows X_2 \leftrightarrows \cdots \leftrightarrows X_n \xrightarrow{k_n} X_{n+1}$$

it is true that

$$\sum_{i=1}^{n} \dot{x}_i = -k_nx_n$$

from which

$$k_nA_n = \sum_{i=1}^{n} x_i^0 ,$$

[3] The problem here was to set a lower limit on the number of intermediates which occur when prothrombin is converted to thrombin by biological activators. The only species the time course of which could be followed was thrombin, the final product. It could be shown (2) by experiment and kinetic analysis of the effect of soybean trypsin inhibitor, that at least one intermediate occurs. The method which is being outlined here was used to establish that not less than two intermediates occur.

where A_n is the area under the $x_n(t)$ curve. In particular if

$$x_2^0 = x_3^0 = \cdots = x_n^0 = 0$$

then $k_i A_i = x_1^0$, for all i such that X_i is converted irreversibly to X_{i+1} with rate constant k_i, independent of which, if any, of the steps between X_1 and X_i are irreversible. This is the basis of the following extension.

Consider the scheme

$$X_1 \underset{k_1}{\overset{k_{-1}}{\leftrightarrows}} X_2 \underset{k_2}{\rightarrow} X_3 \underset{k_3}{\rightarrow} \cdots \rightarrow X_n \underset{k_n}{\rightarrow} X_{n+1}$$

Then if initially only $x_1(t)$ is different from zero, $x_1(t)$ and $x_2(t)$ obey [15], while

$$\dot{x}_r = k_{r-1}x_{r-1} - k_r x_r, \qquad x_r(0) = 0 \tag{16}$$

for $3 \leqq r \leqq n$. The areas A_r are given by

$$A_r = x_1^0/k_r, \qquad r = 2, 3, \cdots, n \tag{17}$$

We accept the intuitive facts (see Note I for formal proofs) that for each $r \geqq 2$ there is a single t such that $\dot{x}_r = 0$ and that the maximum of x_{r-1} occurs at an earlier time than that of x_r. If the maximum of x_r occurs at $t = T_r$ then

$$\begin{gathered} \dot{x}_r(T_r) = 0 \\ x_r(T_r) > x_r(t), \quad \text{for all} \quad t \neq T_r \\ T_2 < T_3 < \cdots < T_n \end{gathered} \tag{18}$$

From [16], [17], and [18]

$$\frac{x_2(T_2)}{A_2} > \frac{x_3(T_3)}{A_3} > \cdots > \frac{x_n(T_n)}{A_n}$$

and applying $T_2 x_2(T_2) \leqq A/e$, we have

$$\frac{1}{eT_2} \geqq \frac{x_2(T_2)}{A_2} > \frac{x_3(T_3)}{A_3} > \cdots > \frac{x_n(T_n)}{A_n} \tag{19}$$

where the first inequality reduces to strict equality if and only if $k_{-1} = k_1 - k_2 = 0$. In the special case $k_{-1} = k_i - k_j = 0$ for all i, j it can be shown (see Note I) that

$$T_r x(T_r)/A_r \geqq 1/e \tag{20}$$

for $2 \leqq r \leqq n$, with equality for $r = 2$. Equations [20] and [19] give the bounds

$$1/e \leqq T_r x(T_r)/A_r \leqq T_r/eT_2 \tag{21}$$

for $n \geqq r > 1$.

Finally, we wish to note briefly the very different situation which obtains when the characteristic roots are not real. If in [8], the λ_i are complex, with real part $-\mu < 0$, it can be shown (Note II) that if $x(t)$ is real and $x(0) = 0$, then for every $T > 0$, such that $\dot{x}(T) = 0$, it is true that $T|x(T)| > \mu T e^{-\mu T}\,|A|$. This is in contrast to the fact that when the λ_i are real and negative (distinct or not), we have the *equality* $T|x(T)| = \lambda T e^{-\lambda T} \ |A|$ which (with $\lambda T e^{-\lambda T} < 1/e$) is the basis of inequality [14] when $\dot{x}(T) = x(0) = 0$.

NOTE I

From [16] of the text, it follows by formal integration and a change of variable that

$$x_r(t) = k_{r-1} \int_0^t x_{r-1}(t - \theta) e_r(\theta) \, d\theta, \qquad r \geqq 3 \qquad \text{[i]}$$

where $e_r(t) = \exp(-k_r t)$. It is a remarkable fact that, given $k_r > 0$ for all r, $x_1^0 > 0$, and the properties of $x_2(t)$ deducible from [15] and [8], it follows from the integral equation [i], that every $x_r(t)$ is positive in the interval $0 < t < \infty$; each $x_r(t)$, $r \geqq 2$, exhibits a single extremum which is a (relative and absolute) maximum; and the maximum of x_{r-1} precedes in time that of x_r.

Differentiation of [i] followed by a change of variable gives

$$\dot{x}_r(t) = k_{r-1} \int_0^t \dot{x}_{r-1}(\theta) e_r(t - \theta) \, d\theta, \qquad r \geqq 3 \qquad \text{[ii]}$$

provided $x_r(0) = 0$ for $r \geqq 2$, which has been assumed. Clearly $\dot{x}_r(t)$ can vanish only if $\dot{x}_{r-1}(\theta)$ changes sign in the interval $0 < \theta < t$. Let $t = t_1$ be the first non-zero value of t for which $\dot{x}_r(t)$ vanishes. Then $\dot{x}_r(t)$ can vanish again for $t = t_2 > t_1$ only if $\dot{x}_{r-1}(\theta)$ changes signs in the interval $t_1 < \theta < t_2$. But $\dot{x}_2(t)$ changes signs only once in the interval $0 < t < \infty$ (since it is of the form [8] with real λ_i) and it follows that $\dot{x}_r(t)$, $r \geqq 2$, can vanish at most once in that interval and since $x_r(0) = x_r(\infty) = 0$, $r \geqq 2$, $\dot{x}_r(t) \geqq 2$, vanishes at least once. It has been shown $\dot{x}_r(t)$ can vanish only if $\dot{x}_{r-1}$ has previously vanished; thus the single extremum of x_r is preceded by that of x_{r-1}. Now by the same kind of argument it follows from [i] that $x_r(t)$ can vanish only if x_{r-1} has previously vanished. But $x_2(t)$ certainly does not vanish in $0 < t < \infty$, (for it is initially zero, with, from [15], $\dot{x}_2(0) > 0$, it asymptotically approaches zero, and $\dot{x}_2(t)$ can vanish only once), and it follows that $x_r(t)$ is positive for $0 < t < \infty$ and the extrema are absolute maxima. This completes the proof of the assertions in [18].

For the special case $k_{-1} = 0$, $k_1 = k_2 = \ldots = k_n = k$ referred to in [20] and [21], the solutions are

$$x_r(t) = x_1^0 \frac{(kt)^{r-1}}{(r-1)!} e^{-kt}, \qquad r = 1, 2, \cdots, n$$

from which $kT_r = r-1$ for $r \geqq 2$. These relations with [17] give

$$T_r x_r(T_r)/A_r = \frac{(r-1)^r}{(r-1)!} e^{-(r-1)} = g(r), \qquad r \geqq 2$$

and it is clear that $g(2) = 1/e$, $g(3) = 4/e^2 > 1/e$. That $g(r) > 1/e$ for $r \geqq 3$ is established as follows: Consider $f(r) = g(r+2)/g(r+1) = (1 + 1/r)^{r+1} \cdot 1/e$. It is to be shown that $f(r) > 1$ for $r \geqq 1$ and hence $1/e = g(2) < g(3) < \ldots < g(n)$. It is sufficient to show that $\ln f(r) > 0$ for $r \geqq 1$ and we write

$$\ln f(r) = (r + 1) \int_1^{1+1/r} \frac{dt}{t} - 1.$$

But $1/t > (1 + 1/r)^{-1}$ in the interval $1 < t < (1 + 1/r)$ and hence

$$\ln f(r) > \frac{(r+1)}{\left(1+\frac{1}{r}\right)} \cdot \frac{1}{r} - 1 = 0$$

This completes the proof of [20].

NOTE II

Let $x(t) = a_1e_1 + a_2e_2$, as in text [8]. If this is the solution of a second order equation and $\lambda_1 = \alpha + i\beta$, where $i = \sqrt{-1}$, then $\lambda_2 = \alpha - i\beta$. If $x(t)$ is to be real, then a_1 and a_2 are also complex conjugates, say $a_1 = a + ib$, $a_2 = a - ib$. In order for A to exist we must have $\alpha < 0$ and to keep this case separate from the case of repeated real roots, already treated, we require $\beta \neq 0$. For any complex number or function f, of t, we denote the real part by $Re(f)$. Then $x(0) = 2\, Re(a_1) = 2a$. If $a = 0$,

$$x(t) = 2\, Re\,(a_1e_1) = -2be^{\alpha t} \sin \beta t \qquad [i]$$

and if $\dot{x}(T) = 0$, T must satisfy $Re(a_1\lambda_1e_1) = 0$, or

$$\alpha \sin \beta T + \beta \cos \beta T = 0 \qquad [ii]$$

From [i] and [ii],

$$x(T) = \frac{2b\beta}{\alpha} e^{\alpha T} \cos \beta T \qquad [iii]$$

The area, A, is

$$A = 2\, Re\,(a_1/\lambda_1) = 2b\beta/\alpha^2 \left[1 + \left(\frac{\beta}{\alpha}\right)^2\right] \qquad [iv]$$

From [iii] and [iv]

$$|x(T)| = |A| \left[1 + \left(\frac{\beta}{\alpha}\right)^2\right] |\alpha|\, e^{\alpha T}\, |\cos \beta T| \qquad [v]$$

When [ii] holds, $\sin \beta T \neq 0$, $\cos \beta T \neq 1$, and $\tan \beta T = -\beta/\alpha$, whence $[1 + (\beta/\alpha)^2]$ $|\cos \beta T| = 1/|\cos \beta T| > 1$. Thus from [v]

$$T\,|x(T)| > |A|\; T\mu e^{-\mu T}$$

where $-\alpha = \mu > 0$, as asserted in the text.

Received for publication, June 1, 1961.

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