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Investigation of rates of chemical reaction using laplace transform method

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ABSTRACT This paper discusses the application of Laplace Transform (LT) method in solving the rate equations for the decomposition of benzocaine, which is a first order reaction and the decomposition of acetyl phenyl salicylate (APS) which involves a competitive sequential four components reaction. The mechanisms of these reactions are already known. The results obtained using LT method can be obtained using any other methods. However we show that, for more complicated systems such as the hydrolysis of APS, LT method is more simple and straight forward compared to other methods.

ABSTRAK Kertas kerja ini membincangkan kegunaan kaedah Laplace Transform untuk menyelesaikan persamaan kadar bagi penguraian benzocaine, tindakbalas tertib satu dan penguraian asetil fenil salisilat (APS) iaitu tindakbalas persaingan serta berurutan empat komponen. Mekanisma bagi kedua-dua tindakbalas diketahui. Hasil yang diperolehi menggunakan LT boleh diperolehi dengan kaedah lain. Bagaimanapun, seperti yang ditunjukkan, bagi sistem yang lebih rumit seperti hidrolisis APS, kaedah LT adalah lebih mudah di bandingkan dengan kaedah lain.

(laplace transform, rate equation, hydrolysis, competitive first order)

INTRODUCTION

Recently we have become interested in the analysis of the rate constants for the drug decomposition reactions. There are a number of kinetic models [1] that are used to describe these reactions. These models vary in complexity and the process involved ranging from simple decomposition of one reactant to form a product to a more complex system such as a four component closed system [2-7]. In order to understand better the kinetic model, we need to know not just the concentration of reactant as a function of time but also the concentration of all products as a function of time.

From the kinetic model, differential rate equations can be written. The integrated form of these rate equations can be obtained either analytically or numerically by using a number of available methods. Some examples of these methods are the separation of variables, the determinant method and the Laplace Transform method. The Euler method, the Runge-Kutta method and the predictor-corrector method are examples of numerical methods of solving differential equations [8]. This paper will discuss the Laplace Transform (LT) method in solving rate equations of two typical kinetic models relevant to the drug decomposition processes. In the LT method, the analytical procedure can be both simplified and shortened considerably. The use of the LT method is quite simple yet powerful in the sense that it can be used to solve complex rate equations. This is due to the availability of computer softwares such as MathCAD [9] and Maple [10] that can give answers to the problems with just a few mouse clicks or with just a one-line command. The LT method can be applied only to linear differential equations [11]. Hence if there is a product of concentration terms in the rate equation, then the LT method can be obtained only if all other concentrations except only one

can be kept constant under pseudo first order conditions.

In the present work, we apply the LT method to the hydrolysis of benzocaine, an anesthetic cream and the hydrolysis of an aspirin pro-drug, acetyl phenyl salicylate (APS). The decomposition mechanisms of these drugs have been studied by Irwin [1]. It has been observed that benzocaine undergoes hydrolysis through a single step process and APS undergoes hydrolysis through a combination of competitive sequential steps. These two case studies clearly bring out the simplicity of applying LT methods in solving complicated drug decompositions processes.

METHOD

Laplace Transform is an integral transform that converts differentiation to integration. The definition of LT is

$$L\{f(t)\} = F(s) = \int_0^\infty \exp(-st) f(t) dt \quad (1)$$

After the expression is integrated, the variable t (for time) is eliminated and the function F(s) depends only on variable s. Therefore applying Laplace Transform on a time dependent function will result in an equation or expression that depends on the s variable.

The key property of LT that makes it useful in solving rate equations is:

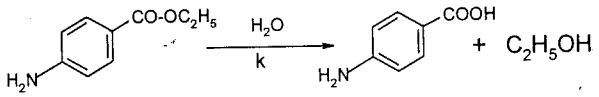
$$L\{f'(t)\} = sL[f(t)] - f(0) \quad (2)$$

where we have used prime to indicate the first derivative and f(0) the value of the function at t=0. This relationship shows that LT converts differentiation into multiplication. Using this property, the application of LT methods to solve rate equations involve the following steps:

(i) Write down the rate equations for the changes in the concentration of all the species involved in the proposed kinetic model.
(ii) Apply the LT to convert the differential equation to an algebraic equation in transformed concentration variables.
(iii) Solve these equations to get the transformed concentrations.
(iv) Apply the inverse LT to get the concentration as a function of time.

RESULTS AND DISCUSSION

We will exemplify the usefulness of the LT method to drug decomposition processes by making use of two different drug decomposition processes, for which the experimental data is already available. As a first case, let us consider the hydrolysis of benzocaine. Benzocaine is found to undergo first order degradation to form 4-aminobenzoic acid as follows:



(A) (B) (C)

The kinetic model for this hydrolysis is:

$$A \xrightarrow{k} B + C$$

where A is benzocaine, B is 4-aminobenzoic acid and C is ethanol and k is the rate constant of this reaction.

The differential forms of the rate equations for this reaction can be written as

$$\frac{dA}{dt} = -kA \quad (3)$$

$$\frac{dB}{dt} = kA \quad (4)$$

$$\frac{dC}{dt} = kA \qquad (5)$$

From equations (4) and (5), the time-dependent concentration of B and C are the same. After applying LT to equations (3) and (4) and using equation (2), we get

$$sa - A_0 = -ka \qquad (6)$$

$$sb - B_0 = ka \qquad (7)$$

where we have used the notations $a = L\{A\}$ and $b = L\{B\}$ with A_0 and B_0 being the initial concentrations of A and B. Now, solving for the transformed concentrations a and b, we get

$$a = \frac{A_0}{s+k} \qquad (8)$$

and

$$b = \frac{ka}{s}, \quad \text{with } B_0 = 0 \qquad (9)$$

To get A, we need to apply the inverse Laplace transformation *viz,* $A = L^{-1}\{a\}$ and $B = L^{-1}\{b\}$. The inverse LT can either be obtained by computer softwares like MathCad or it can be obtained from the table of Laplace Transform. By referring to Table 1, where we have listed a few useful LT pairs, one can easily see that the inverse LT corresponding to equation (8) is (third entry in Table 1)

$$A(t) = A_0 \exp(-kt) \qquad (10)$$

From equation (9), we can get

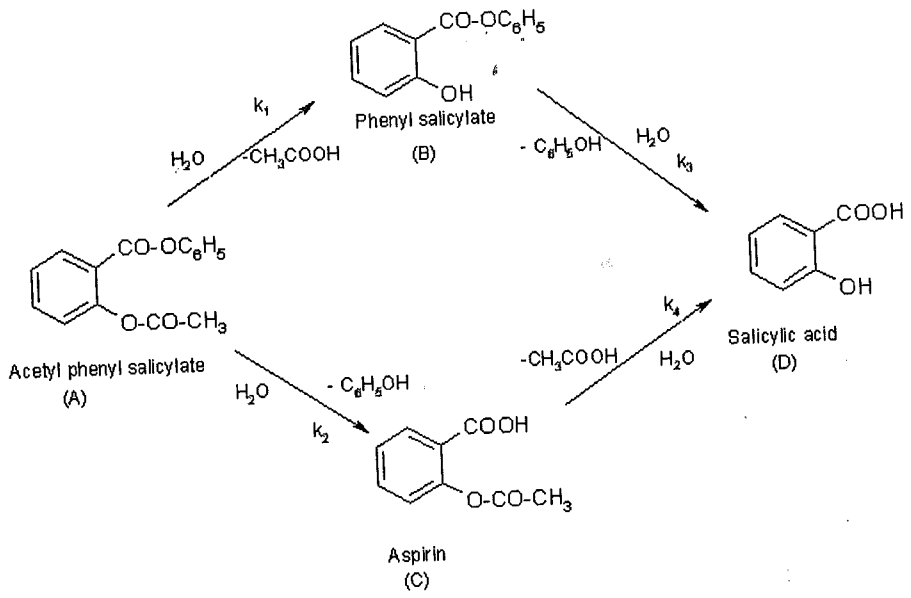
$$b = \frac{kA_0}{s(s+k)} \qquad (11)$$

Using the corresponding inverse LT from Table 1 (fourth entry), we get

$$B(t) = A_0(1 - \exp(-kt)) \qquad (12)$$

Equations (10) and (12) when plotted, will give exponentially decreasing concentration of A and exponentially increasing concentration of B respectively.

The whole procedure of solving the rate equation can be compared to the use of logarithmic transformations in solving the algebraic equations involving products, as shown in Figure 1. Using logarithmic transformations, an algebraic product is converted to a sum, and the result of this sum then inverted back using antilogarithm to get the final result. If the logarithmic transformation can be compared to the LT, then the antilogarithm is similar to the inverse LT and the Table 1 can be compared to the antilogarithm table. Just as one can get the value of the algebraic products without the use of logarithm, the differential rate equations (4) and (5) can be solved to get (10) and (12) without the use of LT. However, for more complicated rate equations, the advantage of using LT over directly solving the differential equations becomes very apparent. This advantage can be exemplified using a more complicated hydrolysis of an aspirin prodrug, namely Acetyl phenyl salicylate(APS). APS undergoes decomposition to yield aspirin through a combination of competitive sequential steps, as given below:



In this reaction, it is very crucial to know the availability of aspirin at a given time. Using the LT method, it is straight forward to know the concentration of all the products and the intermediates involved in the reaction at any time.

The rate equations for this reaction are:

$$\frac{dA}{dt} = -k_1 A - k_2 A = -(k_1 + k_2)A \tag{13}$$

$$\frac{dB}{dt} = k_1 A - k_3 B \tag{14}$$

$$\frac{dC}{dt} = k_2 A - k_4 C \tag{15}$$

$$\frac{dD}{dt} = k_3 B + k_4 C \tag{16}$$

where A = APS, B = phenyl salicylate, C = aspirin, D = salicylic acid. The hydrolysis of APS also produces acetic acid (from A to B and from C to D) and phenol (from A to C and B to D). Hence their concentrations are the same as the concentrations of the main products.

After applying LT to the above equations and using equation (2) and letting $B_0 = C_0 = D_0 = 0$, we get

$$a = \frac{A_0}{s + k_1 + k_2} \tag{17}$$

$$b = \frac{k_1 a}{s + k_3} = \frac{k_1 A_0}{(s + k_3)(s + k_1 + k_2)} \tag{18}$$

$$c = \frac{k_2 a}{s + k_4} = \frac{k_2 A_0}{(s + k_4)(s + k_1 + k_2)} \tag{19}$$

$$d = \frac{k_3 b}{s} + \frac{k_4 c}{s}$$

or

$$d = \frac{k_3 k_1 A_0}{s(s + k_3)(s + k_1 + k_2)} + \frac{k_4 k_2 A_0}{s(s + k_4)(s + k_1 + k_2)} \tag{20}$$

To get the respective concentrations, we need to apply inverse Laplace transformation. For A, equation (17) is similar to equation (8), except that the rate constant k is replaced with $k_1 + k_2$.

$$A(t) = A_0 \exp[-(k_1 + k_2)t] \tag{21}$$

The concentration of B is obtained by applying inverse LT to Eq. (18) and using the Table 1 (fifth entry).

$$B(t) = \frac{k_1 A_0}{k_1 + k_2 - k_3}[\exp(-k_3 t) - \exp(-(k_1 + k_2)t)] \tag{22}$$

The equation for the concentration of C as a function of time is similar to B where the rate constant k_4 is involved instead of k_3. Using the fifth entry in Table1 we get

$$C(t) = \frac{k_2 A_0}{k_1 + k_2 - k_4} X[\exp(-k_4 t) - \exp(-(k_1 + k_2)t)] \quad (23)$$

For the final product D, its concentration can be obtained by taking the inverse LT of equation (20) and using the result of Table 1 (sixth entry) as:

$$D(t) = A_0\left[1 - \frac{k_1 \exp(-k_3 t)}{k_1 + k_2 + k_3} - \frac{k_2 \exp(-k_4 t)}{k_1 + k_2 - k_4} + \frac{(k_3 k_1 + k_4 k_2 - k_3 k_4)\exp[-(k_1 + k_2)t}{(k_1 + k_2 - k_3)(k_1 + k_2 - k_4)}\right] \quad (24)$$

Hence, using LT methods it is straight forward to get the expressions for the concentrations of all the species involved in the reaction. This method can be applied to much more complicated cases, in the similar manner.

The concentration of D increases monotonically with time, whereas B and C increase initially before decreasing again as they form a common product D. This type of information is very useful in determining the temporal availability of drugs under physiological conditions. The use of Mathcad and Maple softwares to get the inverse Laplace Transforms for this reaction are discussed in the Appendix.

CONCLUSIONS

We have applied the Laplace Transform method to two cases of drug decomposition processes. A quick understanding of the variations of the concentrations of different species involved in the drug decompositions can be easily obtained using LT method. These applications show that LT method is a good alternative to direct methods for solving differential rate equations, particularly when the rate process is much complicated. In our case studies we have used tabular form of the LT pairs, which are readily available in mathematical text books. However, in the absence of a suitable table such as Table 1, the LT method can be easily implemented using the softwares like Maple or MathCad.

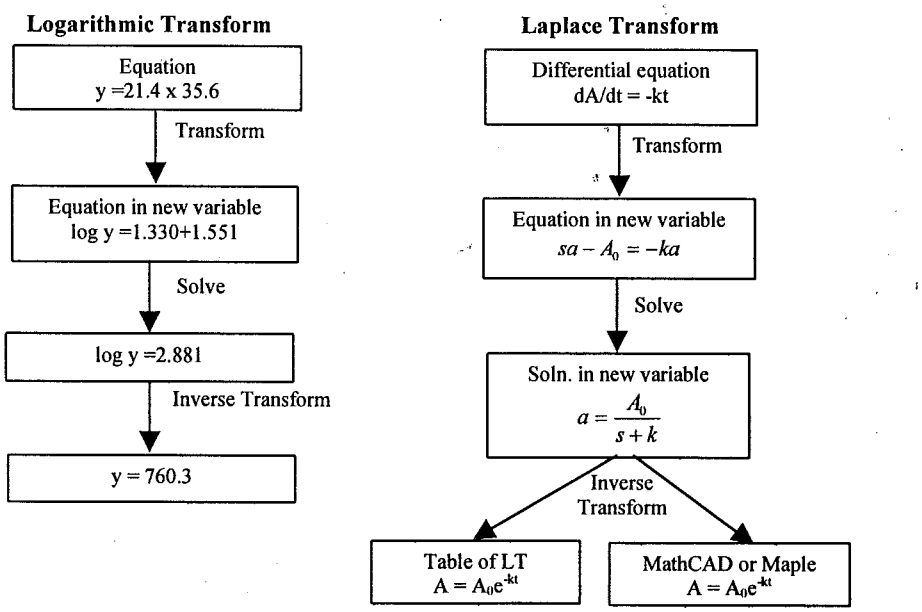


Figure 1. An analogy of solving an algebraic equation using the logarithmic transformation and a differential equation using the Laplace Transform method.

Table 1. Some Useful Laplace Transform Pairs. F(s) is the Laplace Transform of the function f(t).

No.	F (s)	F(t)
1.	$\frac{A_0}{s}$	A_0
2.	$\frac{1}{s^2}$	t
3	$\frac{1}{s+k}$	exp (-kt)
4.	$\frac{1}{s(s+k)}$	$\frac{1}{k}(1-\exp(-kt))$
5.	$\frac{1}{(s+k_1)(s+k_2)}$	$\frac{1}{k_2-k_1}[\exp(-k_1t)-\exp(-k_2t)]$
6.	$\frac{1}{s(s+k_1)(s+k_2)}$	$\frac{1}{k_2k_1}-\frac{\exp(-k_1t)}{k_1(k_2-k_1)}-\frac{\exp(-k_2t)}{k_2(k_1-k_2)}$

APPENDIX 1

Using Maple7 to find the Inverse Laplace Transform of a sequential competitive four component system

First we need to invoke the integral transform command. This can be done by typing **with (inttrans):** We only need to type this command once. The command for getting the inverse Laplace Transform is > **invlaplace(expresion,s,t);** This command will transform the expression written in terms of s variable to a function of t (time).

(i)To find the concentration of A using equation (17), we need to type

>invlaplace(A0/(s+k1+k2),s,t);

Pressing return will produce $A0\ \mathbf{e}^{(-(k1+k2)t)}$ which is equation (21)

(ii) To find B using equation (18), we type the following:

>invlaplace((k1*A0)/((s+k3)*(s+k1+k2)),s,t);

Pressing return will produce

$$\frac{k1\ A0\ (\mathbf{e}^{(-k3\,t)}-\mathbf{e}^{(-(k1+k2)t)})}{k1+k2-k3}$$

which is equation (22).

(iii) To find C using equation (19), the command required and the resulting equation are:

invlaplace((k2*A0)/((s+k4)*(s+k1+k2)),s,t);

$$\frac{k2\ A0\ (-\mathbf{e}^{(-(k1+k2)t)}+\mathbf{e}^{(-k4\,t)})}{-k4+k1+k2}$$

which is equation (23).

(iv) To find D, use equation (20) to type

>invlaplace((k3*k1*A0)/(s*(s+k3)*(s+k1+k2))+(k4*k2*A0)/(s*(s+k4)*(s+k1+k2)), s,t);

$$A0\left(-\frac{e^{(-kk4t)}k2}{k1+k2-k4}+\frac{(k3k1+k4k2-k3k4)e^{(-(k1+k2)t)}}{(k1+k2-k3)(k1+k2-k4)}\right.$$
$$\left.-\frac{e^{(-k3t)}k1}{k1+k2-k3}+1\right)$$

which is the same as equation (24).

APPENDIX 2

Using MathCAD to find the Laplace or Inverse Laplace Transform

The use of MathCAD to get the inverse Laplace transform is quite simple and straightforward. In just a few steps we can get the inverse transform. The answer given by MathCAD for some cases, may require some simplification. The following is an example of how to find the solution to the sequential first order reaction i.e. $A \xrightarrow{k_1} B \xrightarrow{k_2} C$ using MathCAD. We will find the concentrations of A, B and C as a function of time. Recall that (see text)

$$a = \frac{A_0}{s+k} \qquad \text{(A1)}$$

To find A, we need to get the inverse LT using Mathc AD. Type the following (written in bold)

1. Type **A0 /k + s.** The resulting equation should be the same as the right hand side of equation A1.
2. Place the cursor at the letter s.
3. Click the following (in the order written to get the inverse transform.
   Symbolics, Laplace Transform, Inverse Transform. After pressing return, it will produce

   A0 exp(-kt) (A2)

Note: You will get an incorrect answer if the cursor is not at the letter s or if you choose Laplace Transform instead of inverse Laplace Transform.

To find B: applying LT on rate equation for B i.e

$$\frac{dB}{dt} = k_1A - k_2B$$

we will get (letting $B_0 = 0$)

$$b = \frac{k_1A_0}{(s+k_1)(s+k_2)} \qquad \text{(A3)}$$

Type the following;

1. Type **k 1 * A0 sb** (sb= space bar) **/ (s + k1) * (s + k 2)** The equation should be the same as the right hand side of equation A2.
2. Place the cursor at the letter s.
3. Click the following to get the inverse transform *Symbolics, Laplace Transform, Inverse Transform.*
   The resulting equation is

$$B = \frac{k_1A_0}{k_2-k_1}[\exp(-k_1t) - \exp(-k_2t)] \qquad \text{(A4)}$$

Similarly, applying LT on the rate equation involving C i.e

$$\frac{dC}{dt} = k_2B$$

will give us (setting $C_0 = 0$),

$$c = \frac{k_2k_1A_0}{s(s+k_1)(s+k_2)} \qquad \text{(A5)}$$

To find C, type the following:

1. **k2*k1*A0 sb sb** (press space bar twice) **/s*(s+k1)*(s+k2)**
2. Place the cursor at the letter s.
3. Click the following to get the inverse transform. *Symbolics, Laplace Transform, Inverse Transform.*

The resulting equation is

$$C = A_0\left[1-\frac{k_2\exp(-k_1t)}{k_2-k_1}+\frac{k_1\exp(-k_2t)}{k_2-k_1}\right] \qquad \text{(A6)}$$

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