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Title ON THE SOLUTION OF THE NON-LINEAR DIFFERENTIAL EQUATIONS FOR A BIOCHEMICAL ENZYME SYSTEM

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A simple biochemical reaction in stoichiometric form is

$$\underset{\text{(INPUT)}}{Q \xrightarrow{\lambda} \{}S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\text{(TISSUE)}}{ES \xrightarrow{k_2} P} \xrightarrow{k_3} \text{(LOSS)}$$

where Q is the input function, λ is the forcing function coupling coefficient, S is the substrate present, k_1 and k_{-1} are the rate constants for the forward reaction and feed back reaction, respectively, ES is the enzyme-substrate complex which is an unstable intermediate compound, k_2 is the rate constant of disassociation of ES to P, P is the product term or output quantity and k_3 represents the rate constant for loss of product. Thus, we have an open system. Our system contains the well known Law of Conservation of Enzyme.

The rate equations for this reaction form a set of non-linear differential equations. With $C = ES$, we have

$$\frac{dS(t)}{dt} = -k_1 E_T S(t) + k_1 S(t)C(t) + k_{-1} C(t) + \lambda Q$$

$$\frac{dC(t)}{dt} = k_1 E_T S(t) - k_1 S(t)C(t) - (k_{-1} + k_2)C(t)$$

$$\frac{dP(t)}{dt} = k_2 C(t) - k_3 P(t)$$

$$\frac{dE(t)}{dt} = -k_1 E_T S(t) + k_1 S(t)C(t) + (k_{-1} + k_2)C(t) .$$

These equations may be reduced by a certain rotation of axis to a more tractable form. From this form, we transform the major non-linear differential equation into an integral equation of Volterra type. The solution to the non-linear Volterra integral equation is obtained by successive approximations.

ON THE SOLUTION OF THE NON-LINEAR DIFFERENTIAL EQUATIONS FOR A BIOCHEMICAL ENZYME SYSTEM

by

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ON THE SOLUTION OF THE NON-LINEAR DIFFERENTIAL EQUATIONS FOR A BIOCHEMICAL ENZYME SYSTEM

CHAPTER I

INTRODUCTION

The human body is a vast field of biochemical processes, all proceeding simultaneously. How do these processes work? What initially stimulates these processes? What changes occur when the chemistry is unbalanced, and what balances it in the first place?

These questions, and undoubtedly many more, were the questions for which biochemists first sought answers. When the earliest substantial work was done, no one really knows. Biochemistry is a composite field, a field which demands a good working knowledge of both Biology and Chemistry. Only recently, within the last 100 years, have the related sciences, Physics and Mathematics, been introduced into Biochemistry to any extent.

The original work of Michaelis-Menten (4, p. 198-201) in 1913 opened the door for further mathematical study in the field of Biochemistry. The Michaelis-Menten relation

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\rightarrow} P + E$$

was the most important result of that work. Here the E, S, ES, and P stand for Enzyme, Substrate, Enzyme-substrate-complex, and Products respectively (3, p. 9-10). The k_1, k_{-1}, and k_2 are defined as the rate constants of the reaction, this being a closed reaction system. The $k_i (i = 1, -1, 2)$ are defined with the appropriate units to make the stoichiometric relation given above balance dimensionally (Cf. Appendix B, Part 2).

In 1943, B. Chance (4, p. 199-201) made another step forward. He proposed an ingenious technique using mathematical methods for determining groups of reaction rates of rapid enzymatic reactions; however, even his techniques will not tell us anything about the individual k_i (rate constants of the reaction). There remains to be discovered a technique which will evaluate the k_i explicitly.

Since World War II, the field of Mathematical Biochemistry has developed considerably in the direction of Enzyme Kinetics Analysis. This field is growing rapidly and intense interest is now being shown by the number of papers in the various biochemical and biophysical journals.

In 1953, Chance and his associates worked out the necessary details for setting up the Michaelis-Menten chemical reaction in mathematical equation form and obtaining answers from a differential analyzer (3, p. 10). They obtained curves which showed the general form of the dependent variables S, E, ES, and P respectively, all as functions of time; however, no analytical solution to the complicated problem resulted from their study. The rate constants are still uncalculable.

A simple well known example of the Michaelis-Menten relation is the chemical reaction between starch and the enzyme amalyse which is contained in the saliva. When one chews a soda cracker it eventually becomes sweet, since the enzyme reacts with the starch in the cracker to form the product glucose, a simple sugar.

The Michaelis-Menten reaction is then the starting point for our study in this paper. We shall make frequent mention of the "reaction" as a "relation". We shall use these words interchangeably.

Purpose of Study

The Agricultural Chemistry Department at Oregon State University has been interested in Enzyme Kinetics Analysis for some time. In a recent study conducted at Oregon State University, the Michaelis-Menten relation was chosen as a basis for the analysis of a multi-enzyme, multi-substrate system. It was found that steady state equations could be developed in terms of initial quantities of certain substrates and the reaction rate constants. The results of this study seemed to agree with experiment. As a continuation of the work noted above, it was proposed to undertake a study of the complete time solutions for the components of the Michaelis-Menten relation. The possibility of discovering a suitable technique for evaluating the reaction rate constants along with the fact that no mathematical solution or approximation to a solution existed outside of Chance's differential analyzer solution were the main spurring agents. Further, it was suggested that a suitable mathematical technique for predicting the behavior of enzyme-substrate systems would be an extremely useful tool for the biochemist. In the past Chemistry has failed to supply this tool in explicit mathematical equation form. It was forseen that possibly other related fields might find some use for a solution to the Michaelis-Menten relation if their problem can be put in such a form. For example, a chemical engineer may have a complex controller device which would fit the Michaelis-Menten relation scheme. He could adapt the mathematical solution and have his problem solved.

Statement of Problem

The problem which must be either solved or approximated to a good degree of accuracy is that of finding the components S, C, and P of the Michaelis-Menten relation explicitly as functions of time. This means that we must formulate differential equations from the Michaelis-Menten relation and then solve these equations.

Note of Importance

Due to the large number of equations contained in the following text, one should read for an equation statement number contained in the text the word "equation(s)" immediately before each number.

CHAPTER II

DERIVATION OF EQUATIONS

1. System Defined

In considering this problem it was observed that the Michaelis-Menten relation may be extended to correspond with an open system (i. e. a system with an input quantity or forcing function, or a system containing feed back and loss terms). We define our system, based on the Michaelis-Menten relation, as follows

$$\underset{\text{(INPUT)}}{Q} \xrightarrow{\lambda} \Big\{ \underset{\text{(TISSUE)}}{S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES} \xrightarrow{k_2} P \xrightarrow{k_3} \text{(LOSS)}$$

where k_1, k_{-1}, and k_2 are the same rate constants defined as before. However, λ is defined as an assimilation constant or coupling coefficient with suitably chosen units and k_3 is defined as the loss term rate constant. The rate constant k_3 tends to act like the diffusion constant in heat conduction problems.

Consider the input quantity Q. Since we are assuming the existence of explicit solution(s) of the modified Michaelis-Menten relation, we then restrict Q to be a continuous function of time, or piecewise continuous such as is found in a step function.

It is known from previous Enzyme Kinetics Analysis that the modified Michaelis-Menten relation gives us the following set of non-linear differential equations

(2.1.1) $$\frac{dS}{dt} = -k_1 E \cdot S + k_{-1} C + \lambda Q$$

(2.1.2) $$\frac{dC}{dt} = k_1 E \cdot S - (k_{-1} + k_2) C$$

(2.1.3) $$\frac{dP}{dt} = k_2 C - k_3 P$$

(2.1.4) $$\frac{dE}{dt} = -k_1 E \cdot S + (k_{-1} + k_2) C$$

where C stands for the enzyme-substrate complex (3, p. 10). Note here that S, C, and P carry the units of concentration.

A very interesting result can be formulated if we add (2.1.2) and (2.1.4) together.

(2.1.5) $$\frac{dC(t)}{dt} + \frac{dE(t)}{dt} = 0$$

which implies that

(2.1.6) $$C(t) + E(t) = E_T, \quad \text{a constant.}$$

Equation (2.1.6) is a mathematical statement of the Law of Conservation of Enzyme. This Law is a necessary condition for the Michaelis-Menten relation to hold. It has been shown that this Law can be extended to N enzymes and N intermediate enzyme-complexes (3, p. 21). Note that $C(t)$ is the bound enzyme and $E(t)$ is the free enzyme concentration respectively.

Solving for $E(t)$ in (2.1.6), then substituting this result for $E(t)$ in (2.1.1) etc., we obtain the following set of non-linear differential equations

$$(2.1.7) \qquad \overset{\circ}{S}(t) = -k_1 E_T S(t) + k_1 C(t) \cdot S(t) + k_{-1} C(t) + \lambda Q$$

$$(2.1.8) \qquad \overset{\circ}{C}(t) = k_1 E_T S(t) - k_1 C(t) \cdot S(t) - (k_{-1} + k_2) C(t)$$

$$(2.1.9) \qquad \overset{\circ}{P}(t) = k_2 C(t) - k_3 P(t)$$

$$(2.1.10) \qquad \overset{\circ}{E}(t) = k_1 E_T S(t) - k_1 S(t) \cdot C(t) + (k_{-1} + k_2) C(t)$$

where

$$(2.1.11) \qquad \overset{\circ}{S}(t) = \frac{dS}{dt}, \quad \text{etc.}$$

Note here that the non-linearity enters in at the product term $C(t) \cdot S(t)$ (i.e. product of two dependent variables).

$\overset{\circ}{2}$. Assumptions and Conditions on Dependent Variables of System; Derivation of Basic Non-linear Differential Equation

To begin our discussion we notice that (2.1.1) and (2.1.2) are the equations which contain the most information about $S(t)$ and $C(t)$

respectively. This does not mean that we shall ignore (2.1.3) and (2.1.4). We shall make use of (2.1.3) in computing $P(t)$ once we have found $S(t)$ and $C(t)$. We shall make use of (2.1.4) indirectly in that (2.1.2) + (2.1.4) = 0, which gives us the previously mentioned Law of Conservation of Enzyme in differential form. Thus we may use (2.1.6) to find $E(t)$. Also, before we begin the details of a solution to Equations (2.1.1) - (2.1.4), it should be mentioned here that solutions to (2.1.1) and (2.1.2) do not exist in terms of elementary functions (2, p. 102). Thus some kind of convergent approximating sequence of functions, possibly exponential in nature, is one method of approach to a solution. Another technique is to reduce (2.1.1) and (2.1.2) to a set of non-linear integral equations and then look for a convergent sequence. Still another technique is that of analytic continuation on the real axis.

Undoubtedly more techniques than mentioned above exist; however, we seek the approximating solution which is most straightforward. We consider the following assumptions valid for the solution of (2.1.1), (2.1.2), and (2.1.3):

1. S, C, P, and E are all continuous functions of time on the interval $0 \leq t \leq T < \infty$.
2. $\mathring{S}$, $\mathring{C}$, $\mathring{P}$, and $\mathring{E}$ are continuous $0 \leq t \leq T < \infty$.
3. We assume the existence of an approximating sequence for $S = S(t)$ which is convergent and we assume this sequence to be exponential in nature.

A necessary condition on $S = S(t)$ is that $\overset{\circ}{S}(t) \to 0$ as $t \to \infty$. It is also necessary to assume that Q can be bounded in (0, T).

Now that we have our assumptions made we shall proceed to put (2. 1. 7) and (2. 1. 8) into a more tractable form. We can accomplish this by the following substitution. Let

$$S = S^* \cos\theta - C^* \sin\theta$$

and

$$C = S^* \sin\theta + C^* \cos\theta \ .$$

When these transformations are substituted into (2. 1. 1) and (2. 1. 2) respectively we obtain

$$\begin{aligned}(2.2.1) \qquad \overset{\circ}{S}{}^* \cos\theta - \overset{\circ}{C}{}^* \sin\theta &= -k_1 E_T (S^* \cos\theta - C^* \sin\theta) \\ &+ k_1 (S^{*2} \cos\theta \sin\theta - C^{*2} \cos\theta \sin\theta + S^* C^* (\cos^2\theta - \sin^2\theta)) \\ &+ k_{-1} (S^* \sin\theta + C^* \cos\theta) + \lambda Q\end{aligned}$$

and the second equation

$$\begin{aligned}(2.2.2) \qquad \overset{\circ}{S}{}^* \sin\theta + \overset{\circ}{C}{}^* \cos\theta &= k_1 E_T (S^* \cos\theta - C^* \sin\theta) \\ &- k_1 (S^{*2} \cos\theta \sin\theta - C^{*2} \sin\theta \cos\theta + S^* C^* (\cos^2\theta - \sin^2\theta)) \\ &- (k_{-1} + k_2)(S^* \sin\theta + C^* \cos\theta) \ .\end{aligned}$$

Now it will be desirable if the product term $S^* \cdot C^*$ vanishes identically. This will happen only if $\cos^2\theta - \sin^2\theta \equiv 0$ which will be true if and only if $\theta = \pm(2n+1)\pi/4$ and $n = 0, 1, 2 \cdots$. We see that our rotation angle is not unique, but multiple valued. Choosing $\theta = 45°$, since both $\sin\theta$ and $\cos\theta$ are positive in the first quadrant, we find that (2. 2. 1) and (2. 2. 2) reduce to the following set

$$(2.2.3) \qquad \frac{\overset{\circ}{S}^* - \overset{\circ}{C}^*}{\sqrt{2}} = -k_1 E_T\left(\frac{S^* - C^*}{\sqrt{2}}\right) + \frac{k_1}{2}(S^{*2} - C^{*2}) + k_{-1}\left(\frac{S^* + C^*}{\sqrt{2}}\right) + \lambda Q$$

and the second term

$$(2.2.4) \qquad \frac{\overset{\circ}{S}^* + \overset{\circ}{C}^*}{\sqrt{2}} = k_1 E_T\left(\frac{S^* - C^*}{\sqrt{2}}\right) - \frac{k_1}{2}(S^{*2} - C^{*2}) - (k_{-1} + k_2)\left(\frac{S^* + C^*}{\sqrt{2}}\right) .$$

If we add (2. 2. 3) and (2. 2. 4) we obtain

$$(2.2.5) \qquad \frac{2\overset{\circ}{S}^*}{\sqrt{2}} = \frac{-k_2}{\sqrt{2}}(S^* + C^*) + \lambda Q$$

or with further reduction

$$(2.2.6) \qquad 2\overset{\circ}{S}^* + k_2 S^* = -k_2 C^* + \sqrt{2}\,\lambda Q .$$

Solving for C^* in (2. 2. 6) we obtain

$$\text{(2. 2. 7)} \qquad C^* = -(2\overset{\circ}{S}{}^* + k_2 S^* - \sqrt{2}\,\lambda Q)/k_2 \quad .$$

Substituting the C^* found in (2. 27) into (2. 2. 3) yields

$$\text{(2. 2. 8)} \qquad \sqrt{2}\,\overset{\circ\circ}{S}{}^* + \left(\sqrt{2} + \sqrt{2}\,k_1 \frac{E_T}{k_2} + \sqrt{2}\,\frac{k_{-1}}{k_2} - 2\sqrt{2}\,\frac{k_1 \lambda Q}{k_2^2}\right)\overset{\circ}{S}{}^*$$

$$+ \left(\sqrt{2}\,k_1 E_T - \sqrt{2}\,\frac{k_1}{k_2}\,\lambda\,Q\right) S^* + \frac{2k_1}{k_2^2}\,\overset{\circ}{S}{}^{*2} + \frac{2k_1}{k_2}\,\overset{\circ}{S}{}^* S^*$$

$$+ \left(\frac{k_1}{k_2^2}\,\lambda Q - \frac{k_{-1}}{k_2} - \frac{k_1 E_T}{k_2} - 1\right)\lambda Q = 0 \quad .$$

Assuming Q constant in our system, (2. 2. 8) further reduces to

$$\text{(2. 2. 9)} \qquad \overset{\circ\circ}{S}{}^* + a_0 \overset{\circ}{S}{}^* + a_1 S^* + a_2 \overset{\circ}{S}{}^{*2} + a_3 S^* \overset{\circ}{S}{}^* + a_4 = 0$$

with the a_i (i = 0, 1, 2, 3, 4), being defined accordingly from (2. 2. 8) (Cf. Appendix B, Part 1). It should be noted here that the units on the a_i are contained in Appendix B, Part 2.

We shall choose to call (2. 2. 9) our basic non-linear differential equation.

An interesting side light of the basic non-linear differential equation (2. 2. 9) is that it can be put into dimensionless variable form by the following transformations. Let

(2.2.10) $$S^* = \mathscr{s} \cdot \mathcal{S}$$

and

(2.2.11) $$t = \mathscr{t} \cdot \mathcal{T}$$

Substitution of these transformations yields

(2.2.12) $$\frac{\mathcal{S}\overset{\circ\circ}{\mathscr{s}}}{\mathcal{T}^2} + a_0 \frac{\mathcal{S}\mathring{\mathscr{s}}}{\mathcal{T}} + a_1 \mathcal{S}\mathscr{s} + a_2 \frac{\mathcal{S}^2 \mathring{\mathscr{s}}^2}{\mathcal{T}^2} + a_3 \frac{\mathcal{S}^2 \mathscr{s}\mathring{\mathscr{s}}}{\mathcal{T}} + a_4 = 0$$

where

(2.2.13) $$\mathring{\mathscr{s}} = \frac{d\mathscr{s}}{d\mathscr{t}}, \quad \text{etc.}$$

Since $\mathcal{S}$ and $\mathcal{T}$ are not zero, multiply through (2.2.12) by $\frac{\mathcal{T}^2}{\mathcal{S}}$ and obtain

(2.2.14) $$\overset{\circ\circ}{\mathscr{s}} + a_0 \mathcal{T}\mathring{\mathscr{s}} + a_1 \mathcal{T}^2 \mathscr{s} + a_2 \frac{\mathring{\mathscr{s}}^2}{\mathcal{S}} + a_3 \frac{\mathcal{T}\mathscr{s}\mathring{\mathscr{s}}}{\mathcal{S}} + a_4 \frac{\mathcal{T}^2}{\mathcal{S}} = 0.$$

Notice that $\mathscr{s}$ is a dimensionless variable. For the remainder of this paper we shall assume :

(2.2.15)
(1) $\mathcal{S} = 1$ unit of concentration

(2) $\mathcal{T} = T$ units of time .

Thus, our basic non-linear differential equation will be used as it stands except that now S^* is dimensionless.

$\overset{\circ}{3}$. Transformation of Initial Conditions

Now that we have derived the differential equation (2.2.14), we should establish our initial conditions in the rotated system before we continue our discussion of the solution of this equation.

From our transformation equations we obtain

$$S = \frac{S^* - C^*}{\sqrt{2}} \tag{2.3.1}$$

$$C = \frac{S^* + C^*}{\sqrt{2}}$$

and from (2.2.5) we have

$$2\overset{\circ}{S}{}^* + S^* = -C^* + \sqrt{2}\,Q$$

where $k_2 \equiv 1$ and λ is also assumed here as $\lambda \equiv 1$.

If we add S and C together in (2.3.1) and solve for S^* we obtain

$$\frac{S + C}{\sqrt{2}} = S^* . \tag{2.3.2}$$

Now we assume the initial conditions $S(0) = K$, $K > 0$, and $C(0) = 0$. From this we find that

$$S^*(0) = \frac{K}{\sqrt{2}} . \tag{2.3.3}$$

Similarly by subtracting C from S in (2.3.1) we obtain upon solving for C^* the expression

$$\frac{S - C}{\sqrt{2}} = - C^* . \tag{2.3.4}$$

Using the above initial conditions we find that

$$C^*(0) = - \frac{K}{\sqrt{2}} . \tag{2.3.5}$$

These initial conditions in the rotated system have been transformed independently of the rate constants and hence will work for any system such as described by (2.2.9).

The next equation, being (2.2.5) in which we find the initial rate of change of concentration (i.e. $\left.\frac{dS^*}{dt}\right|_{t=0}$), is dependent upon the value of the input quantity Q.

Since, $S^*(0) = \frac{K}{\sqrt{2}}$ and $C^*(0) = - \frac{K}{\sqrt{2}}$,

we then find by substitution of these values into equation (2.2.5)

$$2\overset{\circ}{S}{}^*(0) + \frac{K}{\sqrt{2}} = -\left(-\frac{K}{\sqrt{2}}\right) + \sqrt{2}\, Q \tag{2.3.6}$$

which implies that

$$\overset{\circ}{S}{}^*(0) = \frac{Q}{\sqrt{2}} . \tag{2.3.7}$$

CHAPTER III

INTEGRAL EQUATION APPROACH

Now that we have derived our basic non-linear differential equation (2. 2. 9) and have transformed the initial conditions on this equation, we shall proceed with a discussion of the solution to (2. 2. 14) by first transforming the differential equation to an integral equation and secondly giving an existing theorem.

1°. Equation Transformation

The equation of interest with a singluar point $S^* = 0$ is

$$\text{(3. 1. 1)} \quad \frac{d^2S^*}{dt^2} + T\alpha_0 \frac{dS^*}{dt} + T^2\alpha_1 S^* + \alpha_2\left(\frac{dS^*}{dt}\right)^2 + \alpha_3 TS^*\left(\frac{dS^*}{dt}\right) + T\alpha_4 = 0$$

or

$$\text{(3. 1. 1')} \quad \frac{d^2S^*}{dt^2} = -T\alpha_0 \frac{dS^*}{dt} - T^2\alpha_1 S^* - \alpha_2\left(\frac{dS^*}{dt}\right) - \alpha_3 TS^*\left(\frac{dS^*}{dt}\right) - T^2\alpha_4 \,.$$

Note here that we shall write $\frac{dS^*}{dt} = \mathring{S}^*$ and conversely when convenient.

We see that

$$\text{(3. 1. 2)} \qquad \int_0^t \int_0^{t_1} \overset{\circ\circ}{S}{}^*(\lambda)d\lambda dt_1 = \int_0^t (t-\lambda)\overset{\circ\circ}{S}{}^*(\lambda)d\lambda$$

and

$$(3.1.3) \qquad \int_0^t \int_0^{t_1} \overset{\circ\circ}{S}{}^*(\lambda)\,d\lambda\,dt_1 = S^*(t) - S^*(0) - \overset{\circ}{S}{}^*(0)t .$$

Thus

$$(3.1.4) \qquad S^*(t) - S^*(0) - \overset{\circ}{S}{}^*(0)t = \int_0^t (t-\lambda)\overset{\circ\circ}{S}{}^*(\lambda)\,d\lambda$$

or

$$(3.1.4') \qquad S^*(t) = S^*(0) + \overset{\circ}{S}{}^*(0)t + \int_0^t (t-\lambda)\overset{\circ\circ}{S}{}^*(\lambda)\,d\lambda .$$

Substituting the $S^*(t)$ found in Equation (3.1.4') into the right hand side of (3.1.1') we obtain

$$(3.1.5) \qquad \overset{\circ\circ}{S}{}^*(t) = -\alpha_0 T \{\overset{\circ}{S}{}^*(0) + \int_0^t \overset{\circ\circ}{S}{}^*(\lambda)\,d\lambda \}$$

$$-\alpha_1 T^2 \{S^*(0) + \overset{\circ}{S}{}^*(0)t + \int_0^t (t-\lambda)\overset{\circ\circ}{S}{}^*(\lambda)\,d\lambda$$

$$-\alpha_2 \{\overset{\circ}{S}{}^*(0) + \int_0^t \overset{\circ\circ}{S}{}^*(\lambda)\,d\lambda \}^2$$

$$-\alpha_3 T \{(S^*(0) + \int_0^t (\overset{\circ\circ}{S}(\lambda)\,d\lambda)(S^*(0)+S^*(0)t+\int_0^t (t-\lambda)\overset{\circ\circ}{S}{}^*(\lambda)\,d\lambda)\}$$

$$-\alpha_4 T^2 .$$

Reduction of (3.1.5) yields

$$(3.1.6)\quad \overset{\circ\circ}{S}{*}(t) = -\{a_0 TS*(0) + T^2 a_1 \overset{\circ}{S}{*}(0) + a_2 \{\overset{\circ}{S}{*}(0)\}^2 + a_3 T\overset{\circ}{S}{*}(0)S*(0)$$

$$+ T^2 a_4 + a_1 T^2 \overset{\circ}{S}{*}(0)t + a_3 \{\overset{\circ}{S}{*}(0)\}^2 t\}$$

$$- \{+ a_3 T\overset{\circ}{S}{*}(0)t \int_0^t \overset{\circ\circ}{S}{*}(\lambda)d\lambda + a_0 T \int_0^t \overset{\circ\circ}{S}{*}(\lambda)d\lambda$$

$$+ a_1 T^2 \int_0^t (t-\lambda)\overset{\circ\circ}{S}{*}(\lambda)d\lambda + 2a_2 \overset{\circ}{S}{*}(0) \int_0^t \overset{\circ\circ}{S}{*}(\lambda)d\lambda$$

$$+ a_3 T\overset{\circ}{S}{*}(0) \int_0^t (t-\lambda) \overset{\circ\circ}{S}{*}(\lambda)d\lambda + T a_3 S*(0) \int_0^t \overset{\circ\circ}{S}{*}(\lambda)d\lambda \}$$

$$- a_2 \{ \int_0^t \overset{\circ\circ}{S}{*}(\lambda)d\lambda \}^2 - a_3 \{ \int_0^t \overset{\circ\circ}{S}{*}(\lambda)d\lambda \cdot \int_0^t (t-\lambda)\overset{\circ\circ}{S}{*}(\lambda)d\lambda \} .$$

We now define:

$$(3.1.7)\quad \phi(t) = -\{a_0 T\overset{\circ}{S}{*}(0) + a_1 T^2 \overset{\circ}{S}{*}(0) + a_2 \{\overset{\circ}{S}{*}(0)\}^2 + a_3 T\overset{\circ}{S}{*}(0)S*(0)$$

$$+ a_4 T^2 + T^2 a_1 S*(0)t + T a_3 (S*(0))^2 t\}$$

and

$$k[t, \lambda ; \overset{\circ\circ}{S}{*}(\lambda)] = -\{a_3 T\overset{\circ}{S}{*}(0)\overset{\circ\circ}{S}{*}(\lambda)t + a_0 T\overset{\circ\circ}{S}{*}(\lambda) + T^2 a_1 (t-\lambda)\overset{\circ\circ}{S}{*}(\lambda)$$

$$(3.1.8)\qquad + 2a_2 \overset{\circ}{S}{*}(0)\overset{\circ\circ}{S}{*}(\lambda) + T a_3 \overset{\circ}{S}{*}(0)(t-\lambda)\overset{\circ\circ}{S}{*}(\lambda) + T a_3 S*(0)\overset{\circ\circ}{S}{*}(\lambda)\}.$$

Notice that $\ddot{S}^*(\lambda)$ occurs linearly everywhere in (3.1.8); hence, we see

$$k[t,\lambda;\ddot{S}^*(\lambda)] = k_1(t,\lambda)\cdot\ddot{S}^*(\lambda) \quad . \tag{3.1.9}$$

Now with (3.1.7) and (3.1.8), we shall re-write equation (3.1.6) in the following form

$$\ddot{S}^*(t) = \phi(t) + \int_0^t k_1(t,\lambda)\ddot{S}^*(\lambda)d\lambda - a_2\{\int_0^t \ddot{S}^*(\lambda)d\lambda\}^2 - a_3T\{\int_0^t \ddot{S}^*(\lambda)d\lambda \cdot \int_0^t (t-\lambda)\ddot{S}^*(\lambda)d\lambda\} \quad . \tag{3.1.10}$$

Notice that though (3.1.10) is a non-linear integral equation, it contains a linear Volterra form (2, p. 415).

Suppose that $f(t) = \ddot{S}^*(t)$, then (3.1.10) has the form

$$f(t) = \phi(t) + \int_0^t k(t,\lambda)f(\lambda)d\lambda - a_2\{\int_0^t f(\lambda)d\lambda\}^2 - a_3T\{\int_0^t f(\lambda)d\lambda \cdot \int_0^t (t-\lambda)f(\lambda)d\lambda\} \quad , \tag{3.1.11}$$

or

$$f(t) = \phi(t) + \int_0^t k_1(t,\lambda)f(\lambda)d\lambda + \int_0^t k_2(t,\lambda)f(\lambda)d\lambda \cdot \int_0^t k_3(t,\lambda)f(\lambda)d\lambda \tag{3.1.11'}$$

where $k_1(t,\lambda)$ has been defined in (3.1.9), $k_2(t,\lambda) = 1$, and $k_3(t,\lambda) = -(\alpha_2+\alpha_3 T(t-\lambda))$. We shall now consider the condition under which a solution to (3.1.11') exists.

2. Existence Theorem

If the following assumptions hold :

(a) The function $\phi(t)$ is integrable and bounded,

$$|\phi(t)| \leq M \text{ in } 0 \leq t \leq T ;$$

(b) The following Lipschitz condition is satisfied by $\phi(t)$ in

(3.2.1) $[0,T]$, $|\phi(t) - \phi(t')| < k\,|t - t'|$;

(c) The functions k_1, k_2, and k_3 are integrable and bounded

$$|k_1| < \delta$$
$$|k_2| < \gamma$$
$$|k_3| < \theta$$

in the domain $0 \leq t \leq T$, $f(\lambda) \leq b$, $b > 0$;

(d) The following Lipschitz condition is satisfied by $k_i(t,\lambda)$, $(i = 1,2,3)$ within its domain of definition

(3.2.2) $$|k_i \cdot [t,\lambda; f(\lambda)] - k_i \cdot [t,\lambda; f(\lambda')]\,| < M_i \cdot |f(\lambda) - f(\lambda')|$$

Then (3.1.11') has a solution in $(0, T)$.

Proof:

Employing now the method of successive approximations, commonly known as Picard's method, we shall construct a sequence of functions $\{f_n(t)\}$ and subsequently show uniform convergence of $\{f_n(t)\}$ to show a limit function $f(t)$. We assume as the first approximation

$$f_0(t) = \phi(t) - f(0)$$

from which we get

$$f_1(t) = \phi(t) + \int_0^t k_1 f_0 d\lambda + \int_0^t k_2 f_0 d\lambda \cdot \int_0^t k_3 f_0 d\lambda$$

$$f_2(t) = \phi(t) + \int_0^t k_1 f_1 d\lambda + \int_0^t k_2 f_1 d\lambda \cdot \int_0^t k_3 f_1 d\lambda$$

and in general

$$f_n(t) = \phi(t) + \int_0^t k_1 f_{n-1} d\lambda + \int_0^t k_2 f_{n-1} d\lambda \cdot \int_0^t k_3 f_{n-1} d\lambda \tag{3.2.3}$$

Making use of our assumptions, we now obtain the following bound for $f_1(t)$:

$$|f_1(t)| \leq |\phi + \max(\delta, \gamma, \theta)| \; |t|, \quad |t| < a', \quad a' > 0 \;. \tag{3.2.4}$$

If t is so limited that $|t| \leq \dfrac{|\phi|}{|\phi + \max(\delta, \gamma, \theta)}$ then $|f_1(t)| \leq |\phi|$.

Denoting by h the smaller of the numbers a' and $\left|\dfrac{\phi}{\phi+\max(\delta,\gamma,\theta)}\right|$, we shall have, for each approximation, the inequality

(3. 2. 5) $$|f_n(t)| \leq |\phi| \qquad |t| < h \; .$$

Let us now consider the series:

(3. 2. 6) $$f(t) = f_0(t) + (f_1(t) - f_0(t)) + (f_2(t) - f_1(t)) + \cdots + (f_n(t) - f_{n-1}(t)) + \cdots$$

which by virtue of (3. 2. 3) furnishes the desired solution to (3. 1. 11') provided it converges uniformly. The uniform convergences of the series is readily established from the following considerations.

Since we have

(3. 2. 7) $$f_n(t) - f_{n-1}(t) = \int_0^t (k_1 f_{n-1} - k_1 f_{n-2}) d\lambda + \int_0^t k_2 f_{n-1} d\lambda \cdot \int_0^t k_3 f_{n-1} d\lambda - \int_0^t k_2 f_{n-2} d\lambda \cdot \int_0^t k_3 f_{n-2} d\lambda$$

or

$$f_n - f_{n-1} = \int_0^t (k_1 f_{n-1} - k_1 f_{n-2}) d\lambda + \int_0^t k_2 f_{n-1} d\lambda \cdot \int_0^t (k_3 f_{n-1} - k_3 f_{n-2}) d\lambda + \int_0^t k_3 f_{n-2} d\lambda \cdot \int_0^t (k_2 f_{n-1} - k_2 f_{n-2}) d\lambda \; ;$$

It follows from (3. 2. 2) that we have the inequality

$$(3.2.9) \qquad |f_n - f_{n-1}| \le M_1 \left| \int_0^t (f_{n-1}(\lambda) - f_{n-2}(\lambda) d\lambda \right|$$

$$+ \gamma M_3 \left| \int_0^t f_{n-1} d\lambda \right| \left| \int_0^t (f_{n-1} - f_{n-2}) d\lambda \right|$$

$$+ \theta M_2 \left| \int_0^t f_{n-2} d\lambda \right| \left| \int_0^t (f_{n-1} - f_{n-2}) d\lambda \right| .$$

Since by (3.2.5) $|f_n(t)| \le |\phi|$, (3.2.9) can be written as

$$(3.2.10) \qquad |f_n - f_{n-1}| \le M_1 \int_0^t |f_{n-1} - f_{n-2}| \, |d\lambda| +$$

$$+ \gamma |\phi| \, |t| \, M_3 \int_0^t |f_{n-1} - f_{n-2}| \, |d\lambda|$$

$$+ \theta \, |\phi| \, |t| \, M_2 \int_0^t |f_{n-1} - f_{n-2}| \, |d\lambda| .$$

Define

$$(3.2.11) \qquad |U_n(t)| = |f_n(t) - f_{n-1}(t)| ,$$

then it is seen that for $n = 1, 2, 3, \cdots$

$$|U_1(t)| = |f_1(t) - f_0(t)| \le B_1, \quad B_1 \ge 0$$

$$|U_2(t)| = |f_2(t) - f_1(t)| \le B_2 \le \frac{B_1^2}{2!}$$

$$\vdots \qquad\qquad \vdots$$

$$|U_n(t)| = |f_n(t) - f_{n-1}(t)| \le B_n \le \frac{B_1^n}{n!}$$

where

$$B_1 = M_1 |\phi| \ |t| + \gamma |\phi|^2 M_3 |t|^2 + \theta |\phi|^2 |t|^2 M_2$$

Now by the Weierstrass M-test we have that $\sum_{n=1}^{\infty} U_n(t)$ is a uniformly convergent series since $\sum_{n=1}^{\infty} U_n(t)$ converges absolutely. Thus, since $\sum_{n=1}^{\infty} U_n(t)$ converges uniformly on $(0, T)$ we know that a limit function exists.

3°. Uniqueness of Limit Function

It remains to be proved that $f(t)$ is the unique limit function. To establish this, we assume that $z(t)$ is any other limit, subject to the restrictions

$$|z - f| \le b, \quad |z| \le |\phi|, \quad b > 0 \ .$$

Hence we have

$$z(t) = f_0 + \int_0^t k_1 z(t_1) dt_1 + \int_0^t k_2 z \, dt_1 \cdot \int_0^t k_3 z \, dt_1 \tag{3.3.1}$$

and

$$f_{n+1}(t) = f_0 + \int_0^t k_1 f_n dt_1 + \int_0^t k_2 f_n dt_1 \cdot \int_0^t k_3 f_n dt_1 \tag{3.3.2}$$

from which it follows that

$$(3.3.3) \quad |z - f_{n+1}| \leq \int_0^t |k_1| \; |z - f_n| \, dt_1 + \int_0^t |k_2| \, |z| dt_1 \cdot \int_0^t |k_3 z - k_3 f_n| \, dt_1 + $$

$$+ \int_0^t |k_3 f_n| \, dt_1 \cdot \int_0^t |k_2 (z - f_n)| \, dt_1 \; .$$

By the same argument previously used it can be seen that

$$(3.3.4) \qquad |z - f_n| \leq \frac{B^{\prime n} \; b^n |t|^n}{n!}$$

where

$$B^1 = M_1 |\phi| \; |t| + \gamma |\phi|^2 M_3 |t|^2 + \theta |\phi|^2 M_2 |t|^2$$

Since the right hand member approaches zero as $n \rightarrow \infty$, we see that

$$(3.3.5) \qquad z = \lim_{n \rightarrow \infty} f_n(t) = f(t)$$

thus showing a unique limit.

CHAPTER IV

FURTHER SOLUTION TECHNIQUES

1. Resolvent Kernel (Ref. 1)

Writing (3. 1. 11') in the form

(4. 1. 1) $$f(t) - \int_0^t k_1(t,\lambda) f(\lambda) d\lambda = V(t)$$

where

$$V(t) = \phi(t) + \int_0^t k_2 f(\lambda) d\lambda \cdot \int_0^t k_3(t,\lambda) f(\lambda) d\lambda$$

it is seen that we may rewrite this equation in terms of its resolvent kernel. The sufficient condition is that $V(t)$ be a continuous function of t on $(0, T)$. This condition is satisfied by (3. 1. 7) and by k_1, k_2, and k_3 which are defined under (3. 1. 11'). Hence we write (4. 1. 1) in the equivalent form

(4. 1. 2) $$V(t) + \int_0^t \Gamma(t,\lambda) V(\lambda) d\lambda = f(t)$$

As the kernel k_1 is a polynomial (3. 1. 8), it is relatively easy to find its resolvent kernel $\Gamma(t,\lambda)$ in closed form (1, p. 40). In fact writing

(4.1.3) $k_1(t,\lambda) = d_1 + d_2(t-\lambda)$, d_1 and d_2 non-zero coefficients,

one obtains

$$(4.1.4) \qquad \Gamma(t,\lambda) = B_1 e^{r_1(t-\lambda)} + B_2 e^{r_2(t-\lambda)}$$

where r_1 and r_2 are distinct roots of the equation

$$(4.1.5) \qquad r^2 + d_1 r + d_2 = 0$$

and the B_n $(n = 1, 2)$ satisfy the equations

$$(4.1.6) \qquad B_1 + B_2 = -d_1$$

$$r_1 B_1 + r_2 B_2 = -d_2 + d_1^2$$

Solving for B_1 and B_2 in (4.1.6) we find

$$B_1 = (d_2 - d_1^2 - r_2 d_1)/(r_2 - r_1)$$

(4.1.7) and

$$B_2 = (d_1^2 + r_1 d_1 - d_2)/(r_2 - r_1)$$

Thus $\Gamma(t,\lambda)$ can be written as

$$(4.1.8) \quad \Gamma(t,\lambda) = \left\{\frac{d_2 - d_1^2 - r_2 d_1}{r_2 - r_1}\right\} e^{r_1(t-\lambda)} + \left\{\frac{d_1^2 + r_1 d_1 - d_2}{r_2 - r_1}\right\} e^{r_1(t-\lambda)} .$$

2.° Substitution of Resolvent Kernel

Now that we have the resolvent kernel Γ we shall proceed to substitute for Γ in (4. 1. 2) the expression found in (4. 1. 8). Thus (4. 1. 2) has the form

$$(4.2.1)\quad V(t) + \int_0^t \left(B_1 e^{r_1(t-\lambda)} + B_2 e^{r_2(t-\lambda)} \right) V(\lambda)d\lambda = f(t)$$

with B_1 and B_2 defined by (4. 1. 7). Substituting for $V(t)$ the expression defined in (4. 1. 1), we find (4. 2. 1) takes the form

$$(4.2.2)\quad f(t) = \phi(t) + \int_0^t k_2 f(\lambda)d\lambda \int_0^t k_3 f(\lambda)d\lambda +$$

$$+ \int_0^t \left(B_1 e^{r_1(t-\lambda)} + B_2 e^{r_2(t-\lambda)} \right) \left(\phi(\lambda) + \int_0^\lambda k_2 f(\lambda')d\lambda' \cdot \int_0^\lambda k_3 f(\lambda')d\lambda' \right) d\lambda.$$

Reduction of (4. 2. 2) yields

$$(4.2.3)\quad f(t) = \phi(t) + \int_0^t \left(B_1 e^{r_1(t-\lambda)} + B_2 e^{r_2(t-\lambda)} \right) \phi(\lambda)d\lambda$$

$$+ \int_0^t \left(B_1 e^{r_1(t-\lambda)} + B_2 e^{r_2(t-\lambda)} \right) \left(\int_0^\lambda k_2 f(\lambda')d\lambda' \cdot \int_0^\lambda k_3 f(\lambda')d\lambda' \right) d\lambda$$

$$+ \int_0^t k_2 f(\lambda)d\lambda \cdot \int_0^t k_3 f(\lambda)d\lambda$$

Further we define

(4. 2. 4) $$h(t) = \phi(t) + \int_0^t \left(B_1 e^{r_1(t-\lambda)} + B_2 e^{r_2(t-\lambda)} \right) \phi(\lambda) d\lambda$$

and write (4. 2. 3) as

(4. 2. 5) $$f(t) = h(t) + \int_0^t \Gamma \left\{ \int_0^\lambda k_2 f(\lambda') d\lambda' \cdot \int_0^\lambda k_3 f(\lambda') d\lambda' \right\} d\lambda$$

$$+ \int_0^t k_2 f(\lambda) d\lambda \cdot \int_0^t k_3 f(\lambda) d\lambda \quad .$$

Since $f(t)$ is a continuous function of t on $(0, T)$, define

(4. 2. 6) $$k^{(4)} = \int_0^t (\Gamma + \frac{d}{d\lambda}) \ d\lambda$$

as a linear operator which operates on the product function

$$\int_0^t k_2 f(\lambda) d\lambda \cdot \int_0^t k_3 f(\lambda) d\lambda \ , \text{ i. e.,}$$

$$k^{(4)} \left\{ \int_0^\lambda k_2 f(\lambda') d\lambda' \cdot \int_0^\lambda k_3 f(\lambda') d\lambda' \right\} = \int_0^t (\Gamma + \frac{d}{d\lambda}) \left(\int_0^\lambda k_2 f d\lambda' \cdot \int_0^\lambda k_3 f d\lambda' \right) d\lambda \quad .$$

Hence, with these definitions (4. 2. 5) has the form

(4. 2. 7) $$f(t) = h(t) + k^{(4)} \left\{ \int_0^\lambda k_2 f(\lambda') d\lambda' \cdot \int_0^\lambda k_3 f(\lambda') d\lambda' \right\} .$$

Now since we know that $f(t)$ exists and is continuous and that

$\lim_{n \to \infty} f_n(t) = f(t)$, $\{f_n(t)\}$ uniformly convergent on $(0, T)$, we proceed to use the method of successive approximations to obtain an approximating solution to (4.2.7).

3°. Successive Approximations

The technique used in the proof of the existence theorem (Chapter III) is the method of Picard. It is of very general use and we shall apply it to formulate a few terms $f_n(t)$ of the convergent sequence $\{f_n(t)\}$. We begin by observing that (4.2.7) is the equation which we wish to solve. The solution sequence of f's goes as :

$$(5.3.1)\quad \begin{cases} (a_1) \;\; f_0(t)=h(0) \\ (a_2) \;\; f_1(t)=h(t)+k^{(4)}\{\int_0^t k_2 f_0(\lambda)d\lambda \cdot \int_0^t k_3 f_0(\lambda)d\lambda\} \\ (a_3) \;\; f_2(t)=h(t)+k^{(4)}\{\int_0^t k_2 f_1(\lambda)d\lambda \cdot \int_0^t k_3 f_1(\lambda)d\lambda\} \\ \quad\vdots \qquad\qquad\qquad\qquad \vdots \\ (a_n) \;\; f_n(t)=h(t)+k^{(4)}\{\int_0^t k_2 f_{n-1}(\lambda)d\lambda \cdot \int_0^t k_3 f_{n-1}(\lambda)d\lambda\} \\ \quad\vdots \qquad\qquad\qquad\qquad \vdots \end{cases}$$

That this sequence is uniformly convergent follows from the fact that the kernels are uniformly bounded on $(0, T)$ and that

$|f_n(t)| \leq |\phi|$ for $(0, T)$, all n, and $h(t)$ is a continuous function, integrable $0 \leq t \leq T$. We shall now endeavor to use the ideas discussed in this and preceding chapters to find a solution sequence to a particularly chosen problem. We shall first formulate a convergent sequence of functions $\{f_n(t)\}$; secondly, with two quadratures we shall find the sequence $\{S_n^*(t)\}$ which is the sequence of solutions of (3. 1. 1); thirdly, we find $\{S_n(t)\}$, the sequence of solutions to Equation (2. 1. 7).

CHAPTER V

PARTICULAR PROBLEM

1.° Reduction to Integral Equation Form

If we choose the rate constants in (2. 2. 8) in such a way (Cf. Appendix B, Part 2) that $a_i (i=0, 1, 2, 3)$ in (3. 1. 3) are constant coefficients and with $T = 1$ and $a_4 \equiv 0$, then we find (3. 1. 1) reads as

$$(5.1.1)\quad \frac{d^2S^*}{dt^2} + 3\frac{dS^*}{dt} + S^* + \sqrt{2}\left(\frac{dS^*}{dt}\right)^2 + \sqrt{2}\, S^*\frac{dS^*}{dt} = 0 .$$

Carrying through steps (3. 1. 2) to (3. 1. 8) we find with the initial conditions from (2. 3. 3) and (2. 3. 7)

$$(5.1.2)\quad \frac{d^2S^*}{dt^2} = \phi(t) + \int_0^t k_1(t,\lambda)\left(\frac{d^2S^*}{d\lambda^2}\right) d\lambda + \sqrt{2}\left\{\int_0^t \frac{d^2S^*}{d\lambda^2}\, d\lambda\right\}^2$$

$$+ \sqrt{2}\int_0^t \frac{d^2S^*}{d\lambda^2}\, d\lambda \cdot \int_0^t (t-\lambda)\frac{d^2S^*}{d\lambda^2}\, d\lambda$$

with $\phi(t) = \dfrac{1}{\sqrt{2}}$

and $k_1 = -(4 + t - \lambda)$.

Define

$$(5.1.3) \qquad f(t) = \frac{d^2 S^*}{dt^2}$$

and write (5. 1. 2) as

$$(5.1.4) \qquad f(t) = -\frac{1}{\sqrt{2}} - \int_0^t [4 + (t-\lambda)] f(\lambda) d\lambda$$

$$+ \sqrt{2} \int_0^t f(\lambda) d\lambda \int_0^t (1 + t - \lambda) f(\lambda) d\lambda \ .$$

Notice that (5. 1. 4) is of the form of (3. 1. 11'). Thus as $\phi(t)$, k_1, k_2, k_3 are continuous, integrable, and bounded we know that a solution to (5. 1. 4) exists.

Writing (5. 1. 4) now as

$$(5.1.5) \qquad p_1\text{:} \ f(t) + \int_0^t [4 + (t-\lambda)] f(\lambda) \, d\lambda = V(t)$$

with

$$p_2\text{:} \ V(t) = -\frac{1}{\sqrt{2}} + \sqrt{2} \int_0^t f(\lambda) d\lambda \int_0^t [1 + (t - \lambda) f(\lambda) d\lambda$$

we find that (5. 1. 5) is of the form (4. 1. 1); hence, we can write (5. 1. 5) in the form

$$(5.1.6) \qquad f(t) = V(t) + \int_0^t \Gamma(t,\lambda) V(\lambda) d\lambda$$

where $\Gamma(t,\lambda)$ is the resolvent kernel of $k_1 = 4 + t - \lambda$.

Substituting part (2) of (5. 1. 5) into (5. 1. 6) we find

$$(5.1.7)\quad f(t) = -\frac{1}{\sqrt{2}} + \sqrt{2}\int_0^t f(\lambda)d\lambda \int_0^t [\,1 + (t-\lambda)\,]\, f(\lambda)d\lambda$$

$$+\int_0^t \Gamma(t,\lambda)\,[-\frac{1}{\sqrt{2}} + \sqrt{2}\int_0^\lambda f(\lambda')d\lambda' \int_0^\lambda (1+\lambda-\lambda')f(\lambda')d\lambda'\,]\, d\lambda \quad .$$

Reduction yields

$$f(t) = -\frac{1}{\sqrt{2}} + \int_0^t \Gamma(t,\lambda)(-\frac{1}{\sqrt{2}})\, d\lambda$$

$$+ k^{(4)}\,\{\sqrt{2}\int_0^\lambda f(\lambda')d\lambda' \int_0^\lambda [\,1+(\lambda-\lambda')]\, f(\lambda')d\lambda'\,\}$$

where

$$k^{(4)} = \int_0^t (\Gamma(t,\lambda) + \frac{d}{d\lambda})\, d\lambda \quad .$$

Proceeding now with the resolvent kernel calculation, we find from (4. 1. 3)

$$d_1 = 4$$

$$d_2 = 1 \ .$$

Substituting for d_1 and d_2 into (4. 1. 5) we find the roots r_1 and r_2 of (4. 1. 5) to be

$$(5.1.9) \qquad \begin{aligned} &(a) \quad r_1 = -(2+\sqrt{3}) \;; \\ &(b) \quad r_2 = -(2-\sqrt{3}) \;. \end{aligned}$$

Using (4.1.7) we find

$$(5.1.10) \qquad \begin{aligned} &(c) \quad B_1 = -\left(\frac{7+4\sqrt{3}}{2\sqrt{3}}\right) \;; \\ &(d) \quad B_2 = \frac{13-\sqrt{3}}{2\sqrt{3}} \end{aligned}$$

This defines our resolvent kernel as

$$(5.1.11) \qquad \Gamma(t,\lambda) = B_1 e^{r_1(t-\lambda)} + B_2 e^{r_2(t-\lambda)} \;.$$

Note that even though we have calculated the coefficients here we shall not use numbers in any of the successive approximations. Therefore, we shall continue to write the resolvent kernel as

$$\Gamma(t,\lambda) = B_1 e^{r_1(t-\lambda)} + B_2 e^{r_2(t-\lambda)} \;.$$

Proceeding, we shall use (4.2.4) to find $h(t)$ as a preparatory step to the first approximation. It is found (4.2.4) that

$$(5.1.12) \qquad h(t) = -\frac{1}{\sqrt{2}}\left(1 - \frac{B_1}{r_1} - \frac{B_2}{r_2} + \frac{B_1}{r_1} e^{r_1 t} + \frac{B_2}{r_2} e^{r_2 t}\right) .$$

Now that we have $h(t)$ defined we can write Equation (5.1.8) as

$$(5.1.13)\quad f(t) = h(t) + k^{(4)}\sqrt{2}\left\{\int_0^{\lambda} f(\lambda')d\lambda' \cdot \int_0^{\lambda}(1+\lambda-\lambda')f(\lambda')d\lambda\right\} .$$

Observe that (5. 1. 13) and (4. 2. 7) are of identical form; hence, we shall use the technique of successive approximations to find a convergent sequence $\{f_n(t)\}$ of functions generated by (5. 1. 13).

2.° Successive Approximations

Employing Picard's method now we generate the sequence functions $\{f_n(t)\}$, $n=0, 1, 2, \cdots$. We shall calculate only the first two such terms for illustrative purposes. The higher terms, though much closer to $f(t)$, are very long and laborious to calculate. We begin with $f_0(t)$.

$$(5.2.1)\qquad f_0(t) = h(0) = -\frac{1}{\sqrt{2}} .$$

Corresponding to $f_0(t)$ we have, integrating $f_0(t)$ twice

$$(5.2.2)\qquad S_0^*(t) = C_1 + C_2 t - \frac{1}{2\sqrt{2}}\, t^2$$

where C_1 and C_2 are the integration constants.

With the initial conditions

$$S^*(0) = \frac{1}{\sqrt{2}} \quad \text{and} \quad \overset{\circ}{S}{}^*(0) = 0$$

and with (2. 3. 1) we finally obtain

$$(5.2.3) \qquad S_0(t) = 1 - t - \frac{t^2}{2}$$

which is the first approximation to a solution of (2.1.7).

Proceeding, we find

$$(5.2.4) \quad f_1(t) = h(t) + k^{(4)}\sqrt{2}\left\{\int_0^{t_1} f_0 d\lambda_1 \cdot \int_0^{t_1} (1+t_1-\lambda_1) f_0 d\lambda_1\right\}.$$

Since by (5.2.1) $f_0 = -\frac{1}{\sqrt{2}}$ we arrive at

$$(5.2.5) \quad f_1(t) = h(t) + k^{(4)}\left(+\frac{1}{\sqrt{2}}\right)\left\{\int_0^{t_1} d\lambda_1 \cdot \int_0^{t_1} (1+t_1-\lambda_1) d\lambda_1\right\}.$$

Carrying out the indicated operations we find

$$(5.2.6) \quad f_1(t) = h_0^{(1)}(t) + h_1^{(1)}(t)\, e^{r_1 t} + h_2^{(1)}(t)\, e^{r_2 t}$$

where

$$h_0^{(1)}(t) = -\frac{1}{\sqrt{2}} + \frac{B_1}{\sqrt{2}\, r_1} + \frac{B_2}{r_2\sqrt{2}} - \frac{2B_1}{r_1^3\sqrt{2}} - \frac{2B_2}{r_2^3\sqrt{2}} + \frac{6B_1}{2\sqrt{2}\, r_2^4} + \frac{6B_2}{2\sqrt{2}\, r_2^4} + \frac{t^2}{\sqrt{2}} + \frac{t^3}{2\sqrt{2}}$$

$$h_1^{(1)}(t) = -\frac{B_1}{r_1\sqrt{2}} + \frac{2B_1}{\sqrt{2}\, r_1^3} - \frac{6B_1}{2\sqrt{2}\, r_1^4} + \left(\frac{6B_1}{2\sqrt{2}\, r_1^3} - \frac{2B_1}{\sqrt{2}\, r_1^2}\right) t$$
$$+ \left(\frac{B_1}{r_1\sqrt{2}} - \frac{3B_1}{2\sqrt{2}\, r_1^2}\right) t^2 + \frac{B_1}{2\sqrt{2}\, r_1}\, t^3$$

$$h_2^{(1)}(t) = -\frac{B_2}{r_2\sqrt{2}} + \frac{2B_2}{\sqrt{2}\,r_2^3} - \frac{6B_1}{2\sqrt{2}\,r_2^3} + \left(\frac{6B_2}{2\sqrt{2}\,r_2^3} - \frac{2B_2}{\sqrt{2}\,r_2^2}\right) t$$

$$+ \left(\frac{B_2}{r_2\sqrt{2}} - \frac{3B_2}{2\sqrt{2}\,r_2^2}\right) t^2 + \frac{B_2}{2\sqrt{2}\,r_2} \quad t^3$$

Two quadratures of (5. 2. 6) yield

$$(5.\,2.\,7) \quad S_1^*(t) = \int_0^t \int_0^{t_2} (h_0^{(1)}(\lambda) + h_1^{(1)}(\lambda) e^{r_1\lambda} + h_2^{(1)} e^{r_2\lambda}) d\lambda dt_2 +$$

$$C_1 + C_2 t$$

Reducing, we find

$$(5.\,28) \quad S_1^*(t) = H_0^{(1)}(t) + H_1^{(1)}(t)\, e^{r_1 t} + H_2^{(1)} e^{r_2 t} \quad ,$$

where

$$H_0^{(1)}(t) = C_1 + C_2 t - \left(- \frac{B_1}{r_1\sqrt{2}} + \frac{2B_1}{\sqrt{2}\, r_1^3} - \frac{6B_1}{2\sqrt{2}\, r_1^4} \right)\left(\frac{1}{r_1^2} + \frac{t}{r_1}\right)$$

$$+ \left(\frac{6B_1}{2\sqrt{2}\, r_1^3} - \frac{2B_1}{\sqrt{2}\, r_1^2}\right)\left(\frac{t}{r_1^2} + \frac{1}{r_1^3}\right) + \left(-\frac{B_1}{\sqrt{2}\, r_1} + \frac{3B_1}{2\sqrt{2}\, r_1^2}\right)\left(\frac{2t}{r_1^3} + \frac{6}{r_1^4}\right)$$

$$+ \left(\frac{B_1}{2\sqrt{2}\, r_1}\right)\left(\frac{24}{r_1^5} + \frac{6t}{r_1^4}\right) + \left(\frac{B_2}{r_2\sqrt{2}} - \frac{2B_2}{\sqrt{2}\, r_2^3} + \frac{6B_2}{2\sqrt{2}\, r_2^4}\right)\left(\frac{1}{r_2^2} + \frac{t}{r_2}\right)$$

$$+ \left(\frac{6B_2}{2\sqrt{2}\, r_2^3} - \frac{2B_2}{\sqrt{2}\, r_2^3}\right)\left(\frac{t}{r_2^2} + \frac{1}{r_2^3}\right) + \left(-\frac{B_2}{\sqrt{2}\, r_2} + \frac{3B_2}{2\sqrt{2}\, r_2^2}\right)\left(\frac{2t}{r_2^3} + \frac{6}{r_2^4}\right)$$

$$+ \left(\frac{B_2}{2\sqrt{2}\, r_2} \quad \frac{24}{r_2^5} + \frac{6t}{r_2^4}\right) + \left(-\frac{1}{\sqrt{2}} + \frac{B_1}{r_1\sqrt{2}} + \frac{B_2}{r_2\sqrt{2}} - \frac{2B_1}{\sqrt{2} r_1^3} - \frac{2B_2}{\sqrt{2} r_2^3} + \frac{6B_1}{2\sqrt{2} r_1^4} + \frac{6B_2}{2\sqrt{2} r_2^4}\right)\frac{t^2}{2}$$

$$+ \frac{t^4}{12\sqrt{2}} + \frac{t^5}{40\sqrt{2}} \ ;$$

$$H_1^{(1)}(t) = \left(- \frac{B_1}{r_1^3\sqrt{2}} + \frac{2B_1}{\sqrt{2}\, r_1^5} - \frac{6B_1}{2\sqrt{2}\, r_1^6} \right)$$

$$+ \left(\frac{6B_1}{2\sqrt{2}\, r_1^3} - \frac{2B_1}{\sqrt{2}\, r_1^2}\right)\left(\frac{t}{r_1^2} - \frac{1}{r_1^3}\right) + \left(\frac{B_1}{\sqrt{2}\, r_1} - \frac{3B_1}{2\sqrt{2}\, r_1^2}\right)\left(\frac{t^2}{r_1^2} - \frac{4t}{r_1^3} + \frac{6}{r_1^4}\right)$$

$$+ \left(\frac{B_2}{2\sqrt{2}\, r_2}\right)\left(\frac{t^3}{r_1^2} - \frac{6t^2}{r_1^3} + \frac{18t}{r_1^4} - \frac{24}{r_1^5}\right) \ ;$$

$$H_2^{(1)}(t) = \left(-\frac{B_2}{r_2^3\sqrt{2}} + \frac{2B_2}{\sqrt{2}\,r_2^5} - \frac{6B_2}{r_2^6} \right) +$$

$$+ \left(\frac{6B_2}{2\sqrt{2}\,r_2^3} - \frac{2B_2}{\sqrt{2}\,r_2^2}\,\frac{t}{r_2^2} - \frac{1}{r_2^3} \right) + \left(\frac{B_2}{\sqrt{2}\,r_2} - \frac{3B_2}{2\sqrt{2}\,r_2^2} \right) \left(\frac{t^2}{r_2^2} - \frac{4t}{r_2^3} + \frac{6}{r_2^4} \right)$$

$$\left(\frac{B_2}{2\sqrt{2}\,r_2}\quad \frac{t^3}{r_2^2} - \frac{6t^2}{r_2^3} + \frac{18t}{r_2^4} - \frac{24}{r_2^5} \right)$$

By using formulae (2. 3. 1) and (2. 2. 5) we find

$$(5.2.9)\quad S_1(t) = \sqrt{2}\left((H_0^{(1)}(t) + (r_1+1)\, H_1^{(1)}(t)\, e^{r_1 t} + (r_2+1)\, H_2^{(1)}(t)\, e^{r_2 t} + \frac{d[H_0^{(1)}(t)]}{dt} + \frac{d[H_1^{(1)}(t)]}{dt}\, e^{r_1 t} + \frac{d[H_2^{(1)}(t)]}{dt}\, e^{r_2 t} \right).$$

Equation (5. 2. 9) is the equation for the 2nd approximation for $S = S(t)$ $(S=S(t)$ is the solution to (2. 1. 7)).

Now that we see how the sequence of $\{S_n(t)\}$ is generated by the technique of successive approximations, we shall stop calculating the sequence of $\{S_n(t)\}$ and proceed to show how to calculate the sequence of $\{C_n(t)\}$. Note that the $\{C_n(t)\}$ will also be a uniformly convergent sequence of functions such that $\lim_{n\to\infty} C_n(t) = C(t)$ where $C = C(t)$ is the solution of Equation (2. 1. 8).

$\overset{\circ}{3}$. Calculation of $\{C_n(t)\}$

Using Equations (2. 2. 5) and (2. 3. 1) we find by setting $Q \equiv 0$

$$C_n(t) = -\sqrt{2}\,\overset{\circ}{S}{}^{*}_{n}(t)\ . \tag{5.3.1}$$

We find by Equation (5.2.2) that

$$C_0(t) = -\sqrt{2}\left\{-\frac{t}{\sqrt{2}}\right\} = t\,. \tag{5.3.2}$$

Continuing we find by Equation (5.2.8)

$$C_1(t) = -\sqrt{2}\left\{\frac{d[H_0^{(1)}(t)]}{dt} + \left(r_1H_1^{(1)}(t) + \frac{dH_1^{(1)}(t)}{dt}\right)e^{r_1t} + \left(r_2H_2^{(1)}(t) + \frac{dH_2^{(1)}(t)}{dt}\right)e^{r_1t}\right\}. \tag{5.3.3}$$

Thus it is seen how the $\{C_n(t)\}$ are calculated.

Lastly we shall show how to calculate the sequence of $\{P_n(t)\}$, where $\lim_{n\to\infty} P_n(t) = P(t)$. Note here that $P = P(t)$ is the solution to Equation (2.1.9)

$\overset{\circ}{4}$. Calculation of $\{P_n(t)\}$

Using Equation (2.1.9) and the sequence generated by Equation (5.3.1) we find the sequence

$$P_n(t) = \gamma_n e^{-t} + e^{-t}\int_0^t e^{\tau}C_n(\tau)d\tau \tag{5.4.1}$$

where γ_n is the suitably chosen integration constant for each n.

Thus,

$$(5.4.2) \qquad P_0(t) = \gamma_0 e^{-t} + e^{-t} \int_0^t e^{\tau} \tau d\tau$$

or

$$(5.4.2') \qquad P_0(t) = \gamma_0 e^{-t} + t-1-e^{-t}$$

Continuing, we find with Equation (5.3.3)

$$(5.4.3) \qquad P_1(t) = \gamma_1 e^{-t} + e^{-t} \int_0^t - \sqrt{2} e^{\tau} \quad \{ \frac{d}{d\tau} [H_0^{(1)}(\tau) + H_1^{(1)}(\tau) e^{r_1 \tau} + H_2^{(1)}(\tau) e^{r_2 \tau}]\} d\tau$$

or

$$(5.4.3') \qquad P_1(t) = \gamma_1 e^{-t} - \sqrt{2} e^{-t} \left(e^{\tau} (H_0^{(1)}(\tau) + H_1^{(1)}(\tau) e^{r_1 \tau} + H_2^{(1)}(t) e^{r_2 \tau}) \Big|_0^t - \int_0^t e^{\tau} (H_0^{(1)}(\tau) + H_1^{(1)}(\tau) e^{r_1 \tau} + H_2^{(1)}(\tau) e^{r_2 \tau}) d\tau \right)$$

Thus it is seen that the whole system (2. 1. 7), (2. 1. 8), and (2. 1. 9) can be solved in terms of uniformly convergent sequences. As for finding the solution to Equation (2. 1. 10), one need only use the formula

$$(5.4.4) \qquad E_n(t) = E_T - C_n(t)$$

which is observed to be the Law of Conservation of Enzyme. Hence, the entire system is solved and we now have a set of convergent sequences as the solution to the Michaelis-Menten relation.

In recapping what has been done in this paper we find that differential equations were derived from the Michaelis-Menten relation. These differential equations were transformed under a suitable coordinant axis rotation into a basic non-linear differential equation with initial conditions. We then transformed the basic non-linear differential equation into a non-linear integral equation of Volterra type. The solution to this Volterra integral equation is achieved by the Picard successive approximations technique. The solution of the other parts of the Michaelis-Menten relation then followed.

CHAPTER VI

FUTURE PROPOSED SYSTEM

It was proposed that we use our system as a basis for a larger, more complex system. The question raised is this. What would result if we were to take two of our systems and couple them together in such a way as to have competition between the enzyme-substrate complexes (Cf. Figure 1. p.).

If we choose to restrict ourselves to competition of order one then our question can be answered without too much difficulty. First, we must make certain necessary assumptions about our system. These assumptions are:

6.1. We have an open system (i.e. we have forcing functions and loss terms).

6.2. We have a multi-substrate, one enzyme system.

6.3. We have conservation of enzyme

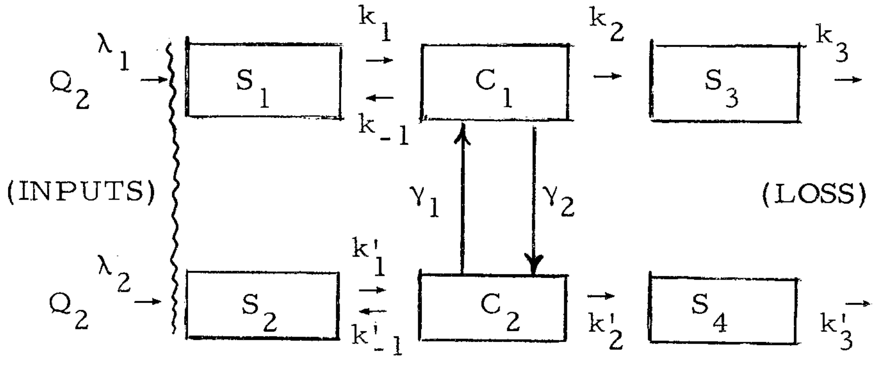
$$E_T = E(t) + C_1(t) + C_2(t) \quad .$$

6.4. We are assuming losses other than those indicated by Figure 1 negligible.

6.5. We have competition in the system. The competition occurs at the enzyme-substrate complex term.

Working with these 5 initial assumptions we propose the following graphical model for this system.

Figure 1



Where Q_1 and Q_2 represent the input or forcing functions. λ_1 and λ_2 represent the coupling coefficients for the forcing functions to the system. As before S_i and C_i $(i = 1, 2)$ stand for the substrate and enzyme-complex respectively. The k'_1, k'_{-1}, k_2, k_3, etc. are rate constants.

Now by choosing a first order reaction system we obtain the following set of non-linear differential equations :

$$
\begin{aligned}
\frac{dS_1(t)}{dt} &= -k_1E(t)S(t) + k_{-1}C_1(t) + \lambda_1Q_1 \\[2ex]
\frac{dS_2(t)}{dt} &= -k^1_1E(t)S(t) + k^1_{-1}C_2(t) + \lambda_2Q_2 \\[2ex]
\frac{dC_1(t)}{dt} &= k_1E(t)S_1(t) - (k_{-1}+k_2)C_1(t) - \gamma_1C_2(t) \\[2ex]
\frac{dC_2(t)}{dt} &= k^1_1E(t)S_2(t) - (k^1_{-1}+k^1_2)C_2(t) - \gamma_2C_1(t) \\[2ex]
\frac{dS_3(t)}{dt} &= -k_3E(t)S_3(t) + k_2C_1(t) \\[2ex]
\frac{dS_4(t)}{dt} &= -k^1_3E(t)S_4(t) + k^1_2C_2(t)
\end{aligned}
\tag{6.6}
$$

We see that this set of 6 non-linear differential equations could possibly be attacked in much the same manner as the problem in this paper was. It is well to remember that the Law of Conservation of Enzyme should be used in the reduction of (C. 6). It should also be pointed out that the $S(t)\cdot C(t)$ product originally comes from the Law of Mass Action in chemistry.

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APPENDIX A

DEFINITIONS

SUBSTRATE*: "The initial reactant of the system; a useful term to describe the amount of starting material."

ENZYME*: "One of a group of proteins whose biochemical function is the catalysis of chemical reactions in living systems."

PRODUCT: The end results of the reaction.

ENZYME-SUBSTRATE COMPLEX*: The unstable intermediate term in most biological processes. It breaks up into the product and possibly some substrate feed back (i. e. internal feedback).

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*(4, p. 201, 252-253)

APPENDIX B

PART I

DEFINITION OF COEFFICIENTS OF BASIC EQUATION (2. 2. 9)

$$a_0 = \left(\frac{2}{\sqrt{2}} + \frac{2}{\sqrt{2}} \cdot \frac{k_{-1} E_T}{k_2} + \frac{k_1}{k_2} \sqrt{2} - 2\sqrt{2}\, \frac{k_1}{k_2^2}\, \lambda Q \right) / (2/\sqrt{2}\, k_2)$$

$$a_1 = \left(\frac{2 k_1 E_T}{\sqrt{2}} - \sqrt{2}\, \frac{k_1}{k_2}\, \lambda Q \right) / (2/\sqrt{2}\, k_2)$$

(B. 1. 1) $$a_2 = \sqrt{2}\, \frac{k_1}{k_2}$$

$$a_3 = \sqrt{2}\, k_1$$

$$a_4 = \left(\frac{k_1}{k_2^2}\, \lambda Q - \frac{k_{-1}}{k_2} - \frac{k_1 E_T}{k_2} - 1 \right) \lambda Q / (2/\sqrt{2}\, k_2)$$

With $k_1 = -k_1 = k_2 = k_3 = \lambda = 1$, $E_T = 1$, $Q \equiv 0$ we have

(B. 1. 2)
$$a_0 = 3$$
$$a_1 = 1$$
$$a_2 = \sqrt{2}$$
$$a_3 = \sqrt{2}$$

which are the coefficients used in the non-linear differential Equation (5. 1. 1).

APPENDIX B

PART II

UNITS ON CONSTANTS

The units for Equations (2. 1. 1), (2. 1. 2), (2. 1. 3) and (2. 1. 4) are as follows

$$k_1 = (\text{conc - time})^{-1}$$

$$k_{-1} = (\text{time})^{-1}$$

(B. 2. 1) $$k_2 = (\text{time})^{-1}$$

$$k_3 = (\text{time})^{-1}$$

$$\lambda = (\text{time})^{-1}$$

The units on the coefficients of (2. 2. 9) are:

$$a_0 = (\text{time})^{-1}$$

$$a_1 = (\text{time})^{-2}$$

(B. 2. 2) $$a_2 = (\text{conc})^{-1}$$

$$a_3 = (\text{conc - time})^{-1}$$

$$a_4 = (\text{conc})\cdot(\text{time})^{-2}$$