MATHEMATICAL MODEL FOR CHEMOTHERAPY OF POLIOMYELITIS IN A VARYING POPULATION

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ABSTRACT

A mathematical model is developed for the solution of a non-linear deterministic model associated with the transmission dynamics of two polio subtypes in the presence of Oral Polio Vaccine (OPV) therapy. The model suggests the optimal level of OPV drug therapy coverage necessary to eradicate the disease in a given population. Unlike the Standard fourth –order Runge –Kutta method (RK4), which fails when certain parameter values and time steps are used in the discretizaion of the model. The new model to be developed gives table convergent numerical result for every time step.

INTRODUCTION

Poliomyelitis a disease caused by a polio virus has infected a lot of Nigerians. This virus is highly infectious, it is transmitted through oral - faucal route in humans been the only vectors (carriers) was critically looked at. And the irreversible paralysis caused by this virus becomes an issue of concern to many people [0]. Owing to the advances in genetic technology of the last two decades, polymerase chain reaction (PCR) technique is being used to study the RNA or DNA form of genetic "code" of polio. This revolutionary application enables the use of genetic information to not only distinguish the two types of polio namely Sub type- 1 and sub type 2, but also to differentiate the strains within the each subtype. DNA sequence from isolates of polio subtype- 1 has led to the recognition of more than two subtypes (or clades) where each subtype is composed of multitude of strain [0].

It is known that most polio infections are caused by three of the sub types of polio (see [0, 5]) and the reference there in. these subtypes differs significantly in geographical distribution. For instance a single subtype1, differ from each subtype in their cell protoplasm and transmission efficiencies.

Since polio transmission is directly related to polio load on individual within a polio infected population, and considering the fact that polio load itself is dramatically reduced by the use of OPV [3] the main aim of this study is to access the potential impact of using active OPV therapy in community when one sub type is endemic and the second sub type is introduced (into the community).

The model considering three sub types of population; the susceptible (X), the polio sub type 1 infected population (Y_1), and the polio sub type 2 infected populations (Y_2). The total population size $N= X + Y_1 + Y_2$ This model categorizes polio infected individual and those with paralyses due to infection by sub type I In the same population Y_i (for i = 1,2). From the general distribution of a system [1] modeled the dynamics of an epidemic disease in a

heterogeneous population, he passed to a non distribution system whose solution coincide with the aggregate solution of the distribution system at last in an expansion phase of the disease[2]. Epidemic models that explicitly take into account the heterogeneous of a population involved distribution parameters system[3] such models are not only complex, for numerical processing, but required distributed data that are usually not available. For this reason, it is desirable to deal with non distributed (aggregate) models usually obtained by an appropriate averaging. A few of these models were simulated using explicit schemes like the Euler and Runge Kutta (RK4) methods. However, explicit methods are known to exhibit contrived chaos properties whenever a discrimination parameters exceeds certain values [4]. Although, chaos can often be avoided, even for Euler methods, by using small time step, the extra computing cost incurred when examining the long time behavior of a dynamical system may be substantial. It is therefore essential to use numerical method which allows large possible time steps that are consistent with stability and accuracy. In this paper, a robust, easy to use, implicit, mathematical model will be developed for the solution of the resulting initial vales problems (IVP) model. The novel numerical method will be seen to have a stability property than the fourth order Runge Kutta Method(RK4) with the assumption that individual infected by one step type do not become infected at a later date by the other subtype.

MATHEMATICAL MODEL

The model works on the assumption that individuals infected by one subtype do not become infected at a later date by the other subtype

SUSCEPTIBLE POPULATION, X

All new individuals recruited into the society at a rate H per year are considered to be susceptible. This population is reduced by natural cessation of birth at a constant rate ℓ or death at a constant rate B_1. The average number of children that are more vulnerable to having the disease is C

$$\frac{\delta X}{\delta t} = H - \mu X - \frac{1}{N} B_1 C X Y_1 - \frac{1}{N} B_2 C X Y_2 \quad t > t_{o,} \quad X(t_o) = X^0 \tag{1}$$

SUBTYPE 1 INFECTED POPULATION Y_1

This population increases through the infection of susceptible by subtype 1 infected individuals. It is diminished through proper sewage disposal of infected individuals, This diseases induced paralysis at a rate y_1(following the infection of subtype 1) and administration of therapy at a rate t thus;

$$\frac{\delta Y_1}{\delta t} = \frac{1}{N} B_1 C X Y_1 - (\mu + y_1 + t) Y_1 \quad t > t_{o,} \quad Y_1(t_o) = Y_1^0 \tag{2}$$

SUBTYPE 2 INFECTED POPULATION Y_2

This population increases through the infection of susceptible by subtype 2 infected individuals. It is reduced by natural cessation of birth, Proper sewage disposal, death and

isolation of infected individuals. This diseases induced paralysis at a rate y_2(following the infection of subtype 1) and administration of therapy at a rate t thus; this suggest the IVP,

$$\frac{\delta y_2}{\delta t} = \frac{1}{\mu} B_2 CXY_2 - (\mu + y_2 + t)Y_2 \quad t > t_{o,} \quad Y_2(t_o) = Y_2^{\,0} \tag{3}$$

In summary, the model is given by non-linear IVP system:

$$\begin{aligned}
&\frac{\delta x}{\delta t} \equiv g_1 = H - \mu X - \frac{1}{N} B_1 CXY_1 - \frac{1}{N} B_2 CXY_2 \;;\; t > t_{o,} \qquad X(t_o) = X^0 \\
&\frac{\delta y_1}{\delta t} \equiv g_2 = \frac{1}{N} B_1 CXY_1 - (\mu + y_1 + t)y_1; \quad t > t_{o,} \quad Y_1(t_o) = Y_1^{\,0} \\
&\frac{\delta y_2}{\delta t} \equiv g_2 = \frac{1}{N} B_2 CXY_2 - (\mu + y_2 + t)Y_2 \quad t > t_{o,} \quad Y_2(t_o) = Y_2^{\,0}
\end{aligned} \tag{4}$$

The initial value problem system equation (4) is WPV transmission population model that monitors the dynamics of two polio subtypes in the presence of active OPV vaccine. It is a modified version of the drug free model. The stability of this dynamical system will be analyzed in section (3) and a robust numerical method for its solution developed in section (4) Numerical experiments is reported in section 5.

STABILITY ANALYSIS

The steady states of the IVP (3) are determined when the line derivative vanish giving

1. Disease free (trivial) critical point (the virus is eradicated)

$$X^* = \frac{H}{\mu,} \qquad Y^*_1 = Y^*_2 = 0 \tag{5}$$

2. Subtype 1 only equilibrium

$$X^* = \frac{H}{(B_1 C - y_1 - t)} \quad , \quad Y_1^* = \frac{H(B_1 C - \mu - y_1 - t)}{(B_1 C - y_1 - t)(\mu + y_1 + t)} \;=\; Y_2 * = 0 \tag{6}$$

(Here the endemic subtype resist while the invading subtype is eradicated)

3. Subtype 2 only equilibrium

$$X^* = \frac{H}{(B_2 C - y_2 - t)} \quad , \quad Y_2^* = \frac{H(B_2 C - \mu - y_2 - t)}{(B_2 C - y_2 - t)(\mu + y_2 + t)} \;=\; Y_1 * = 0 \tag{7}$$

(In this case, the endemic subtype is eradicated and the invading subtype persist)
A critical point is said to be stable if the Eigen values of the Jacobean

$$J = \begin{bmatrix} \frac{\partial g_1}{\partial X} & \frac{\partial g_1}{\partial Y_1} & \frac{\partial g_1}{\partial Y_2} \\ \frac{\partial g_2}{\partial X} & \frac{\partial g_2}{\partial Y_1} & \frac{\partial g_2}{\partial Y_2} \\ \frac{\partial g_3}{\partial X_1} & \frac{\partial g_3}{\partial Y_1} & \frac{\partial g_3}{\partial Y_2} \end{bmatrix} \tag{8}$$

evaluated at a critical point are real and negative or are complex with negative real parts. It is easy to show that the Jacobean associated with g1, g_2 and g_3 given in equation (4) evaluated at the critical point equation (5) is the matrix.

$$J^* = \begin{matrix} -\mu \\ 0 \end{matrix} \begin{bmatrix} & -B_1C & -B_2C \\ 0 & B_1C-(\mu+y_1+t) & 0 \\ 0 & & B_2C-(\mu+y_2+t) \end{bmatrix} \tag{9}$$

Clearly the Eigen values of equation (9) are given by

$$\lambda_1 = -\mu, \quad \lambda_2 = B_1C-(\mu+y_1+t) \text{ And } \lambda_3 = B_2C-(\mu+y_2+t) \tag{10}$$

Making a realistic assumption that all model parameters are positives, it can also be seen from equation 4.8 that $\lambda_1 < 0$, it is also clear that $\lambda_2 < 0$. Provided that

$$\frac{B_1C}{\mu+y_1+t)} < 1 \tag{11}$$

Similarly, $\lambda_3 < 0$ whenever

$$\frac{B_2C}{\mu+y_2+t)} < 1 \tag{12}$$

Thus the disease free equilibrium is stable whenever equation (11) and (12) are satisfied. Equivalently disease can invade if and only if one of the Eigen values λ_2 and λ_3 has a positive real part. This occur when one of he basic reproductive numbers of subtype I, is given by (11) and (12) as

$$R_0^{(i)} = \frac{B_iC}{(\mu+y_i+t)} \tag{13}$$

exceeds unity in magnitude (see, for instance equation (5)-(7) the WPV has basic reproductive number and an inversion reproductive number. This basic reproductive number is the average number of secondary cases that will be reproduced by a single infective, who is infected with the virus. When the entire community is susceptible, based on the analysis

above, if an infected is introduced into the community then that virus will become established if and only if the basic reproductive number for the virus exceeds unity. In summary, if

$R_0^{\ 1} < 1$

then the WPV is eradicated.

FINITE – DIFFERENCE METHOD

To circumvent the contrived chaos (and oscillation in numerical results) associated with the use of explicit methods; an easy to use implicitly derived finite difference method was developed for solving the model IVP in equation 4.3

Starting with the initial value problem for X in equation 4.3 the development of numerical methods may be based on approximating the time derivative by its first order forward difference approximation given by

$$\frac{\partial X}{\partial t} = \frac{X(t+\ell) - X(t)}{\ell} + O(\ell^2) as \ell \to 0 \tag{14}$$

where $\ell > 0$ is an increment in t (the time step). Discretizing the interval $t \geq t_0 = 0$ at the points $t_n = n\ell$(n = 0, 1, 2, 3, ….) the solution at grid point x_n is $x(t_n)$. The solution of an approximating numerical method will be donated by $X^{n.}$ A first order numerical method for solving X in equation (14) based on approximation, the time derivative by equation (14) and making appropriate approximations for the right hand side terms, is

$$M_x : \frac{1}{\ell}(X^{n+1} - X^n) = H - \mu X^{n+1} - \frac{B_1 C X^{n+1} Y_1}{X^n + Y_1^n + Y_2^n} - \frac{B_2 C X^{n+1} Y_2}{X^n + Y_1^n + Y_2^n} \tag{15}$$

Similarly the method for Y_1 and Y_2 is given by

$$M_{y_1} : \frac{1}{\ell}(Y_1^{n+1} - Y_1^{\ n}) = \frac{B_1 C X^{n+1} Y_1^{n+1}}{X^{n+1} + Y_1^n + Y_2^n}(\mu + y_1 + t) Y_1^{n+1} \tag{16}$$

$$M_{y_2} : \frac{1}{\ell}(Y_2^{\ n+1} - Y_2^{\ n}) = \frac{B_2 C X^{n+1} Y_2^{n+1}}{X^{n+1} + Y_1^n + Y_2^n}(\mu + y_2 + t) Y_2^{n+1} \tag{17}$$

Following Mickens (1994), the time step ℓ in equation 15 -17 is approximated as

$$\ell = \Delta t \to \qquad {}^{1-\ell^{-2t}}\!/_{2} \tag{18}$$

This approximation is important in ensuring that the numerical result is free of contrived chaos and oscillation.

Rearranging the method (15)-(17) above, note that (18) gives

$$X^{n+1} = \{X^n + H\Delta t \Big/ [1 + \Delta t(\mu + \frac{C}{X^n + Y_1^n + Y_2^n})B_1 Y_1^n B_2 Y_2^n]\} \tag{19}$$

$$Y_1^{n+1} = Y_1^n \Big/ \{1 + \Delta t[\mu + y_1 + t] - \frac{B_1 C X^{n+1}}{X^{n+1} + Y_1^n + Y_2^n}\} \tag{20}$$

$$Y_2^{n+1} = Y_2^n \Big/ \{1 + \Delta t[\mu + y_2 + t] - \frac{B_2 C X^{n+1}}{X^{n+1} + Y_1^n + Y_2^n}\} \tag{21}$$

It is worth mentioning that although the Gauss Seidal like method (15) - (16) are implicit by construction, the numerical result obtained explicitly at every time step using equations (19) – (20) gives a better result. It can be seen that the principal part of the local truncation error associated with each of the methods above is of order ℓ^2 confirming that the methods are(all) first order accurate.

NUMERICAL EXPERIMENT

To test the behavior, the implicit method of equation (19) – (20) for solving the model Initial Value Problem (IVP) (4), numerous numerical simulations were carried out as follows:

EXPERIMENT 1: EFFECT OF TIME STEP, ℓ

Extensive numerical simulations were carried out using the implicit method to solve equation (4) with various time - steps and the following parameters and initial values

H = 2000, μ = 1/32, t = 0.4, C = 4, y_1 = 1/10, X^0 = 8000, B_1 = 0.06, B_2 = 0.5, y_1 = 0.1, y_2 = 0.05, X^0 = 8000, $Y^0{}_1$ = 200,and $Y^0{}_2$ = 300

These parameters are based on data collected from WHO, Table 1 compares the convergence properties of the implicit method equation (19)- (20), with that of RK4 when used to integrate the initial Value problem equation (4) subject to the same initial values of the variables. It is clearly evident from table 1 that the implicit method is moiré competitive in terms of numerical stability. In all of these simulations, the implicit method was seen to be chaos free and monotonically convergent in the correct critical point. The RK4, however, begins to give solution profile that converged to false fixed points (thereby giving wrong numerical result) for, $3 \leq \ell \leq 3.2$ for, $\ell \geq 3.3$; the RK4 gave divergent results, and therefore fails. Thus unlike explicit methods like equation (19)-(20) (which admits large time – steps) are more suited for solving non- linear IVP`s

EXPERIMENT 2: EFFECT OF BASIC REPRODUCTIVE NUMBER, $R_0^{(I)}$

In order to study the effect of the basic reproductive numbers ($R_0^{(1)}$, $R_0^{(2)}$) of the two polio subtypes, the model IVP (4) was solved using the method (19) (21) with various vales of $R_0^{(1)}$ $R_0^{(2)}$. The results are tabulated in table 2. It can be seen from table 2 that polio virus can only be eradicated if both the basic reproductive numbers (of the two subtypes) are less than unity simultaneously,.

TABLE 1: EFFECTS OF TIME-STEP, ℓ

ℓ	*RK4*	*Implicit method*
0.01	Monotonic convergence	Monotonic convergence
1	Monotonic convergence	Monotonic convergence
3	Wrong solution	Monotonic convergence
3.3	Divergence(method failed)	Monotonic convergence
10	Divergence	Monotonic convergence
100	Divergence	Monotonic convergence

It is also evident that the subtype with the higher reproductive number always dominates the other (with the lower reproductive number) the two subtype coexist when the two reproductive numbers are the same.

TABLE 2: EFFECT OF NUMBER OF BASIC REPRODUCTIVE NUMBERS R_0^1

$R_0^{(1)}$	$R_0^{(2)}$	X *	Y^*_1	Y^*_2
0.45176	0.83117	64000	0	0
0.45177	4.15584	1290	0	4072
4.31765	0.83117	1053	3703	0
1.34783	1.34783	9524	1325	1987
1.82857	4.92307	5714	0	22418

Table 2 shows that whenever R_0^1 is less than unity (R_0^1 < 1) Y_1^* becomes zero(0), meaning that at this point the Critical Immunization threshold is reached and the

transmission will seized because an infected individual can infect less than one person. On the other hand we expect an outbreak if

$(R_0^1 > 1)$.

TABLE 3: EFFECT OF ANTI- RETROVIRAL THERAPY

T	X^*	Y_1^*	Y_2^*
0	5714	0	22,418
0.1	8000	0	9,655
0.2	13,333	0	5,630
0.3	40,000	0	1,967
0.4	64,000	0	0

Table 3 shows that when the time – step is 0.4, the infected individuals becomes zero (0) as a result of the OPV therapy and more susceptible becomes immune

EXPERIMENT 3: EFFECT OF ANTI- RETROVIRAL THERAPY T,

The effectiveness of the drug treatment coverage is monitored by using the numerical method equation (19) – (20) to simulate the model, IVP equation (4) with various level of drug treatment administered within the population. The following parameters and initial values were used.: H = H = 2000, μ = 1/32, C = 4, y_1 = 1/10, X^0 = 8000, B_1 = 0.06, B_2 = 0.1, y_1 = 0.1, y_2 = 0.1, X^0 = 8000, Y^0_1 = 200,and Y^0_2 = 300

The proportion of infected individuals approaches zero when t >= 0.4. This means that for the values of the variable to be zero in these simulations, at least a 40% effective community wide Oral Polio Vaccine therapy is required for the virus to be eradicated.

CONCLUSION

A chaos free Gauss Seidal type implicit method was developed and used for the solution of a transmission model of two polio subtype in the presence Oral Polio Vaccine (OPV). This method was more efficient in terms of numerical stability, than a well known method in literature. The model predicts that, for the virus to be eradicated, the reproductive numbers of the two subtypes must be less than unity simultaneously, and the therapy coverage level must be at least 40%

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