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A competitive numerical method for a chemotherapy model of two HIV subtypes

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Abstract

A competitive Gauss–Seidel-type finite-difference method is developed for the solution of a non-linear deterministic model associated with the transmission dynamics of two HIV subtypes in the presence of antiretroviral therapy. The model suggests the optimal level of 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 discretization of the model, the new implicit finite-difference method to be developed gives stable convergent numerical results for any time-step.

1. Introduction

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 the genetic "code" of HIV. This revolutionary application enables the use of genetic information to not only distinguish the two major types of HIV namely Type 1 (HIV-1) and Type 2 (HIV-2), but also to differentiate strains within each type. DNA sequences from isolates of HIV-1 has led to the recognition of more than 15 subtypes (or clades) where each subtype is composed of multitude of strains [1,5].

It is known that most HIV infections are caused by five of the subtypes of HIV-1 (see [1] and the references therein). These subtypes differ significantly in

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geographical distribution. For instance, a single subtype (Subtype B) predominates in most developed nations, whereas at least two types are co-circulating in many developing countries (Subtypes B and E in Thailand, Subtypes A and D in Uganda) [5]. Additionally, HIV-1 subtypes differ from each other in their cell tropisms and transmission efficiencies [2].

Since HIV transmission is directly related to the HIV load in individuals within a HIV-infected population, and considering the fact that the HIV load itself is dramatically reduced by the use of anti-HIV drugs such as (RT and protease inhibitors or their combinations), the main aim of this study is to assess the potential impact of using an active anti-retroviral therapy in a community when one subtype is endemic and a second subtype is introduced (into the community).

This model considers three sub-populations: the susceptible population (X), the HIV-Subtype-1-infected population (Y_1), and the HIV-Subtype-2-infected population (Y_2). The total population size is $N = X + Y_1 + Y_2$. This model categorizes HIV-infected individuals and those with AIDS due to infection by Subtype-i in the same population Y_i (for $i = 1, 2$).

It is worth mentioning that most of the published studies in the mathematical epidemiology literature contained scant or no detail of the numerical method(s) used to solve the model equations. A few of these models were simulated using explicit schemes like Euler and Runge–Kutta (RK) methods. However, explicit methods are generally known to exhibit contrived chaos whenever the discretization parameters exceed certain values (see, for instance, [3,4]).

Although chaos can often be avoided, even for Euler methods, by using small time steps, the extra computing costs incurred when examining the long-term behaviour of a dynamical system may be substantial. It is therefore essential to use a numerical method which allows the largest possible time-steps that are consistent with stability and accuracy. In this paper, a robust, easy-to-use, implicit, finite-difference method will be developed for the solution of the resulting initial-value problem (IVP) model. The novel numerical method will be seen to have better stability property than the fourth-order Runge–Kutta method (RK4).

2. Mathematical model

Following Porco and Blower [5], it is assumed that individuals infected by one subtype do not become infected at a later date by the other subtype.

2.1. Susceptible population, X

All new individuals recruited into the society at a rate Π *per* year are considered to be susceptibles. This population is reduced by the natural cessation

of sexual activity at a constant rate μ, and by infection with a Subtype-1- or Subtype-2 which may be acquired from each new sexual partner at a rate β_i (β_1 for Subtype-1 and β_2 for Subtype-2). The average number of new sexual partners (or I.V. drug partners with whom needles are shared) is c. Thus,

$$\frac{dX}{dt} = \Pi - \mu X - \frac{1}{N}\beta_1 cXY_1 - \frac{1}{N}\beta_2 cXY_2, \quad t > t_0, \ X(t_0) = X^0. \tag{1}$$

2.2. Subtype-1-infected population, Y_1

This population increases through the infection of susceptibles by Subtype-1-infected individuals. It is diminished by natural cessation of sexual activity, disease-induced death at a rate γ_1 (following infection with Subtype-1) and by the administration of therapy at a per capita rate τ. Thus,

$$\frac{dY_1}{dt} = \frac{1}{N}\beta_1 cXY_1 - (\mu + \gamma_1 + \tau)Y_1, \quad t > t_0, \ Y_1(t_0) = Y_1^0. \tag{2}$$

2.3. Subtype-2-infected individuals, Y_2

This population increases through the infection of susceptibles by Subtype-2-infected individuals. It is reduced by natural cessation of sexual activity, death due to AIDS (following Subtype-2 infection) at a rate γ_2 and by the administration of therapy at a per capita rate τ. This suggests the IVP:

$$\frac{dY_2}{dt} = \frac{1}{N}\beta_2 cXY_2 - (\mu + \gamma_2 + \tau)Y_2, \quad t > t_0, \ Y_2(t_0) = Y_2^0. \tag{3}$$

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

$$\begin{aligned}
\frac{dX}{dt} &\equiv g_1 = \Pi - \mu X - \frac{1}{N}\beta_1 cXY_1 - \frac{1}{N}\beta_2 cXY_2, \quad t > t_0, \quad X(t_0) = X^0, \\
\frac{dY_1}{dt} &\equiv g_2 = \frac{1}{N}\beta_1 cXY_1 - (\mu + \gamma_1 + \tau)Y_1, \quad t > t_0, \quad Y_1(t_0) = Y_1^0, \\
\frac{dY_2}{dt} &\equiv g_3 = \frac{1}{N}\beta_2 cXY_2 - (\mu + \gamma_2 + \tau)Y_2, \quad t > t_0, \ Y_2(t_0) = Y_2^0.
\end{aligned} \tag{4}$$

The IVP system (4) is a HIV transmission population model that monitors the dynamics of two HIV subtypes in the presence of active anti-retroviral drugs. It is a modified version of the drug-free model presented in [5]. The stability of this dynamical system will be analysed in Section 3, and a robust numerical method for its solution developed in Section 4. Numerical experiments are reported in Section 5.

3. Stability analysis

The steady-states of the IVP (4) are determined when the time derivatives vanish giving:

1. Disease-free (trivial) critical point (both subtypes are eradicated)

$$X^* = \frac{\Pi}{\mu}, \quad Y_1^* = Y_2^* = 0. \tag{5}$$

2. Subtype-1-only equilibrium:

$$X^* = \frac{\Pi}{\beta_1 c - \gamma_1 - \tau}, \quad Y_1^* = \frac{\Pi(\beta_1 c - \mu - \gamma_1 - \tau)}{(\beta_1 c - \gamma_1 - \tau)(\mu + \gamma_1 + \tau)}, \quad Y_2^* = 0 \tag{6}$$

(here the endemic subtype persists while the invading subtype is eradicated).

3. Subtype-2-only equilibrium:

$$X^* = \frac{\Pi}{\beta_2 c - \gamma_2 - \tau}, \quad Y_2^* = \frac{\Pi(\beta_2 c - \mu - \gamma_2 - \tau)}{(\beta_2 c - \gamma_2 - \tau)(\mu + \gamma_2 + \tau)}, \quad Y_1^* = 0. \tag{7}$$

(In this case, the endemic subtype is eradicated and the invading subtype persists.)

A critical point is said to be stable if the eigenvalues of the Jacobian

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

evaluated at the critical point, are real and negative or are complex with negative real parts. It is easy to show that the Jacobian associated with g_1, g_2, and g_3 given in (4) evaluated at the trivial critical point (5) is the matrix

$$J^* = \begin{bmatrix} -\mu & -\beta_1 c & -\beta_2 c \\ 0 & \beta_1 c - (\mu + \gamma_1 + \tau) & 0 \\ 0 & 0 & \beta_2 c - (\mu + \gamma_2 + \tau) \end{bmatrix}. \tag{9}$$

Clearly, the three eigenvalues of (9) are given by

$$\lambda_1 = -\mu, \quad \lambda_2 = \beta_1 c - (\mu + \gamma_1 + \tau), \quad \text{and } \lambda_3 = \beta_2 c - (\mu + \gamma_2 + \tau). \tag{10}$$

Making the realistic assumption that all the model parameters are positive, it can be seen from (10) that $\lambda_1 < 0$. It is also clear that $\lambda_2 < 0$ provided

$$\frac{\beta_1 c}{\mu + \gamma_1 + \tau} < 1. \tag{11}$$

Similarly, $\lambda_3 < 0$ whenever

$$\frac{\beta_2 c}{\mu + \gamma_2 + \tau} < 1. \tag{12}$$

Thus, the disease-free equilibrium is stable whenever (11) and (12) are satisfied. Equivalently, disease can invade if and only if at least one of the two eigenvalues (λ_2 or λ_3) has a positive real part. This occurs when one of the basic reproductive numbers of Subtype i, given by (11) and (12) as

$$R_0^{(i)} = \frac{\beta_i c}{\mu + \gamma_i + \tau}, \tag{13}$$

exceeds unity in magnitude (see, for instance, [5–7]. Each subtype has a basic reproductive number and an invasion reproductive number. The basic reproductive number is the average number of secondary cases that will be produced by a single infective, who is infected with that subtype, when the entire community is susceptible. Based on the analyses above, if an infected individual who is infected with a given subtype is introduced into the community, then that subtype will become established if and only if the basic reproductive number for that subtype exceeds unity. In summary, if $R_0^{(i)} < 1$, then the subtype i will be eradicated.

The invasion reproductive number of Subtype-2 when Subtype-1 is at equilibrium is the average number of new infections caused by a single individual infected with Subtype-2, when the Subtype-1 is at equilibrium in the community [5].

4. Finite-difference method

To circumvent the contrived chaos (and oscillations in numerical results) associated with the use of explicit methods, an easy-to-use implicitly-derived finite-difference method will now be constructed for solving the model IVP (4).

Starting with the initial-value problem for X in (4), the development of numerical methods may be based on approximating the time derivative by its first-order forward-difference approximant given by

$$\frac{\mathrm{d}X(t)}{\mathrm{d}t} = \frac{X(t+\ell) - X(t)}{\ell} + \mathrm{O}(\ell^2) \quad \text{as } \ell \to 0, \tag{14}$$

where $\ell > 0$ is an increment in t (the time step). Discretizing the interval $t \geqslant t_0 = 0$ at the points $t_n = n\ell (n = 0, 1, 2, \ldots)$, the solution at the grid point x_n is $x(t_n)$. The solution of an approximating numerical method will be denoted by X^n. A first-order numerical method for solving X in (4) based on approximating the time derivative by (14) and making appropriate approximations for the right-hand-side terms, is

$$M_X: \frac{1}{\ell}\left(X^{n+1}-X^n\right)=\Pi-\mu X^{n+1}-\frac{\beta_1 cX^{n+1}Y_1^n}{X^n+Y_1^n+Y_2^n}-\frac{\beta_2 cX^{n+1}Y_2^n}{X^n+Y_1^n+Y_2^n}. \quad (15)$$

Similarly, the methods for Y_1 and Y_2 are, respectively, given by

$$M_{Y_1}: \frac{1}{\ell}\left(Y_1^{n+1}-Y_1^n\right)=\frac{\beta_1 cX^{n+1}Y_1^{n+1}}{X^{n+1}+Y_1^n+Y_2^n}-(\mu+\gamma_1+\tau)Y_1^{n+1} \quad (16)$$

and

$$M_{Y_2}: \frac{1}{\ell}\left(Y_2^{n+1}-Y_2^n\right)=\frac{\beta_2 cX^{n+1}Y_2^{n+1}}{X^{n+1}+Y_1^{n+1}+Y_2^n}-(\mu+\gamma_2+\tau)Y_2^{n+1}. \quad (17)$$

Following Mickens [8], the time-step, ℓ, in (15)–(17) is approximated by

$$\ell=\Delta t\to\frac{1-e^{-2\ell}}{2}. \quad (18)$$

This approximation is important in ensuring that the numerical results is free of contrived chaos and oscillations.

Rearranging the methods (15)–(17) and noting (18) gives

$$X^{n+1}=(X^n+\Pi\Delta t)\Big/\left\{1+\Delta t\left[\mu+\frac{c}{X^n+Y_1^n+Y_2^n}\left(\beta_1 Y_1^n+\beta_2 Y_2^n\right)\right]\right\}, \quad (19)$$

$$Y_1^{n+1}=Y_1^n\Big/\left\{1+\Delta t\left(\mu+\gamma_1+\tau-\frac{\beta_1 cX^{n+1}}{X^{n+1}+Y_1^n+Y_2^n}\right)\right\}, \quad (20)$$

$$Y_2^{n+1}=Y_2^n\Big/\left\{1+\Delta t\left(\mu+\gamma_2+\tau-\frac{\beta_2 cX^{n+1}}{X^{n+1}+Y_1^{n+1}+Y_2^n}\right)\right\}. \quad (21)$$

It is worth mentioning that although the Gauss–Seidel-like methods (15)–(17) are implicit by construction, the numerical result is obtained explicitly at every time-step using (19)–(21). 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.

5. Numerical experiments

To test the behaviour of the implicit method (19)–(21) for solving the model IVP (4), numerous numerical simulations were carried out as follows:

5.1. Experiment 1: Effect of time-step, ℓ

Extensive numerical simulations were carried out using the implicit method to solve (4) with various time-steps and the following parameter and initial values: $\Pi=2000$, $\mu=1/32$, $\tau=0.4$, $\beta_1=0.06$, $\beta_2=0.5$, $c=4$, $\gamma_1=0.1$,

$\gamma_2 = 0.05$, $X^0 = 8000$, $Y_1^0 = 200$ and $Y_2^0 = 300$. These parameters have been estimated, based on data collected in San Francisco, in [5]. Table 1 compares the convergence properties of the implicit method (19)–(21) with that of RK4 when used to integrate the IVP (4) subject to the same initial and parameter values. It is clearly evident from Table 1 that the implicit method is more competitive in terms of numerical stability. In all of these simulations, the implicit method was seen to be chaos-free and monotonically convergent to the correct critical point. The RK4, however, begins to give solution profiles that converged to false fixed points (thereby giving wrong numerical results) for $3 \leqslant \ell \leqslant 3.2$. For $\ell \geqslant 3.3$, the RK4 gave divergent results, and therefore fails. Thus, unlike explicit methods such as the Euler and RK4 methods, implicit methods like (19)–(21) (which admits large time-steps) are more suited for solving non-linear IVP's.

5.2. Experiment 2: Effect of basic reproductive number, $R_0^{(i)}$

In order to study the effect of the basic reproductive numbers ($R_0^{(1)}$ and $R_0^{(2)}$) of the two HIV subtypes, the model IVP (4) was solved using the method (19)–(21) with various values of $R_0^{(1)}$ and $R_0^{(2)}$. The results are tabulated in Table 2. It can be seen from Table 2 that the HIV disease can only be eradicated if both the basic reproductive numbers (of the two subtypes) are less than unity simultaneously. It is also evident that the Subtype with the higher reproductive

Table 1
Effect 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
1000	Divergence	Monotonic convergence

Table 2
Effect of number of basic reproductive numbers, $R_0^{(i)}$

$R_0^{(1)}$	$R_0^{(2)}$	X^*	Y_1^*	Y_2^*
0.45176	0.83117	64,000	0	0
0.45177	4.15584	1290	0	4072
4.51765	0.83117	1053	3703	0
1.34783	1.34783	9524	1325	1987
1.82857	4.92307	5714	0	22,418

Table 3
Effect of anti-retroviral therapy, τ

τ	X^*	Y_1^*	Y_2^*
0	5714	0	22,418
0.1	8000	0	9655
0.2	13,333	0	5630
0.3	40,000	0	1967
0.4	64,000	0	0

number always dominates the other (with the lower reproductive number). The two subtypes co-exist when the two reproductive numbers are the same.

5.3. Experiment 3: Effect of anti-retroviral therapy, τ

The effectiveness of the drug treatment coverage is monitored by using the numerical method (19)–(21) to simulate the model IVP (4) with various levels of drug treatment administered within the population. The following parameter and initial values were used: $\Pi = 2000, \mu = 1/32, \beta_1 = 0.06, \beta_2 = 0.1, c = 4, \gamma_1 = 0.1, \gamma_2 = 0.1,\ X^0 = 8000, Y_1^0 = 200$ and $Y_2^0 = 300$. It should be noted that since β_2 is chosen to be greater than β_1, Subtype-2 will be expected to dominate Subtype-1. The results, tabulated in Table 3, show that the proportion of infected individuals approaches zero when $\tau \geqslant 0.4$. This means that, for the parameter values in these simulations, at least a 40% effective community-wide anti-retroviral therapy is needed if the virus is to be eradicated.

6. Conclusion

A chaos-free, Gauss–Seidel-type, implicit method was developed and used for the solution of a transmission model of two HIV subtypes in the presence of anti-retroviral drugs. This method was more competitive, in terms of numerical stability, than a well-known method in the literature. The model predicts that, for the virus to be eradicated, the basic reproductive numbers of the two subtypes must be less than unity simultaneously, and that therapy coverage level must be at least 40%.

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