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STABILITY OF CLEARANCE RATE PARAMETER AND ITS SENSITIVITY BEHAVIOUR FROM THE SIMPLEST HIV DYNAMIC MODEL

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ABSTRACT. In this paper we proved the stability theorem of the clearance rate parameter of the simplest HIV dynamic model. The stability analysis of the clearance rate parameter leads to conclude the constancy of the parameter. We have also discussed the sensitivity of the parameter estimate to changes in the other parameters in the model.

1. INTRODUCTION

In the last decade, many mathematical models have been developed to describe the immunological response to infection with human immunodeficiency virus (HIV) e.g., [1, 2]. These models have been used to explain different phenomena. The models proposed have principally been linear and nonlinear ordinary differential equation models, both with and without delay terms. These models focus on the interactions of susceptible cells, infected cells, viruses, and immune cells.

The primary purpose of a mathematical model of HIV transmission is to project population-level outcomes from individual-level inputs. Mathematical modeling studies [4] have contributed to our understanding of the dynamics and disparities in the global spread of HIV and to demonstrate the value that these analytic

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tools have for social and behavioral sciences in HIV prevention research, to identify gaps in the current literature, and to suggest directions for future research.

The simplest HIV dynamic model proposed by Alan S. Perelson and Patrick W. Nelson [3] is

$$\frac{dV}{dt} = P - cV,$$

where P is an unknown function representing the rate of virus production, c is a constant called the clearance rate constant, and V is the virus concentration.

If the drug completely blocks viral infection, (i.e.) $P = 0$, then the model predicts that V will fall exponentially. That is,

$$V(t) = V_0 e^{-ct}, \tag{1.1}$$

where $t = 0$ is the time therapy is initiated and $V(t) = V_0$. Plotting lnV versus t and using linear regression to determine the slope allowed them to estimate c and the half - life of virus in the plasma $t_{\frac{1}{2}} = \frac{ln2}{c}$. Half-life is an important concept used in the modeling of HIV. Half-life is the period over which the concentration of the virus falls to half of its original concentration level.

The notion that virus concentration attains a set - point suggests that before therapy began, the patient was in a quasi-steady state in which $\frac{dV}{dt} = 0$. If this were the case, then by knowing c and the initial virus concentration V_0, one can compute the viral production rate before therapy, that is $P = cV_0$. To compute the total rate of virus production, measure V_0 for each patient and then multiply this concentration by the fluid volume in which virus is expected to be found.

In section 2, we present the estimation of the clearance rate parameter in the simplest dynamic model and prove the stability in section 3. In section 4, we perform sensitivity analysis of the parameter.

2. Estimation of the clearance rate parameter

HIV infects cells that carry the $CD4$ cell surface protein as well as other receptors called coreceptors. Cells that are susceptible to HIV infection are called target cells. Since the virus concentration for simplest HIV dynamic model (1.1) falls exponentially, it follows the Gompertz law. The corresponding Gompertz virus growth rate function can be obtained by integrating equation (1.1) of the following form

$$V_g(t) = e^{\frac{V_0}{c}(1-e^{-ct})}, \tag{2.1}$$

where V_0 is the initial virus concentration and c is the clearane rate parameter (the growth deceleration factor). Equation (2.1) results in

$$\frac{V_0}{c} = \frac{\ln V_g(t)}{(1 - e^{-ct})}.$$

From equation (1.1) we have

$$V_g({t_m}^*) = e^{\frac{V_0}{c}(1-e^{-ct{m}^*})}, \tag{2.2}$$

where t_m is the time at which the cell volume is one less than the maximum and approximates the maximum lifespan ${t_m}^*$. After a little algebraic calculations, equation (2.2) leads to

$${t_m}^* = -\frac{1}{c} \ln \left[1 - \frac{c}{V_0} \ln V_g({t_m}^*) \right].$$

The cumulative intrinsic growth rate of the Gompertz model equation (2.1), is defined by

$$V_{c^*} = \int_0^\infty V_g(t)dt. \tag{2.3}$$

Substitution of (2.1) into (2.3) gives

$$V_{c^*} = \int_0^\infty e^{\frac{V_0}{c}(1-e^{-ct})}$$

A simple substitution of $y = -\frac{V_0}{c}e^{-ct}$ into the above equation and after a little algebra we get

$$-c = \frac{1}{V_{c^*}} e^{-\frac{V_0}{c}} \int_{-\frac{V_0}{c}}^\infty \frac{e^{-y}}{y} dy. \tag{2.4}$$

The integral in the equation (2.4) exists if $c < 0$. If $c > 0$, then $\frac{e^{-y}}{y}$ has a pole at $y = 0$. The existence of the principal value of the above integral for $c > 0$ proves the existence of the parameter.

3. Stability of the growth rate parameter

3.1. **Necessary condition for stability.** Let c_1 and c_2 be two distinct positive solutions of (2.4) with virus growth rate functions $V_{g_1}(t)$ and $V_{g_2}(t)$ respectively. Then

$$c_1 - c_2 = -\frac{1}{V_{c^*}}\left[\int_{z_1}^{\infty}\frac{e^{-y+z_1}}{y}dy - \int_{z_2}^{\infty}\frac{e^{-y+z_2}}{y}dy\right] = -\frac{1}{V_{c^*}}\int_0^{\infty} e^{-w}\left[\frac{1}{w+z_1} - \frac{1}{w+z_2}\right]dw \tag{3.1}$$

where $z_i = -\frac{\ln V_g(t)}{(1-e^{-c_i t_m})}$ for $i = 1, 2$ and $w = (y - z_i)$ for $i = 1, 2$. Set

$$z_1 = \frac{z_1+z_2}{2} + \frac{z_1-z_2}{2}, \quad z_2 = \frac{z_1+z_2}{2} - \frac{z_1-z_2}{2}. \tag{3.2}$$

[Note that $\frac{z_1+z_2}{2}$ is the arithmetic mean and $\frac{z_1-z_2}{2}$ is the perturbation term of z_1, z_2]. Substitution of (3.2) into equation (3.1) results in

$$c_1 - c_2 = -\frac{1}{V_{c^*}}e^{\frac{z_1+z_2}{2}}\int_{\frac{z_1+z_2}{2}}^{\infty} e^{-w}\left[\frac{1}{w+\frac{z_1-z_2}{2}} - \frac{1}{w-\frac{z_1-z_2}{2}}\right]dy \tag{3.3}$$

where $w = u + \frac{z_1+z_2}{2}$. On the RHS of (3.3), the expression

$$\begin{aligned}&\frac{1}{w+\left(\frac{z_1-z_2}{2}\right)} - \frac{1}{w-\left(\frac{z_1-z_2}{2}\right)}\\ &= \frac{1}{w}\left(1 - \frac{z_1-z_2}{2y} + ...\right) - \frac{1}{w}\left(1 + \frac{z_1-z_2}{2w} + \dots\right)\end{aligned} \tag{3.4}$$

can be approximated to $-(\frac{z_1-z_2}{y^2})$ by neglecting higher order perturbation terms in each expression on the RHS of (3.4), since $\left|\frac{z_1-z_2}{z_1+z_2}\right| < 1$.

On account of (3.4), (3.3) becomes

$$c_1 - c_2 = -\frac{1}{V_{c^*}}e^{\frac{z_1+z_2}{2}}\int_{\frac{z_1+z_2}{2}}^{\infty} -\left(\frac{z_1-z_2}{w^2}\right)e^{-w}dw.$$

Further,

$$|c_1 - c_2| \leq \frac{1}{V_{c^*}} e^{\frac{z_1+z_2}{2}} \int\limits_{\frac{z_1+z_2}{2}}^{\infty} \frac{|z_1 - z_2|}{w^2} e^{-w} dw$$

$$\leq \frac{1}{V_{c^*}} |z_1 - z_2| e^{\frac{z_1+z_2}{2}} e^{-\frac{z_1+z_2}{2}} \int\limits_{\frac{z_1+z_2}{2}}^{\infty} \frac{dw}{w^2}.$$

Upon integration we get

$$|c_1 - c_2| \leq \frac{1}{V_{c^*}} \left| \frac{z_1 - z_2}{\frac{z_1+z_2}{2}} \right|. \tag{3.5}$$

Retrieving z_i from (3.2) and substituting into equation (3.5), we get

$$|c_1 - c_2| \leq \frac{1}{V_{c^*}} \left| \frac{\ln V_{g_1}^*(e^{c_2 t_m} - 1) - \ln V_{g_2}^*(e^{c_1 t_m} - 1)}{\frac{\ln V_{g_1}^*(e^{c_2 t_m}-1) + \ln V_{g_2}^*(e^{c_1 t_m}-1)}{2}} \right|$$

$$= \frac{1}{V_{c^*}} \left| \frac{\ln V_{g_1}^* e^{c_2 t_m} - \ln V_{g_2}^* e^{c_1 t_m} - (\ln V_{g_1}^* - \ln V_{g_2}^*)}{\frac{\ln V_{g_1}^* e^{c_2 t_m} + \ln V_{g_2}^* e^{c_1 t_m}}{2} - \frac{(\ln V_{g_1}^* + \ln V_{g_2}^*)}{2}} \right|.$$

Dividing each term by $\frac{\ln V_{g_1}^* + \ln V_{g_2}^*}{2}$ and representing parameter c as a sum of mean and perturbation as follows:

$$c_1 = \frac{c_1 + c_2}{2} + \frac{c_1 - c_2}{2}, \quad c_2 = \frac{c_1 + c_2}{2} - \frac{c_1 - c_2}{2}.$$

and after a little algebra we obtain

$$|c_1 - c_2| \leq \frac{1}{V_{c^*}} \left| \frac{\frac{2 \ln V_{g_1}^*}{\ln V_{g_1}^* + \ln V_{g_2}^*} P - \frac{2 \ln V_{g_2}^*}{\ln V_{g_1}^* + \ln V_{g_2}^*} Q - \frac{\ln V_{g_1}^* - \ln V_{g_2}^*}{\frac{\ln V_{g_1}^* + \ln V_{g_2}^*}{2}} R}{\frac{\ln V_{g_1}^*}{\ln V_{g_1}^* + \ln V_{g_2}^*} P + \frac{\ln V_{g_2}^*}{\ln V_{g_1}^* + \ln V_{g_2}^*} Q - R} \right|, \tag{3.6}$$

where we have denoted $P = e^{-\frac{c_1 - c_2}{2} t_m}$, $Q = e^{\frac{c_1 - c_2}{2} t_m}$ and $R = e^{-\frac{c_1 + c_2}{2} t_m}$. Since

$$e^{\pm \frac{c_1 - c_2}{2} t_m} \approx 1 \pm (\frac{c_1 - c_2}{2}) t_m \tag{3.7}$$

(by neglecting higher order perturbation terms in c_1, c_2) substituting (3.7) into equation (3.6) and simplifying further we obtain

$$|c_1 - c_2| \leq \frac{1}{V_{c^*}} \left| \frac{\frac{\ln V_{g_1}^* - \ln V_{g_2}^*}{\frac{\ln V_{g_1}^* + \ln V_{g_2}^*}{2}} (1 - R) - 2(\frac{c_1 - c_2}{2}) t_m}{(1 - R) + (\frac{c_1 - c_2}{2}) t_m (\frac{\ln V_{g_2}^* - \ln V_{g_1}^*}{\ln V_{g_1}^* + \ln V_{g_2}^*})} \right|. \tag{3.8}$$

In (3.8) the last term in the denominator is a product of two perturbation terms. We neglect this higher order term to get

$$|c_1 - c_2| \leq \frac{1}{V_{c^*}} \left| \frac{\ln V_{g_1}^* - \ln V_{g_2}^*}{\frac{\ln V_{g_1}^* + \ln V_{g_2}^*}{2}} \right| + \frac{1}{V_{c^*}} t_m \left| \frac{c_2 - c_1}{1 - e^{-\frac{c_1+c_2}{2} t_m}} \right|. \tag{3.9}$$

Let

$$\frac{t_m}{V_{c^*}\left[1 - e^{-\frac{c_1+c_2}{2} t_m}\right]} < 1. \tag{3.10}$$

Then $0 < e^{-\frac{c_1+c_2}{2} t_m} < 1 - \frac{t_m}{V_{c^*}}$, which is true when $\frac{t_m}{V_{c^*}} < 1$.

If $\frac{t_m}{V_{c^*}} < 1$, further we have

$$-\left(\frac{c_1 + c_2}{2}\right) t_m < \ln(1 - \frac{t_m}{V_{c^*}})$$

which gives

$$\frac{c_1 + c_2}{2} > \frac{1}{t_m} \ln\left(\frac{1}{1 - \frac{t_m}{V_{c^*}}}\right).$$

Note that the above estimation is independent of the virus growth.

Theorem 3.1. *The clearance rate parameter of the simplest HIV dynamic model c is stable with respect to the virus growth rate function $V_g(t)$, provided $\frac{t_m}{V_{c^*}} < 1$.*

Proof. When (3.10) holds, from (3.9) we get

$$|c_1 - c_2| \left\{ 1 - \left(\frac{t_m}{V_{c^*}\left[1 - e^{-\frac{c_1+c_2}{2} t_m}\right]} \right) \right\} \leq \frac{1}{V_{c^*}} \left| \frac{\ln V_{g_1}^* - \ln V_{g_2}^*}{\frac{\ln V_{g_1}^* + \ln V_{g_2}^*}{2}} \right|$$

or, equivalently

$$|c_1 - c_2| \leq K \frac{1}{V_{c^*}} \left| \frac{\ln V_{g_1}^* - \ln V_{g_2}^*}{\frac{\ln V_{g_1}^* + \ln V_{g_2}^*}{2}} \right|, \tag{3.11}$$

where $K = \frac{1}{1 - \left(\frac{t_m}{V_{c^*}}\left[1 - e^{-\frac{c_1+c_2}{2} t_m}\right]\right)} > 0$. Hence it follows from (3.11) that c is stable for any $V_g(t)$. □

Theorem 3.2. *The clearance rate parameter of the simplest HIV dynamic model c to be stable with respect to the virus growth rate function $V_g(t)$, it is necessary that c be a constant.*

Remark 3.1. *Observe that the experimental data given in Table 2.1 and Table 2.2 confirms the theoretical approach of theorem 2.*

Corollary 3.1. *Since c is a constant, it is clear that c is stable also with respect to t_m.*

TABLE 1. (reprinted from [3])

CD4 count (mm^{-3})	Plasma virus (virions per $ml \times 10^3$)	$t_{1/2}$ (days)	c (day^{-1})	Total virus production (10^9/day)
16	294	0.2	3.8	12.9
408	12	0.3	2.7	0.4
2	52	0.2	3.7	2.9
11	643	0.3	2.1	32.1
412	77	0.2	3.1	3.0

4. SENSITIVITY ANALYSIS OF THE PARAMETER

Sensitivity analysis can be used to determine the functional relationship between virus growth rate and the constituent rates (e.g., survival, growth, maturation, movement), and to project changes in virus growth rate as vital rates change. To find the sensitivity changes, consider (2.4) and the partials of c with respect to $V_g(t), V_{c^*}$ and t_m are given by

$$-\frac{\partial c}{\partial V_g(t)} = \frac{[V_0 - (1/V_{c^*})]/V_g(t)\ln V_g(t)}{1 + (e^{-ct_m}/(e^{-ct_m}-1))t_m[V_0 - (1/V_{c^*})]},$$
$$-\frac{\partial c}{\partial V_{c^*}} = \frac{-c/V_{c^*}}{1 + (e^{-ct_m}/(e^{-ct_m}-1))t_m[V_0 - (1/V_{c^*})]},$$
$$-\frac{\partial c}{\partial t_m} = \frac{-c(e^{-ct_m}/(e^{-ct_m}-1))/[(1/V_{c^*}) - V_0]}{1 + (e^{-ct_m}/(e^{-ct_m}-1))t_m[V_0 - (1/V_{c^*})]}.$$

It can be noted that

$$\frac{\partial c}{\partial V_g(t)} = \frac{[V_0 - (1/V_{c^*})]/V_g(t)lnV_g(t)}{1 + (e^{-ct_m}/(e^{-ct_m}-1))t_m[V_0 - (1/V_{c^*})]} \geq 0 \quad \forall V_g(t), \tag{4.1}$$

$$\frac{\partial c}{\partial V_{c^*}} = \frac{-c/V_{c^*}}{1 + (e^{-ct_m}/(e^{-ct_m}-1))t_m[V_0 - (1/V_{c^*})]} \leq 0, \tag{4.2}$$

TABLE 2. (reprinted from [3])

CD4 count (mm^{-3})	V_0(virions per $ml \times 10^3$)	$t_{1/2}$ (days)	$P = cV_0$ (virions/day$\times 10^9$)
76	193	2.3	0.6
209	80	2.6	0.3
293	41	3.3	0.1
174	121	2.5	0.5
269	88	2.1	0.5
312	175	1.3	1.3
386	185	1.5	1.5
49	554	2.4	1.9
357	15	2.7	0.1
107	130	2.4	0.5
59	70	2.3	0.3
47	100	1.3	0.9
228	101	1.7	0.5
169	55	2.5	0.2
120	126	2.2	0.7
46	244	2.6	1.1
490	18	2.2	0.1
36	23	2.8	0.1
67	256	1.5	2.1
103	99	1.9	0.5

$$\frac{\partial c}{\partial t_m} = \frac{-c(e^{-ct_m}/(e^{-ct_m}-1))/[(1/V_{c^*})-V_0]}{1+(e^{-ct_m}/(e^{-ct_m}-1))t_m[V_0-(1/V_{c^*})]} \leq 0. \tag{4.3}$$

As $V_g(t)$ tends to ∞ in (4.1), (4.2) and (4.3) we get

$$\lim_{V_g(t)\to\infty} \frac{\partial c}{\partial V_g(t)} = 0$$

$$\lim_{V_g(t)\to\infty} \frac{\partial c}{\partial V_{c^*}} = 0$$

$$\lim_{V_g(t)\to\infty} \frac{\partial c}{\partial t_m} = 0.$$

Thus it is clear that c is insensitive to changes in $V_g(t) \to \infty$. That is c does not change rapidly as the virus growth rate increases. On the other hand, if $V_g(t) \to 1$, from equation (4.1) we get

$$\lim_{V_g(t)\to 1} \frac{\partial c}{\partial V_g(t)} = \infty$$

since $1/V_g(t)lnv_g(t) \to \infty$ as $V_g(t) \to 1$. This inturn gives

$$\lim_{V_g(t)\to 1} \frac{\partial c}{\partial V_{c^*}} = -\infty$$

$$\lim_{V_g(t)\to 1} \frac{\partial c}{\partial t_m} = -\infty.$$

Hence when the virus growth rate decreases we see a substantial change in the sensitivity of c with respect to initial virus concentration V_0.

5. Conclusion

The aim of this article is to address the issue of parameter sensitivity of a new method for estimating the clearance rate. The issue of sex differences is not addressed in this article. The clearance rate parameter is either stable with respect to the virus growth rate parameter or constant.

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