On A Mathematical Model of HCV

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***Abstract*— We present a mathematical model to describe the development of HCV virus in a human body. The model says that there are two outcomes to the treatment of HCV, rebound or SVR. We give examples to show that a small change in the treatment regimen may change a rebound outcome to an SVR outcome.**

***Index Terms*—Hepatitis C Virus, Differential equations, Mathematical modeling, Sustained Virologic Response**

I. INTRODUCTION

ONE hundred and seventy million people are infected with HCV (Hepatitis C virus) worldwide [1]. In North America, more than five million people are supposed to be living with HCV [2]. Approximately 30,000 new cases are diagnosed each year, and this situation is projected to get worse as the number of people infected with HCV from blood transfusions before 1990 come to be newly diagnosed. This is because the disease can stay asymptomatic for 20 years and more, and HCV was discovered in 1989. Before 1990, there was no screening of blood against HCV, so that millions of patients were likely to have been infected through blood transfusions. These cases are now coming to light.

Historically, the disease is speculated to have been brought into the United States from West Africa at the time of the slave trade [3]. Today, it kills more people than HIV every year in that country. In some countries, the virus affects almost one in every five adults. If untreated, HCV results in generally fatal liver failure. If treated, the treatment is unsuccessful in over half the patients. Like the Human Immunodeficiency Virus (HIV), HCV can stay dormant for years while attacking the liver all this time.

HCV mutates easily which makes for a large number of mutant viruses. There are six known genotypes (numbered 1 through 6) and more than 50 subtypes (e.g., 1a, 1b, 2a...) [4]. The classical treatment consists of combination of drugs called peginterferon and ribavirin. In the beginning, the disease was treated with ribavirin only, with very little success [5]. However, when ribavirin was given in conjunction with peginterferon, a sharp drop in virion was observed after a while.

It has been observed that the effect of ribavirin increases as the amount of drug in the system goes up and reaches a maximum. The optimum dose of ribavirin is weight based. In patients infected with genotype 1, best results have been observed with a dose of 1000/1200 mg/day (1000 mg/day < 75 kg of weight, 1200 mg/day > 75 kg) over a 48-week treatment course, although higher ribavirin doses are considered for patients > 85 kg. [6]. This applies to patients inflicted with HCV genotype 1. For genotype 2 or 3 (or 4 or 5 or 6), the SVR rates (sustained virologic response, which is defined as virus levels below the detection level, 6 months after the treatment was stopped) are much better [6]. Lower doses may also be advisable for patients who cannot tolerate the side effects of the drugs, the main one being hemolytic anemia (loss of red blood cells at a rate faster than their replacement). Peginterferon is administered weekly, while daily injections of ribavirin are recommended.

There are other drugs on the market. One of them, telaprevir, is a protease inhibitor. However, it has been noted that resistance to the drug can be noticed in patients' virus in less than two days of treatment [7], suggesting that, in all probability, the patient was already infected with resistant virus before therapy.

The virus is very short (approximately 9600 nucleotides) and its lifespan outside a host cell is only three to four hours, suggesting that, to maintain equilibrium, it is replicating very fast inside the host cell. According to one source, 10^{12} HCV virions are produced in a patient daily [8]. The copying mechanism is error prone, so that variants are being produced every day. The survival rate of these variants should be proportional to their fitness, so that some drug resistant virus should be present in an infected patient even before the treatment starts.

HIV has received major attention from the medical community in recent years. HCV is just as serious. While it is true that HIV positivity was a death sentence before the discovery of HAART, and is a manageable illness now, HCV is still a death sentence for a large percentage of people that get infected. It has been suggested that, apart from the liver, which is the main target of the virus, HCV may also affect the nervous system [9]. The genotype 1 of HCV is responsible for most of the infections in North America.

We present a mathematical model which describes the development of HCV, and its resistant variants, in a patient. The results presented in this paper should be useful in a pharmacological/therapeutic context.

We assume that, apart from the variants that are already in the patient's blood stream, it requires only one more mutation at a specific neucleotide for an HCV virus to become resistant to the antiviral drug being administered, i.e for u_0 (virus, together with all its variants, present when the treatment starts) to change into u_1, (virus which is resistant to the drug (telaprevir)). We assume that, in the presence of drug pressure, it is easier for u_0 to change to u_1 than the other way around, so that we assume that the probability of u_1 changing to u_0 is much smaller than the probability of u_0 changing to u_1. We also assume that u_0 changes to u_1 after

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one more mutation at a given nucleotide. HCV has approximately 9600 nucleotides, and its copying mechanism is error prone at the rate of 1 in about 10,000. The virus lives for 2-3 hours outside a cell, so that new viruses are being produced inside the infected cells at about the same rate. The probability of its mutating at any **given** site in 8 replication cycles comes out to be 9.37031×10^{-8} ; in 9 replication cycles it comes out to be 1.04109×10^{-7}. We take this probability to be 10^{-7} which is the value of Q_1 in our model. We assume that the probability of u_0 changing to u_1 is Q_1 and that of u_1 changing to u_0 is $Q_2 = Q_1*Q_1$.

In a recent study, SVR rates in genotype 1 patients were highest in the peginterferon alfa-2a plus ribavirin arm, compared with the interferon alfa-2b plus ribavirin arm or the peginterferon alfa-2a alone arm [10].

II. The Model

A. Set Up

We take one day as the unit of time and one mL as the unit of volume and write

$$F_1(x_1,x_2,u_0,u_1) = A_1 - A_2x_1 - (1-e_1)x_1(A_3u_0 + A_6u_1) \quad (1)$$

$$F_2(x_1,x_2,u_0,u_1) = A_4x_1(p_0u_0 + p_1u_1) - A_5x_2 \quad (2)$$

$$F_3(x_1,x_2,u_0,u_1) = A_9A_4(1 - e_1e_2)[(1-Q_1)p_ox_1u_0 + Q_2p_1x_1u_1] - c_1u_0 \quad (3)$$

$$F_4(x_1,x_2,u_0,u_1) = A_9A_4(1-e_1e_2)[Q_1p_0x_1u_0 + (1-Q_1)(1-Q_2)p_1x_1u_1] - c_1u_1] \quad (4)$$

with $x_1' = F_1$, $x_2' = F_2$, $u_0' = F_3$ and $u_1' = F_4$;

In these equations, x_1, x_2, u_0 and u_1 refer to susceptible cells, virus producing infected cells, wild type virions (including all its variants present before the drug is administered), and virions that develop resistance to telaprevir. The quantities e_1 and e_2 account for the effects of peginterferon alpha and ribavirin respectively. It has been reported that ribavirin (RBV) has little effect if it is administered without the peg IFN α (peginterferon α). In our model, e_2 has no effect if $e_1 = 0$. It has also been noticed that "when IFN effectiveness is high, RBV addition has a negligible influence on viral load, whereas when ∂ is low, RBV increases viral-load decay" [11]. In our model, $\partial = e_1$.

Our model meets both these requirements. If e_1 is large with $0 < e_1 < 1$, then the range over which e_2 is effective i.e., $0 < e_2 < 1/e_1$, is small, while if e_1 is small, this range is large.

The susceptible cells x_1 are attacked by the virions u_0 and u_1 at rates of A_3 and A_6 respectively. Because of fitness considerations we take $A_6 < A_3$. Some of these cells (A_4) produce the infectious virions u_0 and u_1 at rates p_0 and p_1 and die at the rate A_5. Since, eventually, most of the virions produced will be of the drug resistant variety, we assume that $p_1 > p_0$. We also assume that $A_4 < A_3$, so that, if we write $A_4 = A_3(1-\beta)$, then β is a measure of the drug (telaprevir) effect.

B. Positivity of the solution

We write $\boldsymbol{x} = \{x_1, x_2, u_0, u_1\}$. Now notice that we can write our equations as $\boldsymbol{x'}=\boldsymbol{F}(\boldsymbol{x})-\boldsymbol{G}(\boldsymbol{x})$ where $\boldsymbol{F}(\boldsymbol{x})$ and $\boldsymbol{G}(\boldsymbol{x})$ are appropriate vector functions. The function $\boldsymbol{F}(\boldsymbol{x})$ stands for all the 'positive' terms and $\boldsymbol{G}(\boldsymbol{x})$ for all the 'negative' ones in (1) to (4), so that $\boldsymbol{G}(\boldsymbol{x})=\{(1- e_1)\, x_1\, (A_3u_0 + A_6u_1),\, A_5\, x_2,\, c_1u_0,\, c_1u_1\}$ and $\boldsymbol{F}(\boldsymbol{x})$ represents all the remaining terms. Now if the 'particle' $\boldsymbol{x}$ starts in the non-negative space ($x_1 \geq 0$, $x_2 \geq 0$, $u_0 \geq 0$, $u_1 \geq 0$), then it cannot go into the negative space because of $\boldsymbol{F}(\boldsymbol{x})$. Also if $\boldsymbol{x}_i = 0$ $\{i = 1,2,3,4\}$, then the corresponding component of $\boldsymbol{G}(\boldsymbol{x})$ is also zero. Considering that $\boldsymbol{F}(\boldsymbol{x})$ and $\boldsymbol{G}(\boldsymbol{x})$ are polynomials, this proves the invariance of the positive space for the solutions of our model.

C. Basic Reproductive Ratio

The basic reproductive ratio of such a dynamic is a measure that indicates whether the disease will grow or die out. If, when *all* the cells are susceptible, i.e. in the beginning when the disease strikes, a virion, attacking a cell, results in the production of more than one virion *during* the attacking virion's lifetime, the disease will prosper. On the other hand, if such a virion attack results in the production of less than one virion during its lifetime, then the disease will die out. This is because, for example, if one virion produces two of them, then these two will produce four and so on. From, $u_1' = F_4$, we see that the virions u_1 are being produced at the rate of $A_9A_4(1-e_1e_2)(1-Q_1)(1-Q_2)p_1x_1$ *per virion*, while the lifetime of the virion is $1/c_1$. The number of susceptible cells, when all the cells are susceptible, is A_1/A_2. It follows that u_1 will multiply if

$$R_2 = \frac{A_1A_4A_9(1-e_1e_2)p_1(1-Q_1)(1-Q_2)}{A_2c_1} > 1$$

However, even before any u_1 virions are produced, u_0 virions are proliferating. From $u_0'=F_3$, they are being produced at the rate of $A_9A_4(1-e_1e_2)(1-Q_1)p_0x_1$ *per virion*, while the lifetime of the virion is $1/c_1$. It follows, that u_0 will multiply if

$$R_1 = \frac{A_1A_4A_9p_0(1-e_1e_2)(1-Q_1)}{A_2c_1} > 1$$

However, in the absence of any treatment, $e_1=e_2=Q_1=0$, so that, in an HCV patient, u_0 will multiply and the disease will become chronic if and only if

$$R_0 = \frac{A_1A_4A_9p_0}{A_2c_1} > 1$$

D. Points of equilibrium

Before the treatment starts, the disease is chronic and, in this state, the number of virions, u_0 now, being produced, is equal to the number that are dying per unit of time. This implies that there should be a point of equilibrium of our dynamic, with $u_1 = 0$. Indeed, there is. We put $u_1= 0$, and solve $F_1=F_2=F_3=0$ for x_1, x_2 and u_0. The result is

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$$\boldsymbol{P}_2 = \{x_1, x_2, u_0, u_1\}$$
$$= \{\frac{c_1}{A_4A_9(-1+e_1e_2)p_0(-1+Q_1)},$$
$$\frac{A_2c_1 - A_1A_4A_9(-1+e_1e_2)p_0(-1+Q_1)}{A_3A_5A_9(-1+e_1)(-1+e_1e_2)(-1+Q_1)}, \quad (5)$$
$$\frac{A_2c_1 - A_1A_4A_9(-1+e_1e_2)p_0(-1+Q_1)}{A_3c_1(-1+e_1)}, 0\}$$

With these values of x_1, x_2, u_0 and u_1, the values of F_1, F_2, F_3 and F_4 turn out to be 0, 0, 0 and a small number proportional to Q_1. It follows that there is an equilibrium point close to this (near) equilibrium point. At the above point $\boldsymbol{P}_2$, we have $F_1 = F_2 = F_3 = F_4 = 0$, correct to six decimal places.

This result says that (near) equilibrium is reached at a stage when the treatment has started but no resistance has developed. The rate of development of resistance, the value of F_4, is zero to six decimal places. In this state $u_0 > 0$ iff

$$R_1 = \frac{A_1}{A_2x_1} = \frac{A_1A_4A_9p_0(1-e_1e_2)(1-Q_1)}{A_2c_1} > 1$$

However, in the absence of any treatment, $e_1 = e_2 = Q_1 = 0$, so that the point becomes

$$\boldsymbol{P}_1 = \{x_1, x_2, u_0, u_1\} = \{\frac{c_1}{A_4A_9p_0},$$
$$\frac{-A_2c_1 + A_1A_4A_9p_0}{A_3A_5A_9}, \frac{-A_2c_1 + A_1A_4A_9p_0}{A_3c_1}, 0\} \quad (6)$$

The condition of chronicity now becomes, $c_1/(A_4A_9p_0) < A_1/A_2$, or

$$R_0 = \frac{A_1A_4A_9p_0}{A_2c_1} > 1$$

This says that the number of x_1 cells at the relevant equilibrium point must be less than A_1/A_2, a condition which is self-evident from (1.1), considering that the chronic condition implies that the patient has virus in the body and the fact that the first "Quadrant" is invariant.

For $R_0 > 1$, this point $\boldsymbol{P}_1$ can be seen to be stable in the dynamic represented by F_1, F_2 and F_3.

It follows that there are four points of 'equilibrium' of our dynamic, first being the healthy state $\boldsymbol{P}_0 = \{x_1, x_2, u_0, u_1\} = \{A_1/A_2, 0, 0, 0]$. The other one is the chronic state, when there is no treatment. There is also a point of equilibrium when the treatment has started but no resistance has developed and the fourth one is when after a long time after the treatment has started, the disease reaches another 'chronic' state.

This latter stage is reached when ALL the virions have become resistant to the antiviral drug. To arrive at this stage in our model, we put $u_0 = 0$, and solve $F_1 = F_2 = F_4 = 0$. The result is

$$\boldsymbol{P}_3 = \{x_1, x_2, u_0, u_1\}$$
$$= \{\frac{-c_1}{A_4A_9(-1+e_1e_2)p_1(-1+Q_1)(-1+Q_2)},$$
$$\frac{-(A_2c_1 + A_1A_4A_9(-1+e_1e_2)p_1(-1+Q_1)(-1+Q_2))}{A_6A_5A_9(-1+e_1)(-1+e_1e_2)(-1+Q_1)(-1+Q_2)}, \quad (7)$$
$$0, \frac{A_2c_1 + A_1A_4A_9(-1+e_1e_2)p_1(-1+Q_1)(-1+Q_2)}{A_6c_1(-1+e_1)}\}$$

With these values of x_1, x_2, u_0, and u_1, the values of F_1, F_2, F_3 and F_4 turn out to be 0, 0, a small number proportional to Q_2 and 0. This implies that there is an equilibrium point close (up to a term of the order of Q_2) to the above (near) equilibrium point. At the above point $\boldsymbol{P}_3$, we have $F_1 = F_2 = F_3 = F_4 = 0$, correct to (more than) six decimal places. It follows that $u_1 > 0$ at $\boldsymbol{P}_3$ iff

$$R_2 = \frac{A_1A_4A_9(1-e_1e_2)p_1(1-Q_1)(1-Q_2)}{A_2c_1} = \frac{A_1}{A_2x_1} > 1$$

This condition may also be interpreted as saying that the number of healthy cells at $\boldsymbol{P}_3$ is less than A_1/A_2.

We notice that $R_2/R_1 = p_1(1-Q_2)/p_0$. It follows that, if this quantity is greater than one, u_1 is proliferating faster than u_0, and in the dynamic represented by (1) - (4), is the dominant virus. Of course, in the dynamic represented by (1) - (3), there is no u_1, so that $R_1 > 1$ should give you a stable point with $u_0 > 0$. As a matter of fact, with the values of the parameters given in the example one below (R_1=1.02375), the equilibrium point $\boldsymbol{P}_2$ with $u_1 = 0$ was seen to be stable in the model represented by equations (1) - (3). Also, it was seen to be unstable in the model represented by the equations (1) - (4). This is because, in the latter model, u_0 is slowly changing to u_1.

Treatment:

There is another point of equilibrium of our dynamic, the one when there is no disease. This one is $\boldsymbol{P}_0 = (A_1/A_2, 0, 0, 0)$. This point is stable when $R_0 < 1$.

The virus in a chronically ill patient before any treatment is started, is in equilibrium at $\boldsymbol{P}_1$ if $R_0 > 1$. After the treatment, the equilbrium value of the virus may approach $\boldsymbol{P}_0$ or $\boldsymbol{P}_3$. If it approaches $\boldsymbol{P}_3$, we have a rebound, while if it approaches $\boldsymbol{P}_0$, we have an SVR. In what follows, we give examples of both the cases.

It should be emphasized that the point $\boldsymbol{x} = \{x_1, x_2, u_0, u_1\}$ starting from $\boldsymbol{P}_1$, the chronic equilibrium state, will approach $\boldsymbol{P}_3$ if and only if (a) the point $\boldsymbol{P}_3$ is stable and (b) the point $\boldsymbol{P}_1$ is in the "basin of attraction" of the point $\boldsymbol{P}_3$. Of course, if $\boldsymbol{P}_3$ is not stable, then there is no basin of attraction. This basin of attraction remains to be determined. Failing that, it will approach $\boldsymbol{P}_0$. It cannot reach $\boldsymbol{P}_2$ because $\boldsymbol{P}_2$ is unstable in the dynamic represented by (1) - (4). We shall give examples of both these situations.

E. Example

. We take, for all cases we consider,

$A_1 = 10$; $A_2 = A_1/1{,}000{,}000$; $A_3 = .00000001$; $A_5 = .005$; $A_6 = .5A_3$; $A_9 = 1000$; $p_0 = 0.9$; $p_1 = 0.99$; $c_1 = 8$; $e_2 = 0.9$; $Q_1 = .0000001$; $Q_2 = Q_1{*}Q_1$.

Now we take $e_1 = 0.1$ and $A_4 = A_3$. With these values of

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the parameters, we find the points of equilibrium *without* the additional restrictions that $u_0 = 0$ or that $u_1 = 0$. We solve $F_1 = F_2 = F_3 = F_4 = 0$ for x_1, x_2, u_0, and u_1. The result is the three points: {(1.00000*10^6, 0, 0, 0), (976801, 46.3978, 26.3888, 0), (888001, 492.796, 0, 280.278)}.

We also find the equilibrium points *with* the conditions that $u_0 = 0$ for one and $u_1 = 0$ for the other. We have already obtained these solutions. These are provided in (7) and (5) and come to $\{x_1, x_2, u_0, u_1\} = \{888001, 492.796, 0, 280.278\}$ and $\{x_1, x_2, u_0, u_1\} = \{976801, 46.3979, 26.3888, 0\}$, respectively.

Notice the two solutions, one with $u_0 = 0$ and the other one with $u_1 = 0$. These are also the solutions obtained without any such restrictions. We shall not do a similar exercise again. However, we wish to emphasize that in every case that we have presented, this situation is true.

The approach of the equilibrium point, from $\boldsymbol{P}_1$ to either $\boldsymbol{P}_0$ or to $\boldsymbol{P}_3$ is strongly affected by the values of e_1 and e_2 which are the parameters of the treatment, and even more so by the value of A_4.

Case one

We take $e_1 = 0.1$ and $A_4 = A_3$. Solving our model ($x_1' = F_1$, ...) numerically (using *Mathematica* 8.0), we get, at time s = 900,000, $\{x_1, x_2, u_0, u_1\} = \{888017, 480.305, 3.06189\times10^{-11}, 278.353\}$. It is clear that the solution is (slowly) going to $\boldsymbol{P}_3$.

The solution is shown in Figs. 1 and 2. Notice the three distinct phases in Figs. 1 and 2. The latter figure says that we have a rebound in this case. Similar profiles have been observed in actual patients [11]. We have reported the results in Log_{10} form because this is how they are reported in the literature,

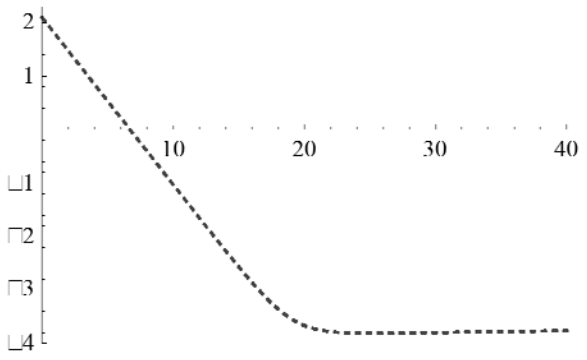

Fig. 1. Plot of $\text{Log}_{10}[u_0(s) + u_1(s)]$, $0 \le s \le 40$ (Case one)

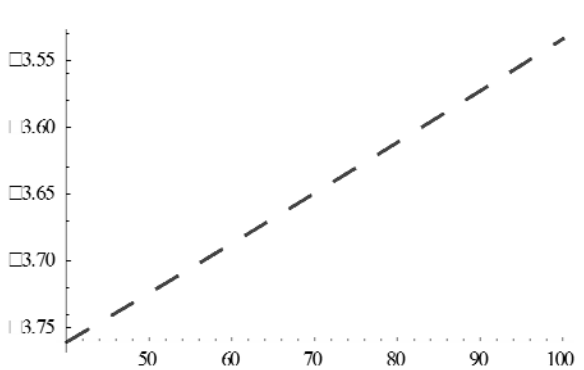

Fig. 2. Plot of $\text{Log}_{10}[u_0(s) + u_1(s)]$, $40 \le s \le 100$ (Case one). The solution shows rebound for e_1=0.1, e_2 = 0.9, $A_4 = A_3$.

Case two

We now solve the same case as above, but with a slightly smaller value of A_4. We take $e_1 = 0.11$ and $A_4 = 0.9A_3$. The numerical solution at time s = 900,000 gives $\{x_1, x_2, u_0, u_1\} = \{999986, 1.5771*10^{-104}, 0, 0\}$ and it is clear that the solution is going to $\boldsymbol{P}_0$, indicating SVR. It should be noted that if the number $u_0 + u_1$ is less than one, then the patient has been cured.

The relevant solution is shown in Figs. 3 and 4. The latter figure says that, because of the protease inhiitor, the solution that was going to a rebound is now going to SVR.

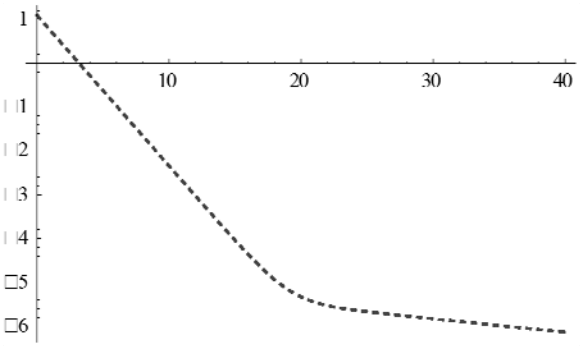

Fig. 3. Plot of $\text{Log}_{10}[u_0(s) + u_1(s)]$, $0 \le s \le 40$ (Case two)

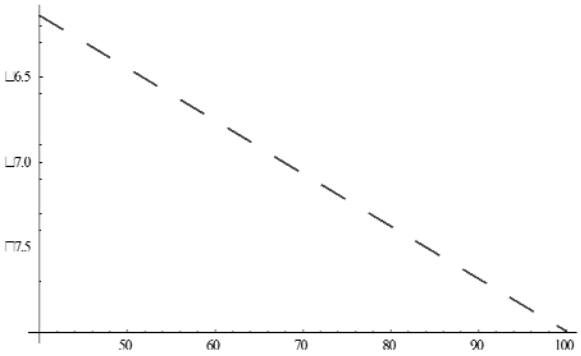

Fig. 4. Plot of $\text{Log}_{10}[u_0(s) + u_1(s)]$, $40 \le s \le 100$ (Case two). The solution shows SVR for e_1=0.11, e_2 = 0.9, $A_4 = 0.9A_3$. Values of other parameters are given in the text.

III. Comments

We have developed an HCV model. The model correctly says that there are two possible outcomes of treatment of a chronically sick patient, either a rebound or SVR. It also points out the conditions under which each outcome will occur. It says that a rebound will occur if the "chronicity point" of the patient is in the basin of attraction of $\boldsymbol{P}_3$, the equilibrium "rebound point" in our model. Treatment changes the location of the rebound point in our model and the rebound occurs if the drugs are not strong enough. However, even with a rather mild dose of a protease inhibitor, such a rebound may change to SVR. It should be noted that the behaviour of the virus in each case is triphasic. Such triphasic behaviour has been noted by other researchers [12].

We need to point out that this is a work in progress. We need to more accurately assess the values of the various parameters in the model and also to delineate the basin of attraction of $\boldsymbol{P}_3$, the ultimate destination of the virus point in the case of rebound.

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