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Research Article

Forecasting & Sensitivity Analysis of the Decay of Viral Load in HCV Infection during Treatment by using Mathematical Tools and Simulation

Dhirendra Kumar Shukla[†*], Arvind Gupta[‡] and Anil Goyal[§]

[†]Department of Basic Sciences, Corporate Institute of Science and Technology, Bhopal (M.P.), India
[‡]Department of Mathematics, Govt. Motilal Vigyan Mahavidyalaya, Bhopal (M.P.), India
[§]Department of Applied Sciences, UIT-Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal (M.P.), India

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Abstract
The present paper gives a brief description of study of decay of viral load in HCV infection during treatment of patients through various mathematical tools. In the study clinical data of few patients have been taken. The basic model of HCV infection adapted by Neumann et al has been taken in to account and explained to understand the decay or flow of viral load. For eight consecutive weeks data of viral load has been taken which is based on clinical data. Then, by using RStudio simulation (R-language) viral load is forecasted further for six more weeks. The forecasted viral load totally resembles with viral load through clinical data established by using Origin Lab. The sensitivity analysis of study of viral load of HCV during treatment for fourteen weeks shows specific pattern which will help in the treatment of Hepatitis C infected patients. In this study immunity of a human body is excluded.

Keywords: *Mathematical model, Graphical presentation (MATLAB), Simulation (RStudio), Forecasting of decay of viral load, Sensitivity analysis (Origin Lab), Clinical data (Data extracted from required references).*

1. Introduction

Hepatitis C infection is one of the most important clinical and public health problems all over the world. HCV stands for Hepatitis C Virus and cause inflammation of liver (Angel Luis Ballesteros, 2005). It occurs due to toxins, viruses, fatty liver diseases, excessive consumption of alcohol in the body, autoimmune diseases and imbalances in chemical substances etc. Hepatitis C affects the liver and caused by a virus that may or may not be curable. If it has not been diagnosed timely then it may cause lifelong infection. In severe case it may leads to cirrhosis and moderate scarring which can turn in to liver cancer, liver failure and death (EASL, 2014). According to Centres for chronic hepatitis C virus associated with elevated liver enzymes, 20% of patients exposed to hepatitis C do not develop chronic infection. Some studies suggest that the development of jaundice during acute infection is associated with spontaneous clearance. Even in those with chronic infection, only 20% develop cirrhosis and its complications usually over a 10 to 20 year time frame. Various epidemiologic risk factors may influence the risk and rate of progression including age at acquisition, male sex, alcohol exposure, genetic factors, and other comorbidities. HCV was first characterized in 1989. The exact mechanism of viral entry into liver cells is not known, but it is associated with several viral and cellular factors including tetraspanin CD81, human scavenger receptor SR-BI, and tight junction molecules Claudin-1 and occluding (http://www .clevelandclinicmeded.com/medicalpubsdieasemanage ment/hepatology/hepatitis-C/).

2. Clinical view

The wide range of diseases in the context of hepatitis C underlines the multifactorial and poly genes nature of HCV infection. Both the viral and host factors contribute to fluctuations in the infection, disease susceptibility and progression and response to treatment (Angel Luis Ballesteros, 2005). This Protocol is the emphasis on the immuno genetics of HCV infection. During the chronic HCV infection, the level of serum HCV RNA does not significantly vary (<0.5 log) on time scales ranging from weeks to months (T. T. Nguyen, 1996). However, when patients chronically infected with HCV are treated with interferon-alpha (IFN) or IFN plus ribavirin, HCV RNA usually decreases after 7 - 10 hours late. The typical decline is biphasic and is comprised of a rapid initial phase lasting for about 1 - 2 days during the HCV RNA, in average cases it can be 1 to 2 protocols in the genotype 1 infected patients and as much as 3 to 4 protocols in the genotype 2 infected patients (A. U. Neumann *et al.*

*Corresponding author: **Dhirendra Kumar Shukla**

1998, 2000). The first phase is followed by a slower second phase of HCV RNA decline. Tri-phasic viral decrease has also been observed in some patients. A tri-phasic decline consists of a first phase (1 - 2 days) with rapid decline of viral load, followed by a shoulder Phase (4 - 28 days), where virus load decays slowly or remains constant and a third phase of re-viral disintegration. In non-responder, there may be no viral decline (zero reaction) or a first phase was not followed by a second phase of decline (partial response), or recoil to baseline levels (C. C. Bergmann *et al*. 2001, E. Herrmann, 2003 & T. L. Kieffer, 2007).

3. Viral load kinetics during treatment

HCV Dynamics assess the ability of the infected host to respond to an antiviral therapy. In patients with chronic HCV infection, several studies have shown the clinical relevance of the initial viral dynamics in the prediction of SVR. The most useful information in the clinical practice comes from the negative predictive value (NPV) of lack of early virological response (EVR) i.e. HCV RNA below the limit of detection or a decrease of $\geq 2\log_{10}$ from baseline at week 12. HCV infected patients without EVR after 12 weeks of HCV therapy has only a 3% chance of SVR (G. L. Davis, 2002, & N. P. Lam, 1997). Untreated HCV infected patients have a dynamic balance where virion production is balanced with viral excretion (sales of 10^{12} virions/day). The justification for the induction strategies is based on the combination of early viral kinetics during the first few weeks with the likelihood of achieving SVR. The highest rate of end of treatment response (ETR) (64%) with a neat SVR (62%) in the HCV genotype 3 is reported that supports extending HCV therapy from 24 to 48 weeks in HCV infected patients although the correct duration of HCV therapy in these patients must be confirmed in large, well-designed, randomised clinical trials (F. J. Torriani, 2004).

4. Treatment for HCV

According to the study, patients with acute hepatitis C virus (HCV) infection seem to have an excellent chance of response to 6 months of standard therapy with Interferon (IFN). For spontaneous resolution is common, no final adjustment of the initiation of therapy can be recommended; however, waiting for 2-4 months after the outbreak of the disease seems appropriate. Treatment for chronic HCV is based on the guidelines of the Infectious Disease Society of America (IDSA) and the American associations for the study of liver diseases (AASLD), in collaboration with the international antiviral society-USA (IAS-USA) (http://emedicine.medscape.com/article/177792-treatment).

The most common treatment for the chronic Hepatitis C is a combination of the antiviral drug Ribavirin (RBV) and interferon (IFN). The aim of the treatment with these drugs is to free the patient`s body from the virus. These drugs can slow down and in some cases stop the virus attack on the liver. The doctor or a liver specialist monitors the treatment to determine its effectiveness. As it is known, currently, there is no vaccine for the protection of hepatitis C. A turning point came in the history of the treatment of the disease with the invention of Interferon in 1990s. The drug enhances the immune system and body's own defence forces against germs to help it against hepatitis C virus. The use of Ribavirin with Interferon fights against the virus and helps in the treatment of HCV. Due to this combination the cure rate jumped from less than 5 % in the 1980s to over 50% of the early 2000s. But Interferon and Ribavirin can have adverse effects also like myalgia, fever, nausea, anxiety and sleep disorders. It may take up to 48 weeks to see the results. 92% to 99% cure rates were reported, depending on the history of the patient with hepatitis C infection (Angel Luis Ballesteros, 2005 & http://emedicine.medscape.com /article /177792-treatment).

5. Virological response

Virological responses of therapy with PegIFN/RBV treatment duration can be tailored to the treatment of virological response. For the treatment of HCV RNA levels should be assessed at three points in time, regardless of the HCV genotype: Baseline and Weeks 4 and 12. The probability of the SVR is directly proportional to the speed of the HCV RNA disappearance. The treatment should be discontinued if in week 12 HCV RNA decline is less than $2\log_{10}$ IU/ml. In the table there is a classification of virological response (EASL, 2014).

Type I: When drug combination is PegIFN/RBV (EASL, 2014), then,

- **Rapid Virological Response (RVR):** Undetectable HCV RNA in a sensitive assay at week 4 of therapy.
- **Early Virological Response (EVR):** HCV RNA detectable at week 4 but undetectable at week 12, maintained up to end of treatment.
- **Delayed Virological Response (DVR):** More than $2\log_{10}$ IU/ml decrease from baseline but detectable HCV RNA at week 12, then undetectable at 24 week and maintained up to end of treatment.
- **Null Response (NR):** Less than $2\log_{10}$ IU/ml decrease in HCV RNA level from baseline at 12 week of therapy.
- **Partial Response (PR):** More than $2\log_{10}$ IU/ml decrease in HCV RNA level from baseline at 12 week of therapy but HCV RNA detectable at 24 week.
- **Break Through (BT):** Reappearance of HCV RNA at any time during treatment after a negative result or increase of $1\log_{10}$ IU/ml.

Type II: When drug combination is PegIFN/RBV + TVR (EASL, 2014), then,

- **Extended Rapid Virological Response (eRVR):** Undetectable HCV RNA in a sensitive assay at week 4 and 12 of therapy.
- **Early Response (ER):** Undetectable HCV RNA in a sensitive assay at week 8 of therapy (after 4 week of BOC).

Type III: When drug combination is PegIFN/RBV + BOC (EASL, 2014), then,

- **Late Response (LR):** Detectable HCV RNA in a sensitive assay at week 8 of therapy, but negative at week 12 (after 8 week of BOC).

6. Mathematical model

A model of HCV infection and the treatment of A. U. Neumann *et al*., 1998, have proved extremely useful in the analysis of HCV RNA decay in drug therapy. Required symbols are mentioned in the table (6.1).

Table 6.1: Symbols with their meanings used in mathematical model

S. No.	Symbols	Particulars
1	T	Target cell
2	I	Infected cell
3	V	Viral particles (virions)
4	s	Constant rate of production of target cell
5	p	Rate of production of viral particles
6	c	Rate of clearance of virions
7	d_T	Death rate of cell
8	β	Constant rate of production of infected cell
9	δ	Rate of loss of infected cell
10	ε	Effectiveness of treatment for partially blocking virion production
11	η	Effectiveness of treatment for reducing the rate of infection

Where ε and η are lying between 0 and 1, 1 assumed as 100% effectiveness of therapy or treatment

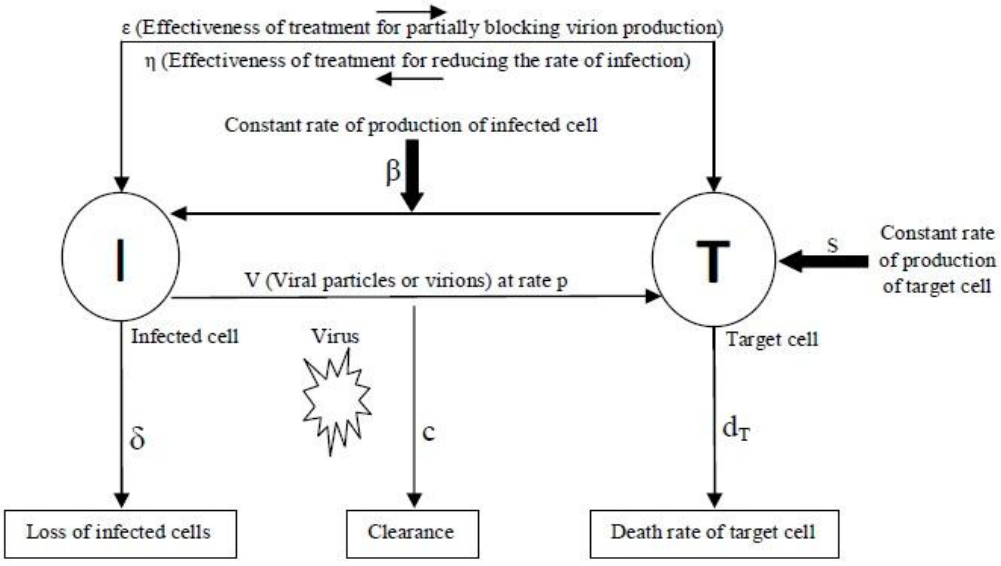


Fig 6.1: Schematic representation of the basic viral dynamic model.

Here Figure (6.1) mentioned to understand the model (A. U. Neumann, 1998). Basic model of viral dynamics given in Figure (6.1) (Libin Rong and Alan S. Perelson, 2010).

According to A. U. Neumann *et al*., 1998, equations that describe the basic model of viral dynamics shown in system (6.1).

$$\left.\begin{aligned} \frac{dT}{dt} &= s - d_T T - (1-\eta)\beta VT \\ \frac{dI}{dt} &= (1-\eta)\beta VT - \delta I \\ \frac{dV}{dt} &= (1-\varepsilon)\, pI - cV \end{aligned}\right\} \quad (6.1)$$

Initial studies show that there is a dose-dependent reduction of HCV RNA levels in the first 24-48 hours, followed by a slower second phase of decline in the number of patients with different doses of IFN-α2B (A. U. Neumann, 1998 & N. P. Lam, 1997). To explain this, predicted that IFN must be with the ability of the infected cells to produce or release virus, and this has recently confirmed in different cell-culture (K. J. Blight, 2000). In addition, it is proposed that if there is only the first stage and assumes that on this time scale the aim and the infected cell remains close to its level before the therapy, then predicts that the initial viral load V_0 or after treatment viral load $V(t)$ is according to the following equation:

$$V(t) = V_0\left[1-\varepsilon+\varepsilon e^{-c(t-t_0)}\right] \quad (6.2)$$

Equation (6.2) is time dependent. Two cases can be seen such as $t = t_0$ and $t = \infty$. Here $\varepsilon = 1$ and $\eta = 1$ (Being a perfect drug).

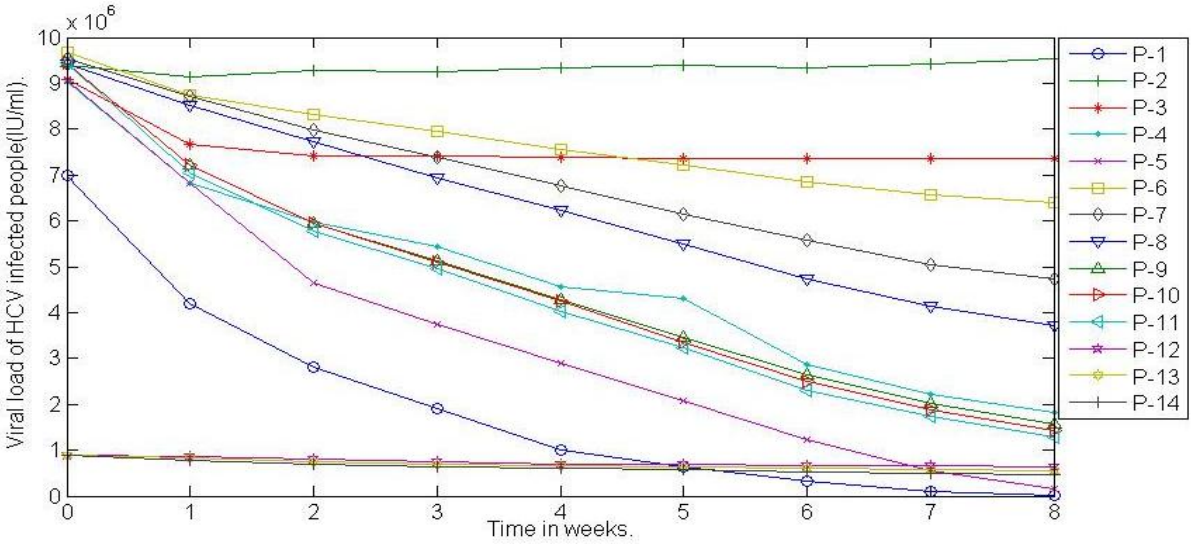
Case I: When in eq(6.2) put $t = t_0$ the initial viral load is $V(t_0) = V_0$. Here $t = t_0$ stands for that patient have not been given any kind of treatment or therapy.

Case II: When in eq(6.2) put $t = t_\infty$ the viral load becomes $V(\infty) = V_0[1-\varepsilon] = 0$. Here $t = t_\infty$ stands for that how long treatment has been given to the patient because in case of HCV infection there is no any specified time duration of the treatment or therapy.

At present, there is no specific medicine to cure HCV infected people. For convenience and to establish the result, the effectiveness of treatment or therapy is assumed as $\varepsilon = 1$ and $\eta = 1$ (Being a perfect drug). If $\varepsilon = 1$ then it means, after the treatment viral load became zero but practically it contradicts our hypothesis because viral load can never be made zero but it could be in the range of undetectable, so if there will be a medicine whose effectiveness tends to 1 then the viral load during or after the treatment will go down and it will be under the range or below the range (undetectable) (Harel Dahari *et al*., 2008).

Table 7.1: Viral load decay of HCV infected persons during treatment of eight weeks.

Viral load decay during treatment of HCV infection														
Weeks	**P-1**	**P-2**	**P-3**	**P-4**	**P-5**	**P-6**	**P-7**	**P-8**	**P-9**	**P-10**	**P-11**	**P-12**	**P-13**	**P-14**
0	6991348	9407539	9080421	9038700	9052870	9684492	9529870	9427589	9445313	9445313	9445313	900032	898589	889096
1	4208967	9129349	7671730	6831084	6832873	8746973	8707124	8510026	7219832	7219832	7056417	858914	836434	786331
2	2814622	9277075	7404760	5975346	4641417	8312031	7978656	7730537	5953533	5953533	5777459	799026	759159	695001
3	1919756	9243088	7406260	5428708	3755708	7960381	7375791	6937426	5130024	5095492	4956075	737014	695006	638873
4	1014409	9347072	7386371	4571725	2886270	7569602	6769930	6222695	4292758	4238863	4037743	695641	653226	606631
5	648327	9389376	7369299	4295555	2086281	7222610	6139667	5481962	3447215	3345715	3230327	679202	629780	571071
6	337570	9323570	7365936	2865996	1225493	6861222	5567289	4730444	2633655	2497958	2307671	662061	606507	533663
7	94579	9424667	7363608	2207578	563596	6568031	5056252	4124511	2011796	1869238	1749171	653443	585476	501053
8	26770	9531485	7365060	1819190	152350	6387109	4721985	3702567	1559409	1415949	1276593	640552	552790	465385

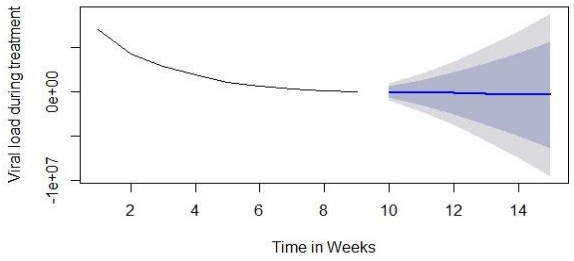


Graph 7.1: Graphical presentation of viral load decay during treatment of HCV infection.

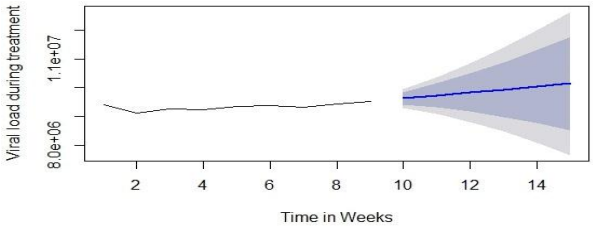
7. Implementation of mathematical tools on data of clinical data

To understand the status of viral load decay during treatment, data of few patients (Angel Luis Ballesteros, 2005, EASL, 2014, Harel Dahari *et al*., 2008) has been used and the forecasting or result has been established by using a mathematical tool (MATLAB) and simulation (RStudio).

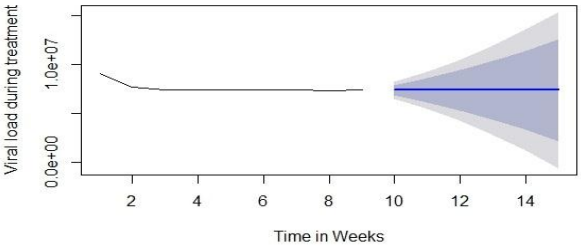
Graph (7.1) is a graphical presentation of viral load decay during treatment of HCV infection. This graph is based on data given in table (7.1). Table (7.1) contains viral load decay of any HCV infected person during treatment of eight weeks. Now to interpret the forecasting for the decay of viral load RStudio (A kind of simulation) has been used. By this simulator the study tried to find out the future status of the decay of viral load. Given table (7.1) describe viral load during eight weeks and for convenience and to explain the process, further, six viral loads are explained i.e. up to fourteen weeks in the output of individuals.



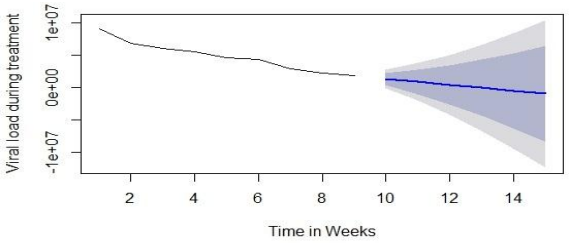
Graph 7.2: Forecasting of viral load decay for P-1



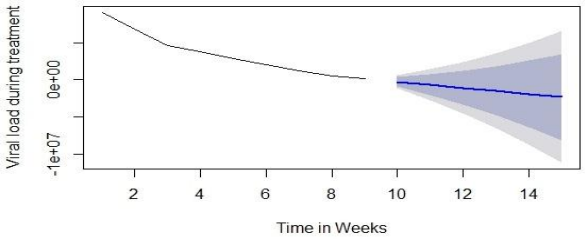
Graph 7.3: Forecasting of viral load decay for P-2



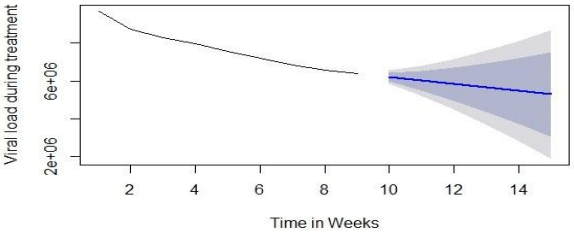
Graph 7.4: Forecasting of viral load decay for P-3



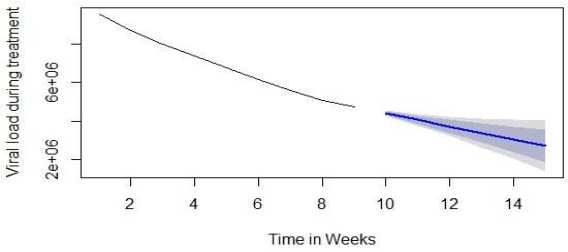
Graph 7.5: Forecasting of viral load decay for P-4



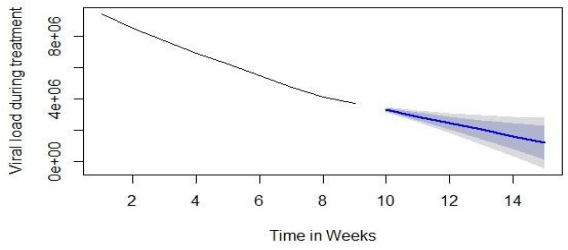
Graph 7.6: Forecasting of viral load decay for P-5



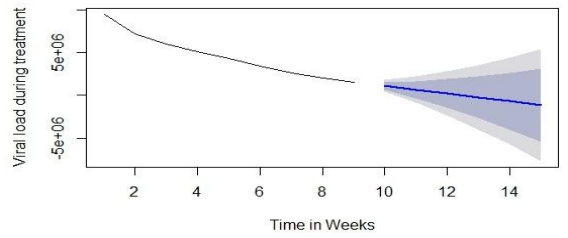
Graph 7.7: Forecasting of viral load decay for P-6.



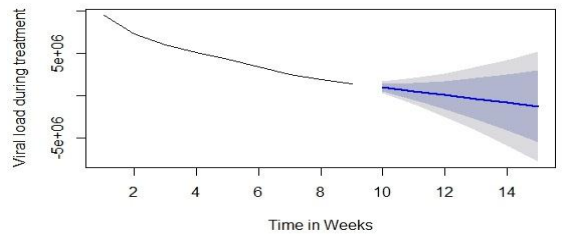
Graph 7.8: Forecasting of viral load decay for P-7



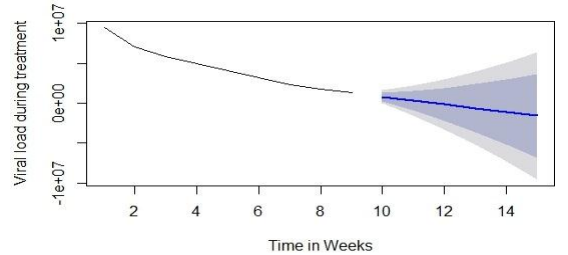
Graph 7.9: Forecasting of viral load decay for P-8



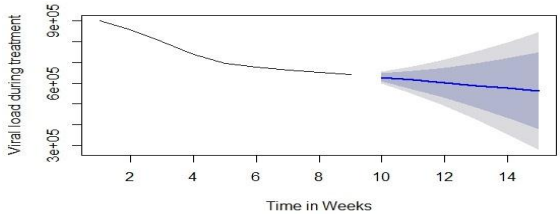
Graph 7.10: Forecasting of viral load decay for P-9



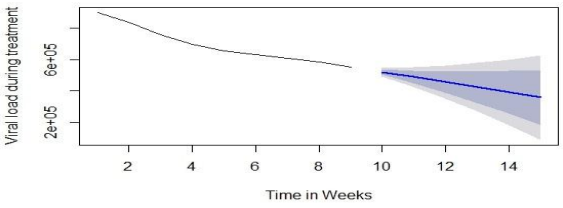
Graph 7.11: Forecasting of viral load decay for P-10



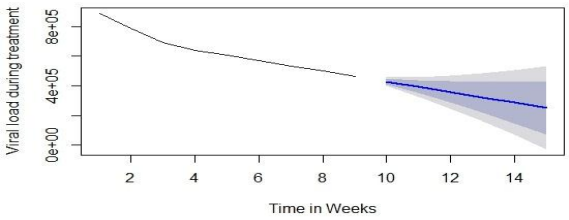
Graph 7.12: Forecasting of viral load decay for P-11



Graph 7.13: Forecasting of viral load decay for P-12

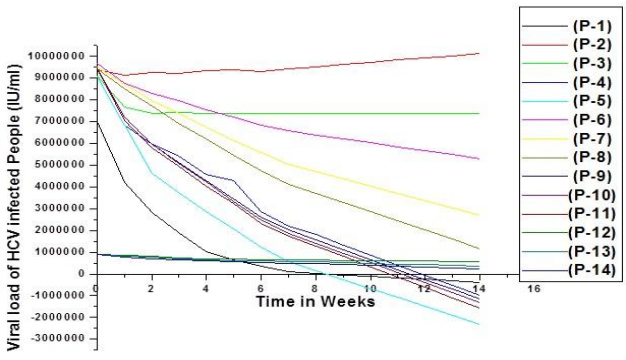


Graph 7.14: Forecasting of viral load decay for P-13



Graph 7.15: Forecasting of viral load decay for P-14

It is important to know that table (7.1) contains viral load on the basis of clinical data and graph (7.1) explains status of decay of viral load from 1st day of treatment to 8th week by using table (7.1). After that to forecast possible decay of viral RStudio simulation has been used for each and every patient and it gives next six values i.e. values from 9th week to 14th week. The forecasted values obtained from simulation are mentioned in table (7.2).



Graph 7.16: Sensitivity analysis of viral load decay during treatment of HCV infection

Table 7.2: Forecasting of viral load decay during treatment of HCV infection using RStudio simulation.

Viral load decay during treatment of HCV infection														
Weeks	**P-1**	**P-2**	**P-3**	**P-4**	**P-5**	**P-6**	**P-7**	**P-8**	**P-9**	**P-10**	**P-11**	**P-12**	**P-13**	**P-14**
9	-41039	9623699	7366512	1327143	-258896	6206187	4387718	3280623	1107022	962660	804015	627661	520104	429717
10	-108848	9727423	7367964	865675	-670142	6025265	4053451	2858679	654635	509371	331437	614770	487418	394049
11	-176657	9831146	7369416	404208	-1081388	5844343	3719184	2436735	202248	56082	-141141	601879	454732	358381
12	-244466	9934870	7370868	-57260	-1492634	5663421	3384917	2014791	-250139	-397207	-613719	588988	422046	322713
13	-312275	10038593	7372320	-518727	-1903880	5482499	3050650	1592847	-702526	-850496	-1086297	576097	389360	287045
14	-380084	10142316	7373772	-980194	-2315126	5301577	2716383	1170903	-1154913	-1303785	-1558875	563206	356674	251377

Graph (7.16) shows sensitivity between clinical data and forecasted data of viral load through OriginLab.

Conclusion

To conclude, on the basis of basic model of HCV infection adapted by Neumann *et al*, the decay of viral load is examined during the treatment and accordingly the drug combination is administered to the patients. Efficiency of drug varies from person to person.

The study shows that when clinical data is simulated to forecast viral load for six more weeks, there exists connectivity between clinical data and forecasted data. Then, following three types of cases arise,

1) Case- I: No further treatment is required*
2) Case- II: Further treatment is required*
3) Case- III: Nothing can be done*

The above mentioned cases are detected for sensitivity analysis of decay of viral load in HCV infection by using OriginLab.

It can be seen that patients P-1, P-4, P-5, P-9, P-10 and P-11 fall under case- I, where no further treatment is required as the disease is cured or virus is not detected. However the recovery duration varies from patient to patient for e.g. P-1 recovers in 8^{th} week, P-4 in between 11^{th} -12^{th} week, P-5 in between 8^{th} -9^{th} week, P-9 in between 11^{th} -12^{th} week, P-10 in 11^{th} week.

In case- II, patients P-6, P-7, P-8, P-12, P-13 and P-14 need more treatment and time for convalescence.

In case- III, it can be seen that in patient P-2 the viral load is gradually increasing and in P-3 the situation is almost constant which means they are inclining towards severe stage of Hepatitis C disease.

*: The entire conclusion is based on the study.

Future scope

The study of Forecasting & Sensitivity Analysis of the Decay of Viral Load in HCV Infection during Treatment by using Mathematical Tools and Simulation has many fold outcomes. It is expected to help the research scholars working in the field of Bio-medical and Bio-mathematical sciences to understand and predict the phenomenon of disease and also to develop more effective models or tools which will help in the treatment control and prevention of the disease.

References

A. U. Neumann, N. P. Lam, H. Dahari *et al*. (1998), Hepatitis C Viral Dynamics in Vivo and the Antiviral Efficacy of Interferon-Alpha Therapy. Science, Vol. 282, pp. 103-107.

A. U. Neumann, N. P. Lam, H. Dahari, *et al*. (2000), Differences in Viral Dynamics Between Genotypes 1 and 2 of Hepatitis C Virus, J Infect Dis. Vol. 182, pp. 28-35.

Angel Luis Ballesteros, Daniel Fuster, Ramon Planas, Bonaventura Clotet and Cristina Tural (2005), Role of Viral Kinetics under HCV Therapy in HIV/HCV-Coinfected

Patients, Journal of Antimicrobial Chemotherapy, Vol. 55, pp. 824–827.

C. C. Bergmann, J. E. Layden, R. S. Levy Drummer, *et al*. (2001), Clinical Implications of a New Triphasic Model for Hepatitis C Viral Kinetics During Ifnalpha Therapy, Hepatology, Vol. 34.

E. Herrmann, J. H. Lee, G. Marinos, *et al*. (2003) Effect of Ribavirin on Hepatitis C Viral Kinetics in Patients Treated with Pegylated Interferon, Hepatology, Vol. 37, pp. 1351-1358.

European Association for the Study of the Liver (2014), EASL Clinical Practice Guidelines: Management of Hepatitis C Virus Infection Journal of Hepatology, Vol. 60, pp. 392–420.

F. J. Torriani, M. Rodriguez-Torres, J. K. Rockstroh *et al*. (2004),Peginterferon Alfa-2a Plus Ribavirin for Chronic Hepatitis C Virus Infection in HIV Patients, New Engl J Med, Vol. 351, pp. 438-450.

G. L. Davis (2002), Monitoring of Viral Levels during Therapy of Hepatitis C, Hepatology, Vol. 36, pp. 145-151

Harel Dahari, Jennifer E. LaydenAlmer, Alan S. Perelson and Thomas J. Layden (2008), Hepatitis C Viral Kinetics in Special Populations, Current Hepatitis Reports, Vol. 7, Issue 3, pp. 97-105.

http://emedicine.medscape.com/article/177792-treatment

http://www.clevelandclinicmeded.com/medicalpubsdiease management/hepatology/hepatitis-C/

K. J. Blight, A. A. Kolykhalov and C. M. Rice (2000), Efficient Initiation of HCV RNA Replication in Cell Culture, Science, Vol. 290, pp. 1972-1974.

Libin Rong and Alan S. Perelson (2010), Treatment of Hepatitis C Virus Infection with Interferon and Small Molecule Direct Antivirals: Viral Kinetics and Modeling, Crit Rev Immunol, Vol. 30, Issue 2, pp. 131-148.

M. Fried, M. Shiffman, K. R. Reddy, C. Smith *et al*. (2002), Peg-interferon Alfa-2a Plus Ribavirin for Chronic Hepatitis C Virus Infection, New Engl J Med, Vol. 347, pp. 975-982.

N. P. Lam, A. U. Neumann, D. R. Gretch *et al*. (1997), Dose Dependent Acute Clearance of Hepatitis C Genotype 1 Virus with Interferon Alfa, Hepatology, Vol. 26, pp. 226-231.

T. L. Kieffer, C. Sarrazin, J. S. Miller *et al*. (2007), Telaprevir and Pgylated Interferon-Alpha-2a Inhibit Wild Type and Resistant Genotype 1 Hepatitis C Virus Replication in Patients, Hepatology, Vol. 46, pp. 631-639.

T. T. Nguyen, A. Sedghi-Vaziri, L. B. Wilkes *et al.* (1996), Fluctuations in Viral Load (HCV RNA) are Relatively Insignificant in Untreated Patients with Chronic HCV Infection, J Viral Hepat, Vol. 3, pp. 75-78.