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

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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 adopted 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 into liver cancer, liver failure and death (EASL, 2014). According to Centers 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 CDB1, human scavenger receptor SR-BI, and tight junction molecules Claudin-1 and occluding (http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/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.)
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 ≥2log₁₀ 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 10² 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 2log₁₀ 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 2log₁₀ 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 2log₁₀ IU/ml decrease in HCV RNA level from baseline at 12 week of therapy.
- **Partial Response (PR):** More than 2log₁₀ 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 1log₁₀ 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


### Table 6.1: Symbols with their meanings used in mathematical model

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

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.](image)

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).

\[
\begin{align*}
\frac{dT}{dt} &= s - d_T T - (1 - \eta) \beta VT \\
\frac{dI}{dt} &= (1 - \eta) \beta VT - \delta I \\
\frac{dV}{dt} &= (1 - \varepsilon) pI - cV
\end{align*}
\]  

(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 one infected cell being located 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:

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

(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>
<thead>
<tr>
<th>Table 7.1: Viral load decay of HCV infected persons during treatment of eight weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weeks</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
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<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>
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

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

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

<table>
<thead>
<tr>
<th>Weeks</th>
<th>P-1</th>
<th>P-2</th>
<th>P-3</th>
<th>P-4</th>
<th>P-5</th>
<th>P-6</th>
<th>P-7</th>
<th>P-8</th>
<th>P-9</th>
<th>P-10</th>
<th>P-11</th>
<th>P-12</th>
<th>P-13</th>
<th>P-14</th>
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<tr>
<td>9</td>
<td>-41939</td>
<td>-108848</td>
<td>-176657</td>
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<td>-312275</td>
<td>-380084</td>
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<td>-1195052</td>
<td>-1264274</td>
<td>-1333496</td>
</tr>
</tbody>
</table>

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 8th week, P-4 in between 11th -12th week, P-5 in between 8th - 9th week, P-9 in between 11th - 12th week, P-10 in 11th 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.

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