Prognosis and Diagnosis in Hepatitis C using Expert Systems and Statistical Analyses

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Abstract: This paper analyses a large database with hepatitis C virus infected patients. There are made a lot of statistical analyses on the records of this database in order to determine the evolution of biological parameters during the treatment. That's for what it was also implemented an expert system which offered predictions about the same parameters, using artificial neural networks. The results of the statistical analyses and the expert siysystem predictions indicate the same conclusions.It encourages the use of such a system to facilitate the physician work.

Keywords: hepatitis C virus infection, statistical analysis, artificial neural networks

1 Introduction

Hepatitis C is a serious and frequent disease and its evolution has to be carefully overseen during the treatment. Even the efficency of the hepatitis C treatment inproves continously, the burden of this infection will remain a major issue for the next several decades.

The patients have been kept under observation for 12 months to establish the treatment's influence on the evolution of the biological indicators. Three different treatment schemes have been instituted:

- Simple Interferon (IFN);

- Peg interferon α-2a;

- Peg interferon α-2b.

The biological parameters were determined every three months and their evolution in time was monitored, trying to establish the relations between the biological indicators values (*TGP, TGO, GGT, ARN VHC*) and time, on patient groups sampled on their answer to the treatment. There are six types of reactions to the treatment considered as *answer-code*: 0-responder, 1-no responder to IFN, 2-no responder to Peg IFN, 3-backslide in treatment with IFN, 4-backslide in treatment with Peg IFN, 5-recess any treatment.

The correlations *biological indicators – time – code of reaction* have been 3D represented as functions of *z=f(x,y)* type. The obtained results are presented in chapter 2.

On the other hand, the article presents (in chapter 3) an artificial neural network trained to predict the evolution of the biological indicators. By introducing the patients personal data, as well as the results of biological tests at the treatment start and the presumed code of reaction, the expert system can indicate the evolution in time of the illness. The use of the neural network presents the same conclusions as the statistical analysis.

2 Statistical Analysis

The investigated population contained 193 patients registered at the Emergency Clinical Hospital in Timisoara, Gastroenterology Department between 2003 and 2005 (120 women and 73 men aged between 14 and 67 years in old).

The study of the 3D correlations was made for the main biological indicators. For data processing the *TableCurve 3D* software was used. It can make the nonparametric interpolation of some 3D data multitudes by using the homogeneous grid method. Different calculating algorithms have been used (Akima [1], [2], [3], Bicubic [2], B-Spline [4], Preusser [6, 7], Renka [8], [9], [10], [11] and Watson [12]) and it has been observed that the Watson algorithm gave the biggest values of the correlation coefficient R^2. Therefore all the 3D representations and regressions established for the *z=f(x,y)* functions was represented by using this algorithm.

Even the information in the database is incomplete (there are patients which didn't follow the treatment for 12 months or were not periodically showed up for analyses) the indicated processing method can overpass it. Based on Watson algorithm the missing data have been calculated by extrapolation [12].

2.1 The TGP Biological Indicator Analysis

The *TGP=f(time, answer-code)* indicator analysis, as a answer- to the *IFN* treatment (Figure 1.a), shows, for answer-code 0 patients, an emphasized decrease of the *TGP* indicator in the first three months of treatment from the initial value $TGP\_0=2.190$ to the value $TGP\_3=1.109$, followed by a milder decrease until the end of investigation where $TGP\_12=1$. For the other answer-codes, the representation shows some differencies. For example, the maximum value of the *TGP* indicator $TGP\_0=3.525$ for answer-code 4 and a smaller value $TGP\_0=2.590$ for answer-code 2. The represented surface allows the predicted evolution of all the answer-codes to be followed. The missing values can be obtained from the graphic representation. Therefore, for answer-code 5 for example, where there were values only for the initial phase and for the 3 month period, it can be observed that the representation gives calculated information even for the following months. For the 6 months phase the *IFN* treatment leads to a value $TGP\_6=1.5$, then it rises to $TGP\_9=1.8$ and decreases again in the next period of time. Such values are readable on the graphic for all answer- codes in all temporal phases of the study.

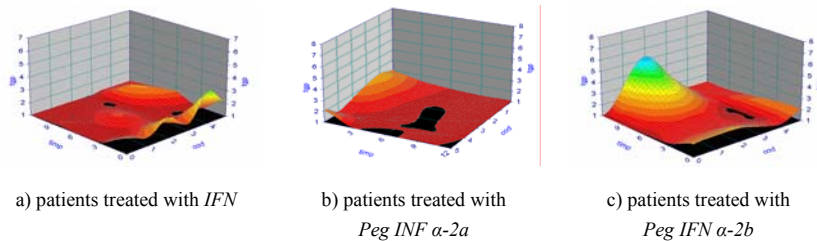| a) patients treated with *IFN* | b) patients treated with *Peg INF α-2a* | c) patients treated with *Peg IFN α-2b* |

Figure 1

The variation as function of time and answer code of the *TGP* indicator

The analysis of the same indicator for *Peg IFN α-2a* treatment (Figure 1.b) shows a practically continuous decrease of the indicator's value from $TGP\_0=2.018$ to $TGP\_12=1.093$ for patients with answer-code 0.

The representation verifies correctly enough the data for answer- code 4, where $TGP\_0=1.190$ and once with 6th month of the study it should stabilize at the indicator's value of 1. However, it can be observed from the representation that the technique of data extrapolation changes the *TGP* value in the period of 9-12 month. Therefore, at the end it is not obtained *TGP* measured value 1, but an estimated value of *1.008*, which represents an error of 0.8%. In conclusion, the verification of the existent data in the representation leads to the certitude that the estimated data are valid, having an acceptable error coefficient.

The same observations are valid for the surface *TGP=f(time, answer-code)* for the treatment with *Peg IFN α-2b* (Figure 1.c). It can be observed that patients with answer- code 2 do not react to this treatment and that the indicator's value rises

from *TGP_0=2.184* to *TGP_12=5.258*. For patients with answer- codes 1 and 3, for whom there is no information in the database, the representation in Figure 1.b allows a relatively correct prediction, its correlation coefficient being $R^2=0.75$.

This way of approaching the problem makes the estimation of the *TGP* indicator's values a 70% true. It is calculated through the summing up of the probabilities induced by the correlation coefficients values and the statistical belief used.

2.2 The TGO Biological Indicator Analysis

The *TGO=f(time, answer code)* indicator analysis has been done in the same manner. It is represented in Figure 2 (a, b and c), for the three types of treatments.

a) patients treated with *IFN*

b) patients treated with *Peg INF α-2a*
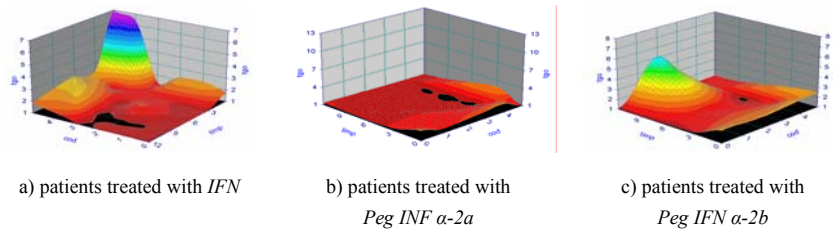
c) patients treated with *Peg IFN α-2b*

Figure 2

The variation as function of time and answer code of the *TGO* indicator

By comparing figures 2.b and 2.c it can be observed that the *Peg IFN α-2a* treatment is more efficient than the *Peg IFN α-2b* treatment because the decrease of the indicator's value is continuous for the former and it is predicted a lower final value than for the latter. The representations allow the *TGO* indicator's value to be assessed for patients with answer-codes 3 and 5 which are not present in the database and which have been estimated through the Watson algorithm. These data are very important, especially for the answer-code 5 patients that have stopped the treatment because of collateral effects.

2.3 The GGT Biological Indicator Analysis

The *GGT=f(time, answer-code)* indicator was similarly analyzed. The obtained graphical representations are presented in Figure 3 (a, b and c) for the three types of treatment.

It is proved that the *Peg IFN α-2b* treatment is the most efficient, as the *GGT* indicator's value decreases from *GGT_0=4.974* to *GGT_12=1.314*. The same treatment has a fluctuant influence on the code 2 patients. In the first 6 months the treatment leads to a decrease value of the indicator from *GGT_0=2.843* to *GGT_6=1.158*, followed by a come back to *GGT_12=3.472*.

a) patients treated with *IFN*   b) patients treated with   c) patients treated with
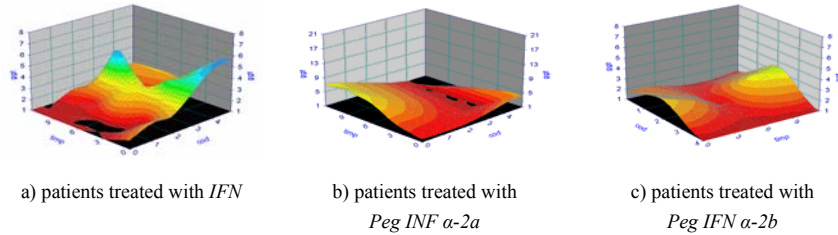   *Peg INF α-2a*   *Peg IFN α-2b*

Figure 3
The variation as function of time and answer code of the *GGT* indicator

The data in Figure 3.b definitely show the inefficiency of the *Peg IFN α-2a* treatment over the value of the *GGT* indicator for answer-code 0 patients. The representation presents an estimation of the reaction of the answer-code 2 patients, for whom there was no data starting with the 6th month of the study. For the same patients, it is estimated the value *GGT_12=5*, the correlation coefficient of the representation being $R^2=0.74$. Answer-code 2 patients are no-responders to the *PegIFN* treatment, therefore it is important to know what is the predicted value of the indicator on the areas in which the database is incomplete.

2.4   The ARN VHC Biological Indicator Analysis

The variation of the *ARN VHC=f(time, answer-code)* indicator is represented in Figure 4 (a, b and c) for the three types of treatment. Regarding the evolution of this indicator, all treatments are efficient.

It is observed that the patients which have been no-responders to the *IFN* treatment (answer-code 1) have a positive evolution in the first three months of treatment, followed by a decrease in the next period, but at a lower value of the indicator than the initial. From now the missing data can be completed by predicting that an eventual continuation of the treatment could lead to a significant decrease of the *ARN VHC* value. As a result, the patient would become a responder.

a) patients treated with *IFN*   b) patients treated with   c) patients treated with
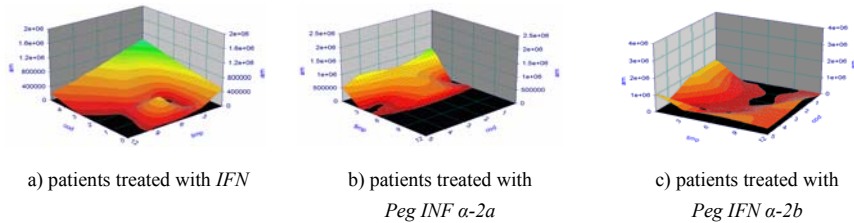   *Peg INF α-2a*   *Peg IFN α-2b*

Figure 4
The variation as function of time and answer code of the *ARN VHC* indicator

In addition to this, the figure gives probable information of the indicator's values for answer-code 3 patients, information that does not exist in the database. For these, with a probability of 65%, the initial value of the indicator could be *ARN VHC_0 ≅ 750000*. So, this information could be taken into consideration together with another indicators, in order to attach a code, as realistic as possible, to the patients considered in a future study. Figures 4.b and 4.c are useful for the prediction of the values of the *ARN VHC* indicator for patients with answer-codes 4 and 5, for whom the database is also incomplete.

3   Expert System for Diagnosis and Prediction

Artificial neural networks are a branch of the artificial intelligence and they have been developed to reproduce human reason and intelligence. The initial idea was that, in order to reproduce intelligence, it would be necessary to build systems with architecture similar to the brain one. Therefore, artificial neural networks are built by the interconnection of certain primary elements, whose structure is similar to the biological neuron. Like the human brain, these artificial neural networks are able to recognize patterns, manage data and, most important, they have the ability of learning [5].

The same conclusions as before have been obtained throw the implementation of an expert system. In a primary phase, it suggests the diagnosis for a new patient (Figure 5). It is necessary to specify the values of three markers *AgHBs, anti-VHC* and *anti-VHD*.
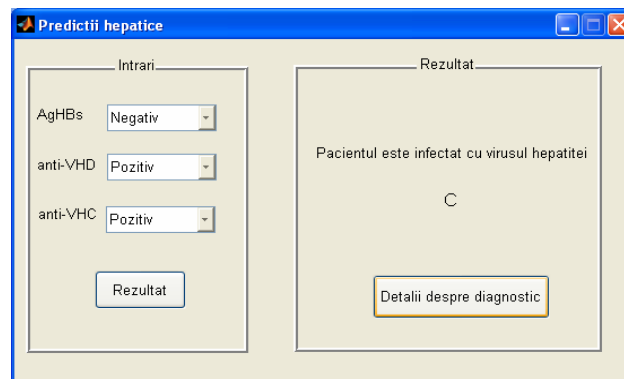

Figure 5
Expert system for hepatitis diagnosis

The development of this part of the system is based on logical inference, the most common method of implementation of the human reasoning. It is necessary to

have a set of primary rules in order to implement such an expert system. According to these rules, conclusions will be drawn. In this case, the rule that leads to the suggestion of hepatitis C as a diagnosis is:

IF (AgHBs=Negative) *AND* (anti-VHC=Positive) *THEN* Hepatitis C

Next, if it is discovered that the patient is infected with hepatitis C virus, it is made the prediction of the biological indicators evolution according to the treatment to be applied (Figure 6).

This part of the system is implemented using a feed-forward neural network with back-propagation learning algorithm. Such a network receives a series of inputs and its outputs are the results of the problem. Between the two levels (input and output) there can be a number of hidden levels. The elements on each level (neurons) are interconnected throw links called synapses. These have a weight, which can be modified along the training of the network.

Figure 6
The prediction of biological indicators evolution

The most important characteristic of artificial neural network is the learning capacity (i.e. its capacity of adapting to the informational environment specific to the problem it is solving).

In this case, the system has been designed as a network of neural networks. For each of the four biological indicators that have been studied, there are four layers of neural networks. The networks on the first layer receive as inputs: patient's age, sex, location (rural/urban), treatment scheme, Knodell score, hepatic fibrosis score and value of the parameter for which the prediction is made, at the initial moment (before the treatment start). These networks have only one output (i.e. the value of the parameter at 3 months). On the following layer the networks have the same structure as the first layer ones, but they have in addition, as inputs, the outputs of

the networks on the former layers; therefore, the networks on the last layer will have not 7 inputs (as the networks on the first layer) but 10.

The application has been projected in the Matlab 7.0 environment, which has a toolbox totally dedicated to the neuronal calculus. The system offers for each evaluated biological indicator predictions regarding the next 12 months evolution, indicating its growing tendency, its stabilizing or decreasing tendency.

Conclusions

The statistical analysis, as well as, the implemented expert system offers the possibility to predict the evolution of patients in time. The hepatitis C treatment is very expensive and severe side effects can appear very often. Therefore, it is important to identify those patients who most probably can react to the treatment, so that the others can be protected from a treatment with no benefits. That's for what the use of an expert system can support the physician decision concerning the treatment.

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