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Understanding the Dynamics of Hepatic Fibrosis in Hepatitis C Patients

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Abstract Hepatitis C virus (HCV) is the most common chronic disease in Egyptian society. It seems often as a silent disease and causing no symptoms until much of the liver has been damaged. In this paper, we propose a conceptual system dynamic for HCV model to present the different life cycle stages of this disease. VENSIM-PLE is utilized to achieve this study. To understand the nature and the factors that causing this disease, we can get early chance to take different measures to prevent or minimize the occurrence of it. Then, we get the ability to decrease the mortality rate from late stage, cirrhosis, by appropriate treatments. The accumulation of the consecutive stages of the HCV disease is an S-shape in the cirrhosis stage. This result suggests a good control on the HCV death rate.

Keywords System dynamics, HCV Model, Liver Fibrosis, Simulation Model

Introduction

Hepatitis C is an infectious disease primarily affecting the liver, caused by the HCV. The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. The major problem of HCV infection is the progression to cirrhosis and its potential complications such as hepatocellular carcinoma and then to die [1]. Infection with HCV represents a public health problem with an alarming prevalence throughout the world [2-3]. HCV is spread primarily by blood contact associated with intravenous drug use, poorly sterilized medical equipment and transfusions such as intravenous drugs, IV drug use and HCV-infected mother [3-4]. Current understanding of HCV infection has been advanced by the concept of liver fibrosis progression as demonstrated in Fig. 1 [5].

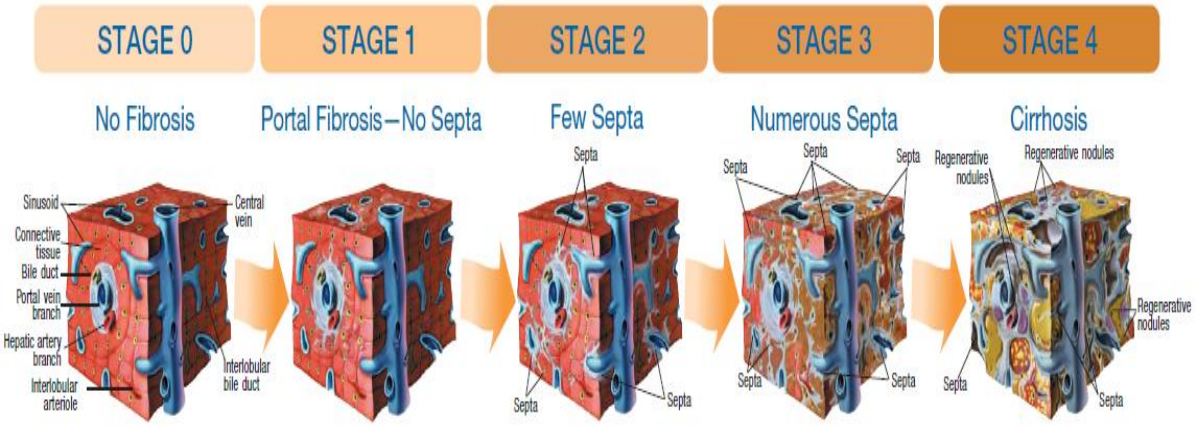

Figure 1: Progression Stages of Liver Disease [5].

Fibrosis is the deleterious but variable consequence of chronic inflammation [4-7]. HCV is usually only lethal when it leads to cirrhosis, the last stage of liver fibrosis. Therefore, an estimate of fibrosis progression represents an important surrogate endpoint for evaluation of the vulnerability of an individual patient and for assessment of the impact of treatment on natural history [2, 3]. The liver goes through five different fibrosis stages to reach to the cirrhosis: no fibrosis (F0), portal fibrosis without septa (F1), fibrosis with few septa (F2), fibrosis with numerous septa (F3), and cirrhosis (F4) [4,6,12]. Little effect on liver function is seen during stages F0, F1 and F2; fibrosis is largely limited, and most of the working cells of the liver stay well supplied with blood and oxygen. By stage F3, however, the scarring has progressed to the point that the function of the liver cells is affected, and blood flow through the liver is altered. Fluids and bile may begin to build up in the liver causing it begins to discolour [11]. In stage F4, abnormal blood flow may result in a build-up of fluid in the abdomen, a condition known as ascites. Failure of liver cells to function often results in symptoms such as generalized weakness, anorexia, malaise, weight loss, and jaundice; yellowing of the skin [5,7]. Several factors have been clearly shown to be associated with fibrosis progression rate. In this work, Age, Consumption of alcohol, Smoking and Stresses factors are selected to provide an integrated structure of a system dynamic model for Hepatic Fibrosis HCV [1-7]. The system dynamics become an important methodology for the behaviour of the scientific models. It can be used to achieve the basic concepts for a model through a feedback structure in decision-making, which will generate by the iteration of many nonlinear loops over time [8-9]. The significant of this work is to understand the behaviour of our dynamic model over time. This dynamic model gave the chance to take different measures to prevent or minimize the occurrence of this disease and provide the ability to decrease the mortality rate from late stage, cirrhosis, by appropriate treatments.

Methodology

HCV dynamic model presents five fibrosis stages (i.e., F0 to F4) existing in a society with constant population N. There is a time delay between each two stages which depends on the several factors including stresses S, smoking K, age a, and excessive drinking of alcohol h [4,7]. The transition rate between consecutive stages mainly depends on these factors. This transition is sequentially occurred. This implies the disease develops from the first stage F0 to the third stage F3 after passing through the second stage F2 and so on. In fact, when the values of these factors increase, the virus rapidly spreads and at the same time the transition rate from one stage to another will increase too. People who reach the final stage of infection (*i.e.*, cirrhosis, F4) may die after a short time. This time depends on treatments and previous factors. For this model we utilized the most of these variables to achieve the core advantage for this study. The life cycle of the hepatitis C is very long, so time horizon is selected to be 30 years as many studies referred [4,7]. The reference SIR model of this study is presented in [9].

Our model is built using VENSIM PLE in two mapping styles which are Causal loop diagram (CLD) and Stock and flow diagram (SFD). CLDs emphasize the feedback structure of a system, while SFDs emphasize their underlying physical structure [8, 12]. Fig. 2 shows the CLD of this model where several loops represents the five stages of the HCV disease in conjunction with related variables such as mortality rate, death population, treatment, contact rate, and infectivity. HCV model also consists of several feedback loops caused by these five stages. Reinforcing Positive Feedback Loops "**R**" explaining the increase fibrosis rate from one stage to another. Balancing Negative Feedback Loops "**B**" explaining the decrease of that rate. The arrows entering to the variable represent the effect of variables to each other. The positive sign on the arrow means positive effect, while the negative sign means negative effect. Fig.3 shows the SFD dynamic model that contains Stocks, Flows, Convertors, and Connectors.

The spread of HCV disease starts from Fibrosis rate, FR0 that rely directly on some input factors such as contact rate, CR, Infectivity, i and total population, N as in the following equation:

$$FibrosisRate, FR_0 = \frac{CR \times F0 \times i \times F1}{N}, \quad (1)$$

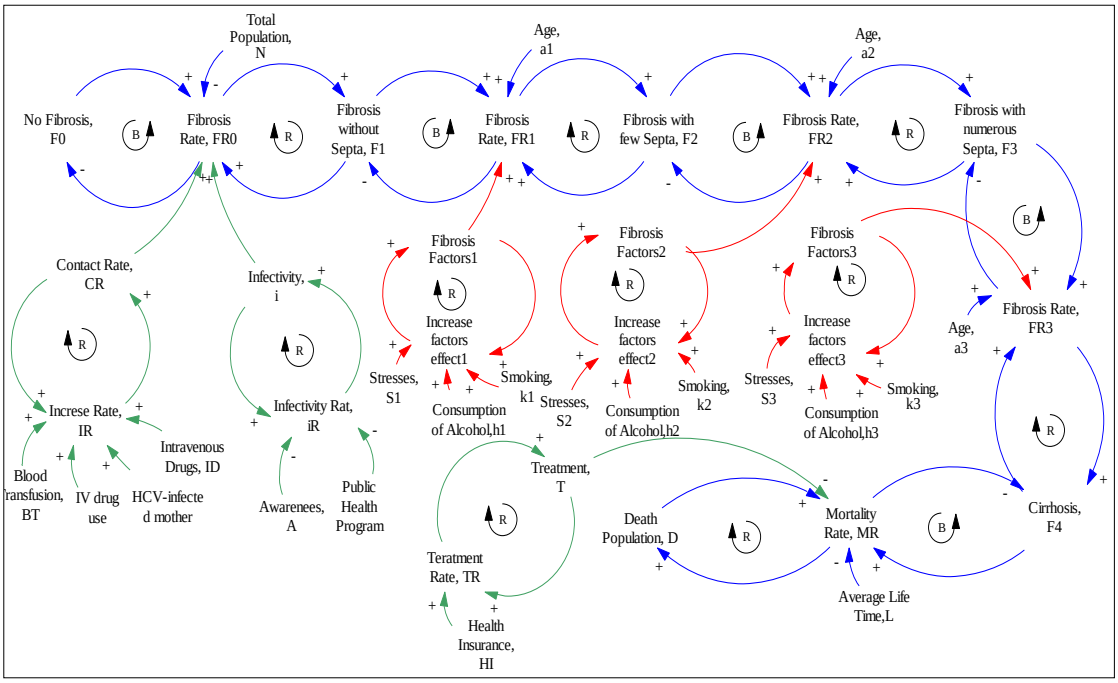

Figure 2: Causal loop conceptual diagram (CLD) of the HCV model

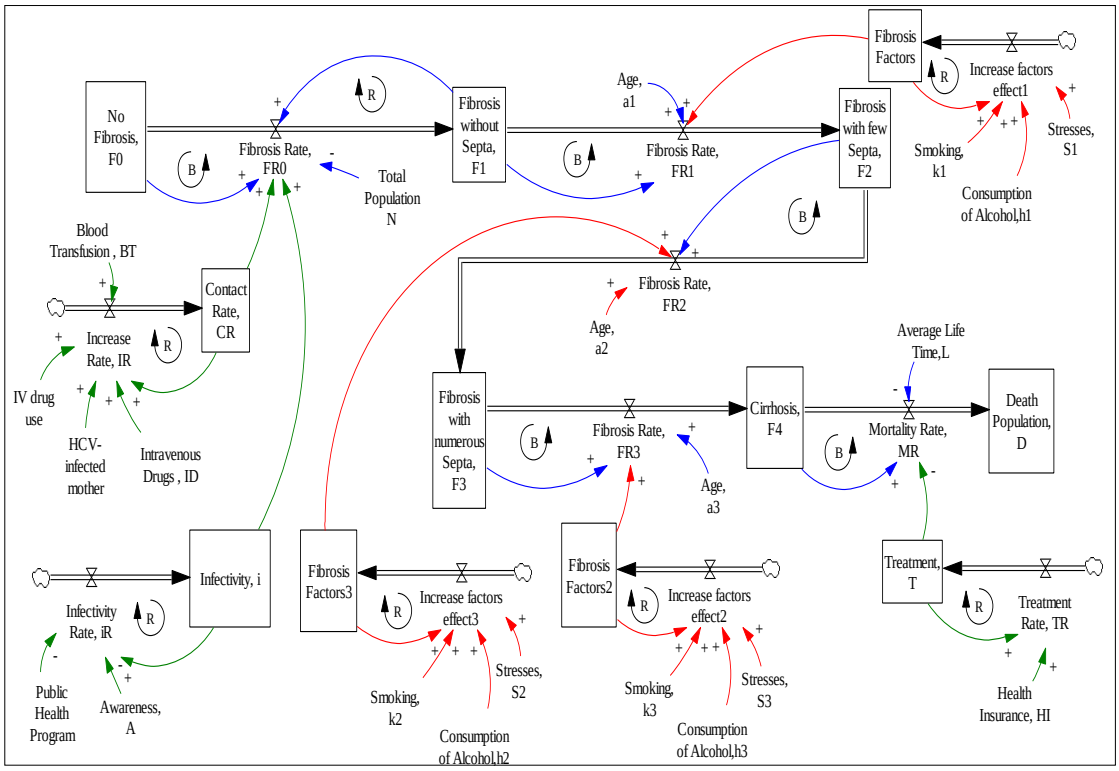

Figure 3: Stock and flow conceptual diagram (SFD) of the HCV model

The transition of the fibrosis after the disease appears between its different stages depends on the particular factors that affect immediately on behaviour of the patients as represented in the following equation:

$$FibrosisRate, FR_i = \frac{Fibrosis, F_i}{a \times S \times K \times h}; i = 1,2,3 \quad (2)$$

where, a, S, k, and h are age, stress, smoking and drinking of alcohol, respectively. The mortality rate (MR) expresses the death rate of people after infected by HCV and reaching to the dangerous stages (i.e., cirrhosis). Average Life time (L) and Treatment (T) are the two factors that affect directly on the behaviour of this rate as in the following form:

$$MortalityRate, MR = \frac{Cirrhosis, F4}{averageLiveTime, L \times Treatment, T}. \quad (3)$$

The origin of Eq.1, Eq.2 and Eq.3 for the fibrosis rates are existed in [9]. The unit of these equations are person per year.

Table 1 shows the most common variables in this model such as stocks, flows, and converter with their equations. To achieve our HCV dynamic model, we should have a reference model that provide us full information about how we can build our successfully model. The selecting of reference model should not arbitrary, meanwhile it must coincide with the work idea. Thus, for our model we utilized the Susceptible, Infectious and Recovered (SIR) model to be our reference model to facilitate building our model. The time horizon for this model is 30 years which represents the number of period in this model [4,9,12]. The cycle life of the hepatitis C is very long [7].

Table 1: Common variables of HCV model with their Equations, Units and Specifications

S. No.	Variable Name	Equation	Unit	Specification
1	No Fibrosis, "F0"	$F0 = -FR0$	Person	Stock
2	Fibrosis without Septa, "F1"	$F1 = FR0 - FR1$	Person	Stock
3	Fibrosis with few Septa, "F2"	$F2 = FR1 - FR2$	Person	Stock
4	Fibrosis with numerous Septa, "F3"	$F3 = FR2 - FR3$	Person	Stock
5	Cirrhosis, "F4"	$F4 = FR3 - MR$	Person	Stock
6	Death Population, "D"	$D = MR$	Person	Stock
7	Treatment Rate, "TR"	$TR = T \times HI$	1/Year	Flow
8	Awareness "A"	Constant	-	Input
9	Blood Transfusion, "BT"	Constant	-	Input
10	Intravenous Drugs, "ID"	Constant	-	Input
11	Smoking, "k"	Constant	-	Input
12	Consumption of Alcohol, "h"	Constant	-	Input
13	Stresses, "s"	Constant	-	Input

Abbreviations: Health Insurance (HI), Treatment (T).

Results and Discussion

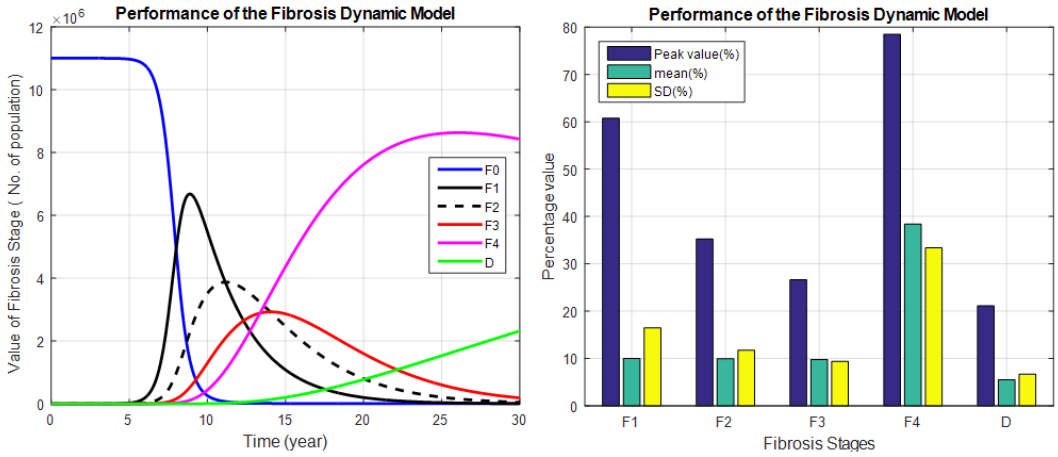

Figure 4: Fibrosis Life Cycle F0 to F4 and their characterization Peak-value, Mean and SD

The proposed model was verified using VENSIM PLE software [10]. The values of the awareness (A), Blood Transfusion (BT), and Intravenous Drugs (ID) input converters are 0.05, 0.5 and 0.25 respectively which are referred to the baseline run as Case 0 as illustrated in table 2. Fig. 4 shows the results of HCV disease transition from F0 to F4 of baseline run. We observe from this figure the results are similar to those of the SIR reference model as presented in [9], but the cirrhosis stage is shifted to the right in the time horizon due to the existing of the intermediate stages F1, F2, and F3 which are not exiting in the SIR model. Peak-value, Mean and, Standard Deviation (SD) for all fibrosis stages are demonstrated too.

Figure 5(a) shows the mortality rate which increases as the disease reaches the cirrhosis stage because the liver cells are entirely damaged at this level of infection. At the same time, the behavior of the accumulative population death increases as clear in Fig.5 (b).

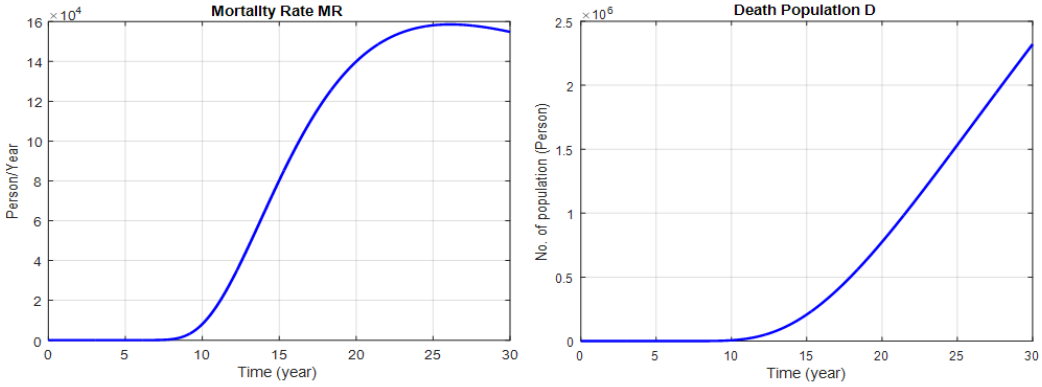

Figure 5: (a) Population Death and (b) Death Rate

The proposed model was verified using VENSIM PLE software [10]. The values of the awareness (A), Blood Transfusion (BT), and Intravenous Drugs (ID) input converters are 0.05, 0.5 and 0.25 respectively which are referred to the baseline run as Case 0 as illustrated in table 2. Fig. 4 shows the results of HCV disease transition from F0 to F4 of baseline run. We observe from this figure the results are similar to those of the SIR reference model as presented in [9], but the cirrhosis stage is shifted to the right in the time horizon due to the existing of the intermediate stages F1, F2, and F3 which are not exiting in the SIR model. Peak-value, Mean and, Standard Deviation (SD) for all fibrosis stages are demonstrated too.

Table 2 shows the effect of the variables awareness "A", blood transfusion "BT" and intravenous drugs "ID" to the percentage of all the population peak, mean, and standard deviation values in each fibrosis stage considering the values in Case 0 to be the reference for all cases.

Table 2: Sensitivity of A, BT, and ID variables with the peak-value (P), mean (μ), and standard deviation (σ) of all population fibrosis stages

Case	Variables			Measurements	Fibrosis Stages Population (%)				
	A	BT	ID		F1	F2	F3	F4	D
				P	60.74	35.23	26.63	78.46	21.1
0	0.05	0.5	0.25	μ	9.97	9.9	9.75	38.36	5.49
				σ	16.46	11.4	9.38	33.36	6.67
				P	30.29	24.02	19.82	27.06	1.42
1	0.06	0.5	0.25	μ	7.1	4.87	2.88	2.64	0.11
				σ	10.73	8.29	5.56	5.91	0.27
				P	54.2	33.85	26.03	78.16	17.85
2	0.05	0.4	0.25	μ	9.94	9.85	9.55	32.48	4.04
				σ	15.43	11.37	9.31	32.54	5.43
				P	65.59	35.95	26.9	78.56	23.08
3	0.05	0.5	0.30	μ	9.97	9.94	9.83	41.95	6.53
				σ	17.13	11.94	9.42	33.24	7.42

In this study, we focused on the sensitivity of only the above three variables which are A, BT, and ID .The peak value of F0 is equal to the number of population, N, in all cases. From Case 1 we note that a slight increase in awareness from 0.05 to 0.06 leads to extreme decrease in all of the population death "D" peak-value from 21.1 to 1.42 with mean value (from 5.49 to 0.11) and standard deviation value (from 6.67 to 0.27). The decreasing of transfusion of blood infectious with HCV "BT" from 0.5 to 0.4 cause to decrease the fibrosis rate. Due to this the population death "D" peak-value is decreased from 21.1 to 17.85 with mean value (from 5.49 to 4.04) and standard deviation value (from 6.67 to 5.43) as illustrated in Case 2. Also increasing of "ID" (from 0.25 to 0.30) leads to increase the fibrosis rate which leading to increase in all of the population death "D" peak-value (from 21.1 to 23.08), mean value (from 5.49 to 6.53) and standard deviation value (from 6.67 to 7.42) as illustrated in Case 3. Fig. 6 shows the bar charts of the peak, mean and standard deviation values of all population fibrosis stages.

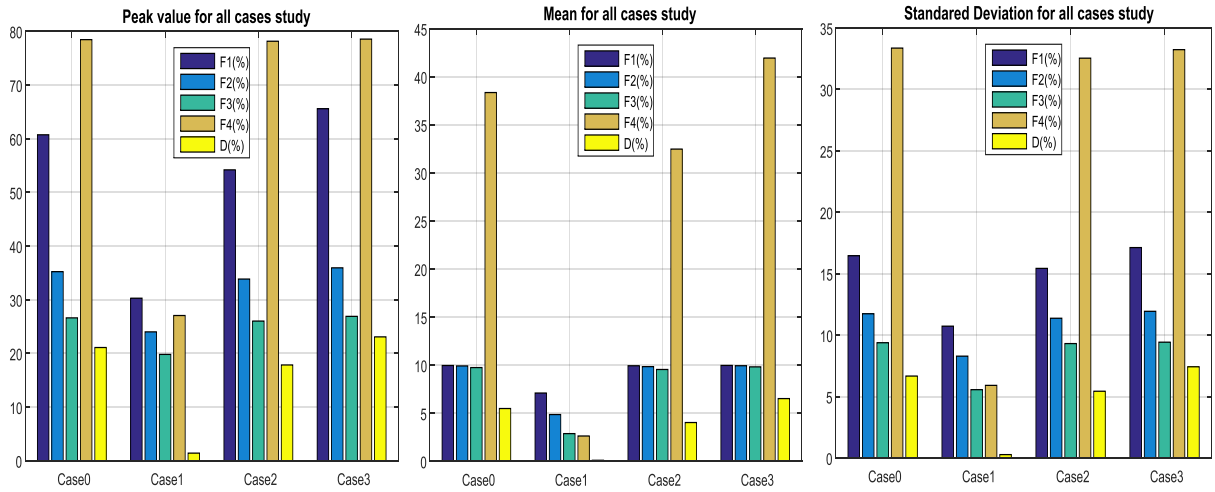

Figure 6: Percentage value of (a) peak-value, P, (b) mean value μ, (c) standard deviation σ for all fibrosis stages

Fig. 7 shows the behaviours of both cirrhosis and population death stages for all cases. Increasing the cirrhosis leads to increase the death population. In each case we can clearly observe the different changes of F4 and D corresponding to any input variables change as reported in Table 2. For example, when we change the BT from 0.5 to 0.4, in Case 2, the cirrhosis is decreased and then the population death is decreased as well.

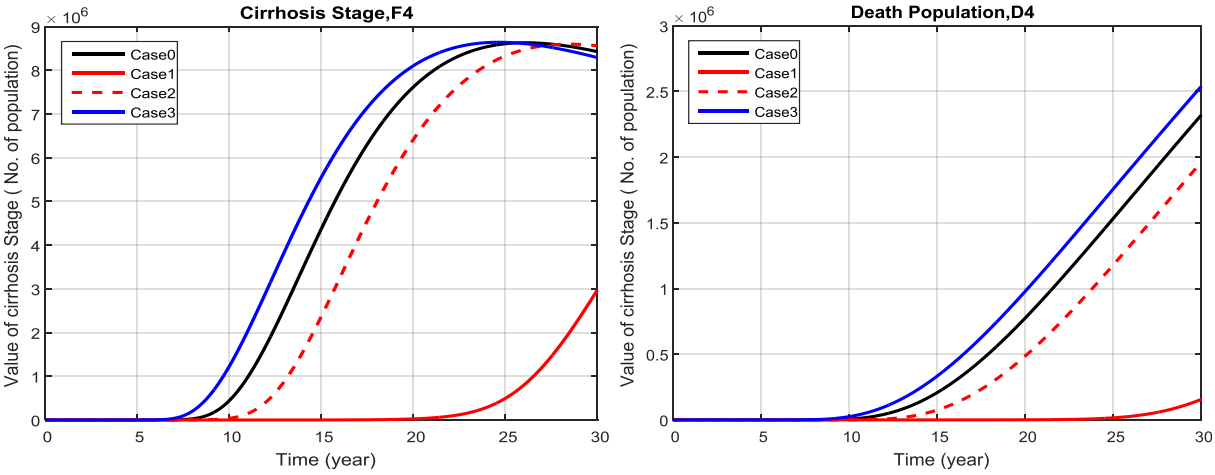

Figure 7: Behavior of cirrhosis F4 and death population D for all Cases due to Sensitivity of A, BT, and ID

Other studies we made for different variables stress (S), smoking (K) and alcohol consumption (h) that entered to the model after F1 till F4 stage. In this work, we also represent the effect of S1, K1 and h1, between F1 and F2 stages, because they provide more behaviour clearance and performance as reported in Table 3. The results in table 2 show that the population death is strongly decreased from 21.1 to 1.42 when increasing the awareness "A" by a slight value of 0.01(as in case1). This observation has motivated us to study the model behavior with the change the value of A to be 0.06 and use this status as a reference case and then study again the impact of S1, K1, and h1 on the model. Table 4 shows the result of this study for all fibrosis stages. By comparison the results that shown in Table 3 and 4, we note that the peak value of the population death in each case (i.e., case1 to case3) is clearly decreased from 17.99, 15.9 and 16.5 to 0.14, 0.13, and 0.13 respectively. This means that the awareness A is the important factor to support the people life through the life cycle of HCV virus.

Table 3: Sensitivity of S1, K1, and h1variables with the peak-value (P), mean (μ) and standard deviation (σ) of All Population Fibrosis Stages with A = 0.05

Case	Variables			Measurements	Fibrosis Stages Population (%)				
	S1	K1	h1		F1	F2	F3	F4	D
				P	60.74	35.23	26.63	78.46	21.10
0	0.30	0.30	0.30	μ	9.97	9.9	9.75	38.36	5.49
				σ	16.46	11.4	9.38	33.36	6.67
				P	76.09	24.70	20.30	73.38	17.99
1	0.20	0.30	0.30	μ	19.51	9.53	9.13	32.71	4.46
				σ	22.12	8.47	7.26	29.56	5.54
				P	82.41	19.13	16.41	67.19	15.19
2	0.30	0.10	0.30	μ	27.58	8.80	8.23	27.63	3.64
				σ	24.50	6.60	6.00	25.76	4.60
				P	79.78	21.53	18.13	70.44	16.50
3	0.30	0.30	0.15	μ	23.75	9.19	8.69	30.02	4.02
				σ	23.52	7.40	6.55	27.60	5.04

Similar to the above study, we observe in Fig. 8 the peak, mean, and standard deviation values for all population fibrosis stages. Also Fig. 9 shows the behaviors of both cirrhosis and population death stages for all cases due to the sensitivity of S1, K1, and h1.

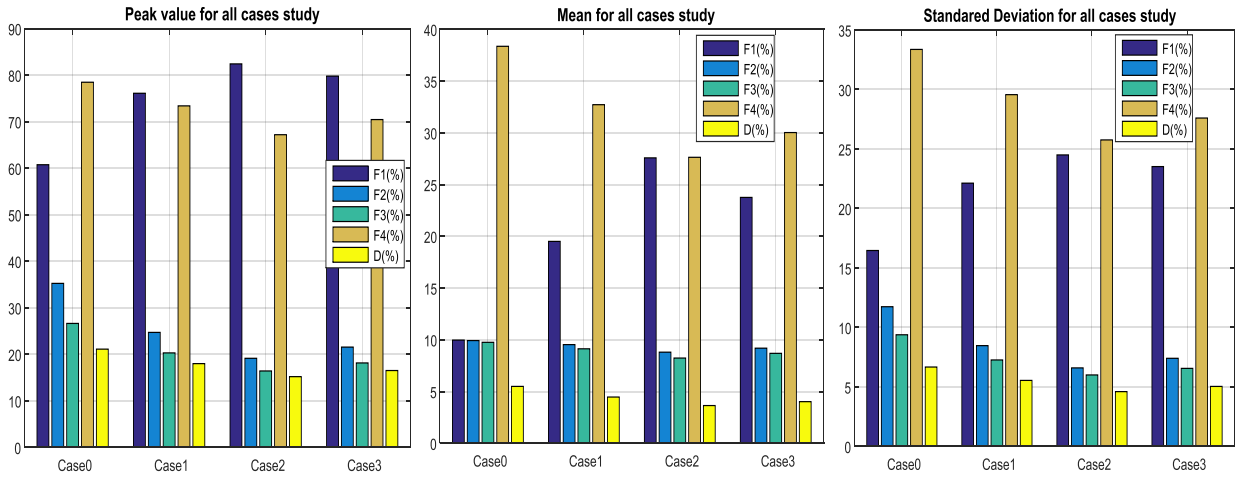

Figure 8: Percentage value of (a) peak-value, P, (b) mean value μ, (c) standard deviation σ for all fibrosis stages

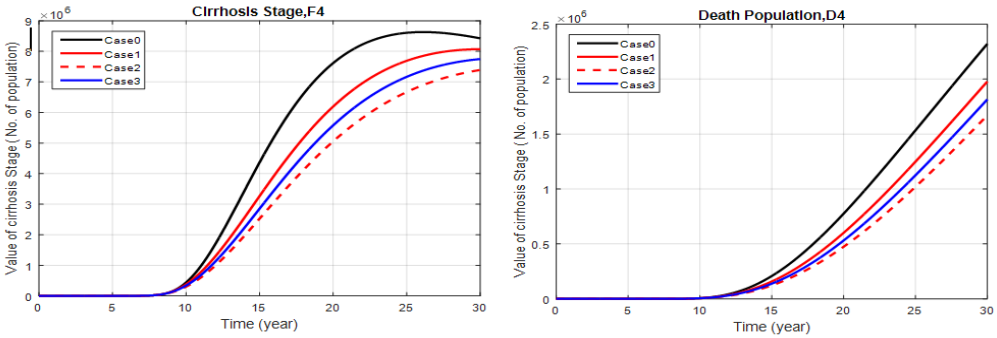

Figure 9: Behavior of Cirrhosis F4 and Death Population D for All Cases Due to Sensitivity of K1,S1, and h1 with A = 0.05

Table 4: Sensitivity of S, K1, and h1 in terms of the peak-value (P), mean (μ) and standard deviation (σ) of all population fibrosis stages with A = 0.06

Cases	Variables			Measurements	Fibrosis Stages Population (%)				
	S1	K1	h1		F1	F2	F3	F4	D
				P	30.29	24.02	19.82	27.06	1.42
0	0.30	0.30	0.30	μ	7.1	4.87	2.88	2.64	0.11
				σ	10.73	8.29	5.56	5.91	0.27
				P	58.38	22.54	19.16	22.58	0.14
1	0.20	0.30	0.30	μ	17.1	7.37	5.70	9.67	0.02
				σ	20.23	8.83	7.70	16.44	0.03
				P	68.76	18.14	15.86	17.41	0.13
2	0.30	0.10	0.30	μ	22.71	6.45	5.07	8.83	0.02
				σ	24.82	7.38	6.50	14.54	0.03
				P	64.55	20.12	17.37	20.10	0.13
3	0.30	0.30	0.15	μ	20.15	6.91	5.44	9.34	0.02
				σ	22.58	8.05	7.07	15.57	0.03

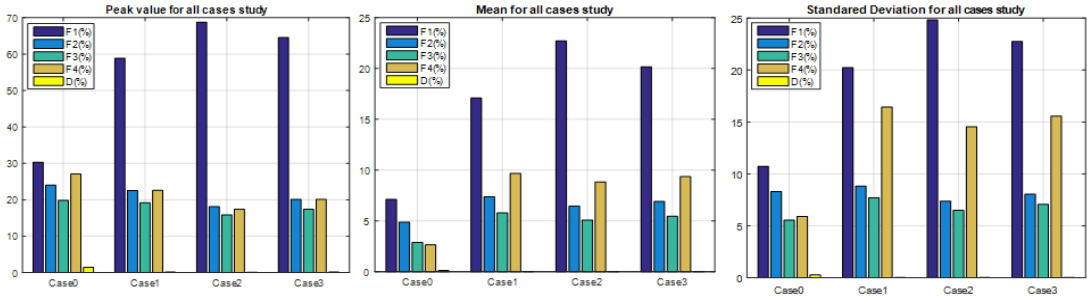

Figure 10: Percentage value of (a) peak-value, P, (b) mean value μ, (c) standard deviation σ for all fibrosis stages

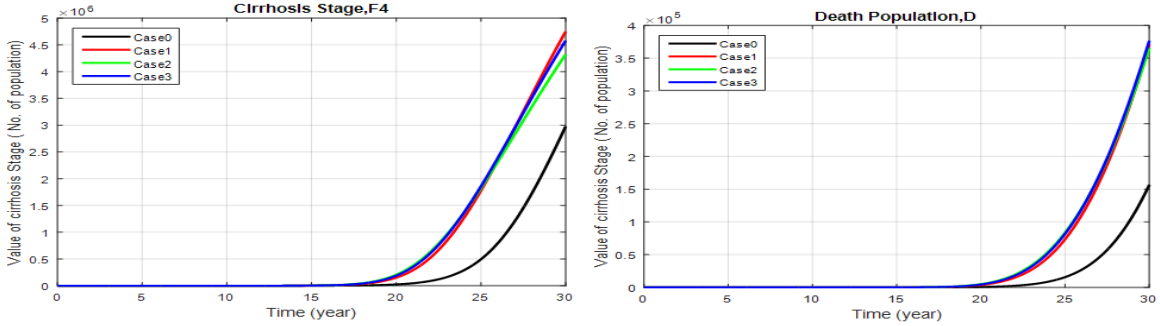

Figure 11: Behavior of Cirrhosis F4 and Death Population D for all cases due to sensitivity of K, S, and h1with A = 0.06

Fig.12 illustrates the system behavior for cirrhosis F4 and death population D in baseline run (Case0 & A = 0.05) but at different values of Health Insurance (HI). Increasing the HI values lead to increase a cumulative population in a cirrhosis stage and decrease the population death.

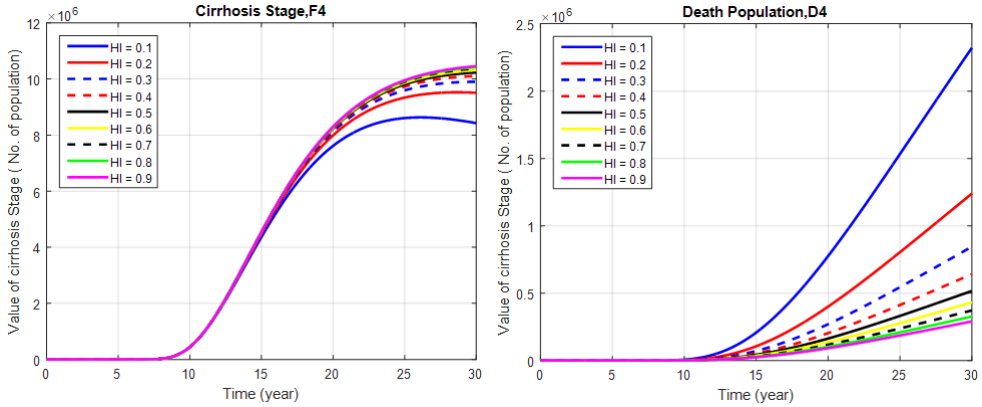

Figure 12: Behavior of cirrhosis F4 and Death Population D due to Sensitivity of HI

The previous results were obtained in the condition of constant variables, but when using time-varying variables, the results of the model are delayed with the same behavior as shown in Fig. 13.

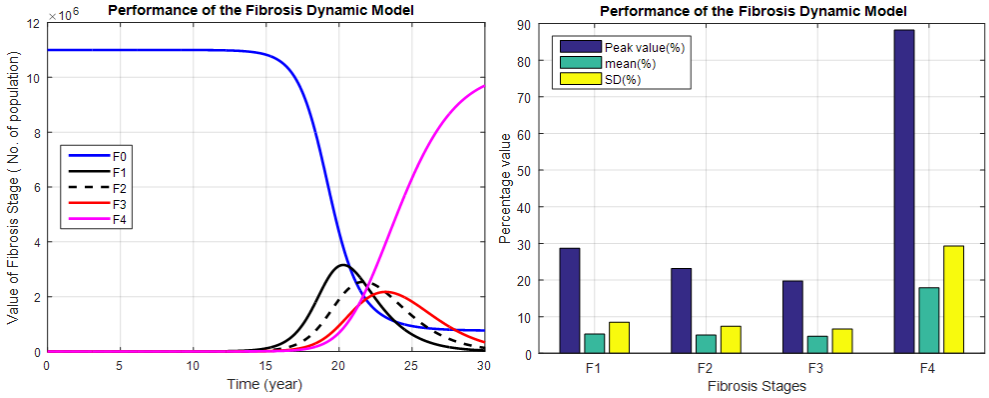

Figure 13: Fibrosis Stages F0 to F4 with Time-varying Variables

Conclusion

HCV system dynamics model of hepatic fibrosis in hepatitis C patients was useful tool to understand the behavior of HCV disease in all its different stages. All HCV disease stages as well as many factors affecting the transition among these stages are used to build this model. The increasing of the awareness for population, they will become more cautious to prevent themselves from propagation of the HCV disease through the life. This mean the people will try to decrease as much as possible the factors that cause in the spread of disease such as stress, smoking and alcohol consumption etc. Then the mortality rate will decrease with time and the people will support them life from distortion. So, the awareness is the most important variable to help us for a long life. The results suggested further development of this model to include additional processes such as liver implantation to reverse the flow of the status of patients from harmful cirrhosis stage to the recovery stage with no fibrosis.

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