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Stability analysis of dynamic models of hepatitis B virus with treatment

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ABSTRACT

An Hepatitis B epidemic model with treatment is investigated. The model allows for the some infected individuals to move from the symptomatic phase to the asymptomatic phase by all sorts of treatment methods. The model exhibits two equilibria, namely, the disease-free equilibrium (DFE) and the endemic equilibrium. The stability of these two equilibria is controlled by the basic reproduction number R_0. It is shown that if R_0 is less than one, the disease-free equilibrium is locally asymptotically stable and R_0 is greater than one, the unique endemic equilibrium is locally asymptotically stable. By computer simulation it is found that if the growth rate of pharmacological effect of the lamivadine to the free virus increases, the symptomatic phase decreases. Numerical simulations are also carried out to investigate the influence of certain parameters on the spread of disease, to support the analytical results. Also, sensitivity analysis of the endemic equilibrium point is carried out.

Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a major global health problem and the most serious type of viral hepatitis. It is a viral infection that attacks the liver and can cause both acute and chronic disease (WHO, 2002) [1]. About 2 billion people worldwide have been infected with the virus and about 350million live with chronic infection. An estimated 600 000 persons die each year due to the acute or chronic consequences of hepatitis B (WHO, 2010) [2]. About 25% of adults who become chronically infected during childhood later die from liver cancer or cirrhosis (scarring of the liver) caused by the chronic infection. HBV is 50 to 100 times more infectious than HIV (WHO, 2010). HBV is an important occupational hazard for health workers, and 50 million new cases are diagnosed annually (WHO, 2010).

The treat of increasing hepatitis B is mainly sexual, household or perinatal exposure to infected person.

Avoidance of perinatal HBV transmission is an important step in controlling hepatitis B. Transmission from a HBeAg-positive to her infant may occur in utero, at the time of birth, or after birth. The rate of infection can be as high as 90%. However, neonatal vaccination is highly efficacious (95%). It efficacy indicates that most infections occur at or shortly before birth. On the other hand, caesarean section seems not to be vertically transmitted disease like HIV. The risk of transmission from mother to infant is related to the HBV replication rate in the mother. There seems to be a direct correction between maternal HBV DNA levels and the likelihood of transmission. In mothers with highly replication HBV, the risk of transmission may be up to 85 to 90%, and it continuously lowers with lower HBV DNA levels Burk *et al*. [3].

Recently drugs called interferon or lamivudine have been used to treat patients with chronic hepatitis B. Considering the need for various long-term treatments, it is necessary to construct a mathematical model that enables us to study the dynamics of HBV (Moskovitz et.al.[4]; Nowak et.al.[5]). In this paper, according to clinical symptoms, we first establish the ODE model with two infective stages before hepatitis B i.e., the asymptomatic phase and the symptomatic phase. By all sorts of treatment methods, some individuals with the symptomatic phase can be transformed into asymptomatic individuals. One of our purpose into investigate the effect of treatment on the long term dynamics of the disease.

The organization of this paper is as follows: In Sec. 2, we introduce our mathematical model and boundness of solutions. In Sec. 3 and 4, we analyze our model with regard to equilibria and their stabilities. Computer simulations are performed to illustrate the feasibility of our analytical findings in Sec. 5. In Sec. 6, we now study sensitivity analysis of the endemic equilibrium to changes in the value of the different parameters associated with the system. In the last Sec. 7, we present the conclusion based on our analysis.

The Mathematical Model

We propose the following mathematical model to describe the viral dynamics of the anti-HBV infection treatment with lamivudine.

During processing the lamivadine therapy, we assume that the immune model of HBV infection has the form:

$$\begin{aligned}
\frac{dS}{dt} &= \lambda - dS - bSV, \\
\frac{dI}{dt} &= bSV - (a - k_1)I + \alpha J, \\
\frac{dJ}{dt} &= k_1 I - (c + k_2 + \alpha)J, \\
\frac{dV}{dt} &= k_2 J - uV - k_3 J, \\
\frac{dE}{dt} &= k_3 J - k_4 E,
\end{aligned} \tag{2.1}$$

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Where the 5 variables- S, I, J, V and E represent the numbers of uninfected cells, asymptomatic phase, symptomatic phase, free virus, and cytotoxic cells, respectively. Here we only consider two stages of the infectious period according to clinic stages and papers [6-7], i.e., the asymptomatic phase (I) and the symptomatic phase (J). λ is the rate of reproduced susceptible cells. Uninfected cells die at rate dS, and become infect at rate bSV, where b is the rate constant describing the infection process. Asymptomatic phase are produced at rate bSV and die at rate aI. k_1 and k_2 are transfer rate constant from the asymptomatic phase I to the symptomatic phase J and from the symptomatic phase to the HBV cases, respectively. Symptomatic phase die out at rate cJ. α is the treatment rate from the symptomatic phase J to the asymptomatic phase I. Free virus are produced from symptomatic phase at rate $k_2 J$ and removed at rate uV. k_3 represent the pharmacological effect of the lamivadine to the free virus. Cytotoxic cells are produced at rate $k_3 J$ and removed at rate $k_4 E$. $\lambda, d, b, a, k_1, k_2, k_3, k_4, \alpha, c, u$ are positive constant and will be determined by antiviral immune responses.

It follows from system (2.1) that

$$\frac{dS}{dt}+\frac{dI}{dt}+\frac{dJ}{dt}=\lambda-dS-aI-cJ-k_2J.$$

$$\frac{d}{dt}(S+I+J)\le\lambda-\eta(S+I+J), \text{ where}$$

$$\eta=\min(d,c,a).$$

Then $\lim_{t\to\infty} Sup(S+I+J)\le\frac{\lambda}{\eta}$.

From fourth equation of system (2.1), we get

$$\frac{dV}{dt}+uV\le\frac{\lambda(k_2-k_3)}{\eta}.$$

On solving above differential equation, we get

$$V\le\frac{\lambda(k_2-k_3)}{\eta u}\left(1-\frac{1}{e^{ut}}\right).$$

When $t\to\infty$, we have

$$0\le V\le\frac{\lambda(k_2-k_3)}{u\eta}, \text{ where } k_2>k_3.$$

Also, from fifth equation of system (2.1), we get

$$\frac{dE}{dt}+k_4E\le\frac{\lambda k_3}{\eta}.$$

On solving above differential equation, we get

$$E\le\frac{\lambda k_3}{\eta k_4}\left(1-\frac{1}{e^{K_4t}}\right).$$

When $t\to\infty$, we have

$$0\le E\le\frac{\lambda k_3}{\eta k_4}.$$

Thus the feasible region for system (2.1) is

$\Gamma=\{(S,I,J,V,E)\in R_+^5: S+I+J\le\lambda/\eta,\ 0\le V\le V_m,\ 0\le E\le\lambda k_3/\eta k_4,\ S>0, I\ge0, J\ge0, V\ge0, E\ge0\}$,

where $\eta=\min(d,a,c)$ and $V_m=\lambda(k_2-k_3)/u,\ \ k_2>k_3$.

Let $Int\,\Gamma$ denote the interior of Γ. It is easy to verify that the region Γ is a positively invariant with respect to system (2.1).

Analysis of Equilibrium Points

Now we investigate the existence of equilibria of system (2.1). System (2.1) has always a disease-free equilibrium $E_0(\lambda\backslash d,0,0,0)$ and unique endemic equilibrium $E_1(S^*,I^*,J^*V^*,E^*)$.

Existence of disease -free equilibrium $E_0(\lambda/d,0,0,0)$:

Here λ/d is the solution of the following equation;

$$\lambda-dS=0.$$

Clearly, $S=\lambda/d>0$. So the equilibrium point $E_0(\lambda/d,0,0,0)$ exist.

Existence of endemic equilibrium $E_1(S^*,I^*,J^*V^*,E^*)$:

The non trivial endemic equilibrium point $E_1(S^*,I^*,J^*V^*,E^*)$ is the positive solution of the following algebraic equations;

$$\lambda-dS^*-bS^*V^*=0. \quad (3.1)$$

$$bS^*V^*-(a+k_1)I^*+\alpha J^*=0. \quad (3.2)$$

$$k_1I^*-(c+k_2+\alpha)J^*=0. \quad (3.3)$$

$$k_2J^*-uV^*-k_3J^*=0. \quad (3.4)$$

$$k_3J^*-k_4E^*=0. \quad (3.5)$$

Now from equation (3.2), (3.3), (3.4) and (3.5) we can write,

$$bS^*V^*=(a+k_1)I^*-\alpha J^*. \quad (3.6)$$

$$k_1I^*=(c+k_2+\alpha)J^*. \quad (3.7)$$

$$V^*=\frac{(k_2-k_3)J^*}{u}. \quad (3.8)$$

$$E^*=\frac{k_3J^*}{k_4}. \quad (3.9)$$

Now using equation (3.7), (3.8) in equation (3.6) we can write,

$$\frac{bS^*(k_2-k_3)J^*}{u}=\frac{(a+k_1)(c+k_2+\alpha)J^*}{k_1}-\alpha J^*.$$

$$bS^*(k_2-k_3)k_1=(a+k_1)(c+k_2+\alpha)u-\alpha uk_1.$$

$$S^*=\frac{[(a+k_1)(c+k_2)+\alpha a]u}{k_1b(k_2-k_3)}.$$

From equation (3.1), (3.8), (3.7) and (3.9) we get,

$$V^*=\frac{d}{b}(R_0-1),\ J^*=\frac{ud(R_0-1)}{b(k_2-k_3)},$$

$$I^*=\frac{(c+k_2+\alpha)ud(R_0-1)}{b(k_2-k_3)k_1} \text{ and } E^*=\frac{k_3ud(R_0-1)}{bk_4(k_2-k_3)}.$$

Where $R_0 = \frac{\lambda}{dS^*} = \frac{\lambda k_1 b(k_2 - k_3)}{ud[(a+k_1)(c+k_2)+\alpha a]}$ is the basic reproduction number. Hence non trivial endemic equilibrium point $E_1(S^*, I^*, J^*V^*, E^*)$ exists if $R_0 > 1$.

Stability Analysis

In this section, we shall investigate the local geometric properties of the equilibria of the system (2.1).

Linearizing system (2.1) about the disease-free equilibrium E_0 gives the following Jacobian matrix;

$$M_0 = \begin{bmatrix} -d & 0 & 0 & -b\lambda/d & 0 \\ 0 & -(a+k_1) & \alpha & b\lambda/d & 0 \\ 0 & k_1 & -(c+k_2+\alpha) & 0 & 0 \\ 0 & 0 & (k_2-k_3) & -u & 0 \\ 0 & 0 & k_3 & 0 & -k_4 \end{bmatrix}$$

we obtain that two of the eigenvalues of M_0 is $-d$ and $-k_4$. The other three roots are determined by the following characteristic equation about M_0.

$$\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 = 0. \quad (4.1)$$

Where $p_1 = (u+a+k_1+c+k_2+\alpha)$,

$p_2 = (a+k_1)(c+k_2+u) + a\alpha$,

and $p_3 = u[(a+k_1)(c+k_2)+a\alpha] - \left(\frac{b\lambda k_1(k_2-k_3)}{d}\right)$. (4.2)

If $R_0 < 1$, then

$$u[(a+k_1)(c+k_2)+a\alpha] - \left(\frac{b\lambda k_1(k_2-k_3)}{d}\right) > 0. \quad (4.3)$$

Thus, from (4.3) we have $p_3 > 0$. Therefore, all roots of the equation (4.1) have negative real parts if and only if $R_0 < 1$. So, E_0 is locally asymptotically stable for $R_0 < 1$. If $R_0 = 1$, one eigenvalue of (4.1) is 0 and it is simple. If $R_0 > 1$, the characteristic equation (4.1) has positive eigenvalue. So, E_0 is thus unstable and we first establish the following result for E_0.

Theorem (4.4). If $R_0 < 1$, the disease-free equilibrium E_0 of system (2.1) is locally asymptotically stable. If $R_0 = 1$, E_0 is locally stable. If $R_0 > 1$, E_0 is a saddle point.

Also, we linearizing the system (2.1) about the endemic equilibrium E_1 gives the following Jacobin matrix;

$$M_1 = \begin{bmatrix} -d-bV^* & 0 & 0 & -bS^* & 0 \\ bV^* & -(a+k_1) & \alpha & bS^* & 0 \\ 0 & k_1 & -(c+k_2+\alpha) & 0 & 0 \\ 0 & 0 & (k_2-k_3) & -u & 0 \\ 0 & 0 & k_3 & 0 & -k_4 \end{bmatrix}$$

Now we can write characteristic equation about E_1 is

$$(\lambda+k_4)(\lambda^4 + q_1\lambda^3 + q_2\lambda^2 + q_3\lambda + q_4) = 0. \quad (4.5)$$

where $q_1 = (d+bV^*+a+k_1+c+k_2+\alpha+u)$,

$q_2 = u(d+bV^*+a+k_1+c+k_2+\alpha) + (a+k_1)(c+k_2) + a\alpha + (d+bV^*)(a+k_1+c+k_2+\alpha)$,

$q_3 = k_1(k_2-k_3)bS^* + u\{k_1\alpha + (d+bV^*)(a+k_1+c+k_2+\alpha) - (a+k_1)(c+k_2+\alpha)\} + (d+bV^*)k_1\alpha + (d+bV^*)(a+k_1)(c+k_2+\alpha)$,

$q_4 = u(d+bV^*)\{a(c+k_2+\alpha) + k_1(c+k_2)\} + (k_2-k_3)k_1bS^*d$,

for each $q_i > 0$, $i = 1,2,3,4$. Now by using Routh-Hurwitz Criteria as q_1, q_3 and q_4 are always positive we can write, $q_1q_2q_3 > q_3^2 + q_1^2q_4$.

Hence by this criteria we can say that endemic equilibrium E_1 is locally asymptotically stable if $R_0 > 1$.

Numerical Simulation

In this section, we present numerically simulation to explain the existence of equilibria of the model as well as the feasibility of stability conditions numerically for a set of parameter values.

To study the dynamical behavior of the model, numerical simulation of the system (2.1) is carried out by MATLAB 6.1, using the following parameter values;

$\lambda = 1.4, b = 0.02, d = 0.1, a = 0.9, k_1 = 0.9, \alpha = 0.04, c = 0.2, k_2 = 0.9, k_3 = 0.2, k_4 = 0.03, u = 0.06.$ (5.1)

with these values of parameters it can be checked that the endemic equilibrium E_1 exists and is given by, $S^* = 9.600$, $I^* = 0.2488$, $J^* = 0.1964$, $V^* = 2.2917$ and $E^* = 1.3095$.

The eigenvalues of the variational matrix corresponding to the endemic equilibrium of the model are,

$-1.73592, \quad -1.26799, \quad -0.120196, \quad -0.03, \quad -0.0202971.$

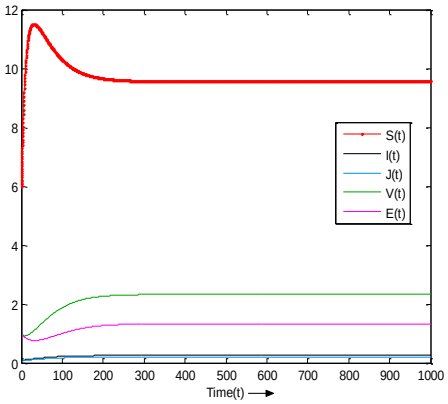

Figure (1)

The results of numerically simulation are displayed graphically in figure (1) variation of S, I, J, V and E with time for the consider parameters set (5.1). In figures (2-3) shows the effect of parameters b and k_2 on the symptomatic phase. It is noted from these figures that as the parameter values increases, the symptomatic phase increases. Also, in figure (4) shows the effect of parameter k_3 on the symptomatic phase. From this figure it is concluded that as the parameter value increases, the symptomatic phase decreases.

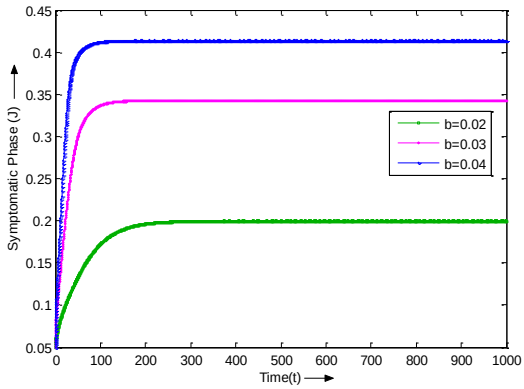

Figure (2)

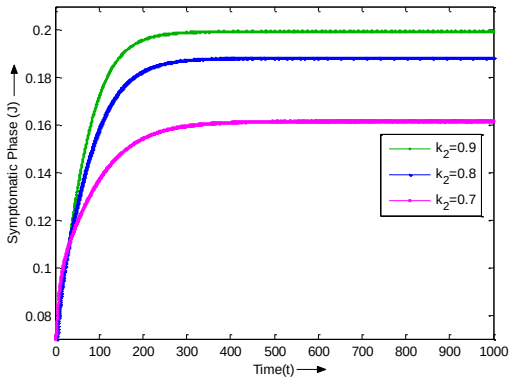

Figure (3)

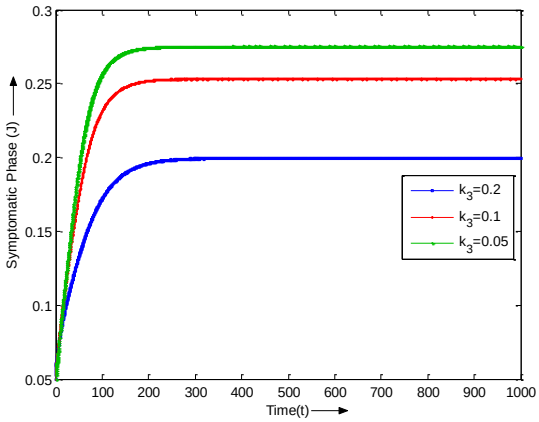

Figure (4)

Sensitivity Analysis

We now study sensitivity of the endemic equilibrium to changes in the value of the different parameters associated with the system. The results are shown in table 1. The purpose of this analysis is to identify the parameters, which are sensitive; estimation of these parameters in the field studies is to be done with sufficient care.

Sensitivity of the endemic equilibrium point to changes in the parameter values is described in Table 1. Regarding sensitivity of the endemic equilibrium level of uninfected cell $S^*(t)$ the following features are observed:

1. It is no sensitivity to changes in the value of parameters λ, d and k_4.
2. It is less sensitivity to changes in the value of parameters a, k_1, α, k_2, u and k_3.
3. It is highly sensitivity to changes in the value of parameters b and c.

The equilibrium level of asymptomatic phase $I^*(t)$ exhibits the following characteristics:

1. It is no sensitivity to changes in the value of parameter k_4.
2. It is highly sensitivity to change in the value of parameters $\lambda, d, a, k_1, k_2, b$ and u.
3. It is less sensitivity to changes in the value of parameters α, c and k_3.

The equilibrium level of symptomatic phase $J^*(t)$ exhibits the following characteristics:

1. It is no sensitivity to changes in the value of parameter k_4.
2. It is highly sensitivity to change in the value of parameters $\lambda, b, d, a, k_1, k_2$ and u.
3. It is less sensitivity to changes in the value of parameters α, c and k_3.

The equilibrium level of free virus $V^*(t)$ exhibits the following characteristics:

1. It is no sensitivity to changes in the value of parameter k_4.
2. It is highly sensitivity to change in the value of parameters $b, \lambda, d, a, k_1, k_2$ and u.
3. It is less sensitivity to changes in the value of parameters c, α and k_3.

The equilibrium level of cytotoxic cells $E^*(t)$ exhibits the following characteristics:

1. It is highly sensitivity to change in the value of parameters $\lambda, b, d, a, k_1, k_2, k_4$ and u.
2. It is less sensitivity to changes in the value of parameters α, c and k_3.

Since the spread of epidemic in the population is direct outcome of endemic symptomatic phase, determination of the equilibrium level of the symptomatic phase is the primary problem and more attention needs to be given to the estimation of those parameters to which symptomatic phase is more sensitive. In this context, more care should be taken to estimate the parameters $\lambda, b, d, a, k_1, k_2$ and u.

Conclusion

In this paper, we develop a mathematical model to explore the impact of treatment on the transmission dynamics of hepatitis B virus. According to papers [6-7], the period of infection is divided into the asymptomatic phase and the symptomatic phase. By all sorts of treatment methods, individuals with the symptomatic phase can be transformed into asymptomatic phase individuals. The model exhibits two equilibria, namely, the disease-free equilibrium (DFE) and the endemic equilibrium. The stability of these two equilibria is controlled by the basic reproduction number R_0. It is shown that if $R_0 < 1$, the disease-free equilibrium is locally asymptotically stable and $R_0 > 1$, the unique endemic equilibrium is locally asymptotically stable.

It is concluded from the computer simulation if the growth rate of pharmacological effect of the lamivadine to the free virus and rate constant describing the infection process increases, the symptomatic phase decreases and increases respectively. Also if, transfer rate constant from symptomatic phase to the free virus increases, the symptomatic phase increases. Sensitivity analysis of the endemic equilibrium to changes in the value of the different parameters associated with the system is done and it is found that parameters $\lambda, b, d, a, k_1, k_2$ and u are the most sensitive parameters to the infective period.

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Table 1. Percentage changes in the endemic equilibrium corresponding to different percentage changes in the parameters

S.No.	Parameter	Change(%)	Change(%) in S^*	Change(%) in I^*	Change(%) in J^*	Change(%) in V^*	Change(%) in E^*
1.	$\lambda = 1.4$	+50	0.00	159.0836	159.1140	159.0871	159.0988
		+20	0.00	63.6254	63.6456	63.6339	63.6426
		-20	0.00	-63.6254	-63.6456	-63.6383	-63.6349
		-50	0.00	-159.0836	-159.1140	-159.0915	-159.0912
2.	$b = 0.02$	+50	-33.3333	72.7491	72.7596	72.7233	72.7300
		+20	-16.667	36.3745	36.4052	36.3616	36.3650
		-20	25.000	-54.5418	-54.5315	-54.5446	-54.5475
		-50	100.00	-218.1672	-218.1771	-218.1786	-218.1825
3.	$d = 0.1$	+50	0.00	-109.0836	-109.1140	-109.0893	-109.0874
		+20	0.00	-43.6495	-43.6354	-43.6357	-43.6349
		-20	0.00	43.6495	43.6345	43.6357	43.6426
		-50	0.00	109.0836	109.1140	109.0893	109.0930
4.	$a = 0.9$	+50	25.4468	-64.5498	-64.5621	-64.5416	-64.5437
		+20	10.1781	-29.3810	-29.3788	-29.3973	-29.3928
		-20	-10.1781	36.0530	36.0997	36.0562	36.0595
		-50	-25.4468	108.6012	108.6558	108.5962	108.6063
5.	$k_1 = 0.9$	+50	-16.9593	10.0080	65.0203	65.0041	65.0095
		+20	-8.4822	7.9180	29.5315	29.4890	29.4921
		-20	12.7260	-19.8954	-35.8961	-35.9165	-35.9144
		-50	50.8927	-114.6302	-105.7877	-107.3177	-107.3157
6.	$\alpha = 0.04$	+50	0.8927	-1.1254	-2.8004	-2.8188	-2.8102
		+20	0.3572	-0.4421	-1.12016	-1.1345	-1.1302
		-20	-0.3572	0.4421	1.1710	1.1388	1.1454
		-50	-0.8927	1.0852	2.9022	2.8668	2.8713
7.	$c = 0.2$	+50	8.9281	-19.5739	-26.0692	-26.0810	-26.0786
		+20	3.5718	-7.8376	-10.9470	-10.9743	-10.9736
		-20	-3.5718	7.8778	11.8126	11.7816	11.7831
		-50	-8.9281	19.6945	31.2118	31.1908	31.1951
8.	$k_2 = 0.9$	+50	-14.6739	31.3504	-5.8044	54.7148	-5.8190
		+20	-7.6708	16.4389	0.61099	26.4301	0.5727
		-20	12.9812	-28.0948	-14.5621	-36.5580	-14.5933
		-50	67.500	-147.8795	-179.0224	-128.2235	-179.0225
9.	$k_4 = 0.03$	+50	0.00	0.00	0.00	0.00	-33.3333
		+20	0.00	0.00	0.00	0.00	-16.6628
		-20	0.00	0.00	0.00	0.00	25.0019
		-50	0.00	0.00	0.00	0.00	100.00
10.	$u = 0.06$	+50	50.00	-109.0836	-109.1140	-106.0610	-109.0874
		+20	20.00	-43.6495	-43.6354	-53.0305	-43.6349
		-20	-20.00	43.6495	43.6354	79.5435	43.6426
		-50	-50.00	109.0836	109.1140	318.1742	109.0950
11.	$k_3 = 0.2$	+50	16.667	-36.3745	-36.3543	-45.4553	-4.5437
		+20	6.0604	-13.2234	-13.1873	-18.1830	4.1313
		-20	-5.4052	11.8167	11.8126	18.1786	-10.5612
		-50	-12.50	27.2909	27.2912	45.4509	-36.3650