International Journal of Recent Technology and Engineering (IJRTE)
ISSN: 2277-3878, Volume-8 Issue-5, January 2020

Dynamics of a Multi-Stage Epidemic Model with and without Treatment

Smriti Agrawal, Akanksha Dubey, Nimisha Mishra, Joydip Dhar

Abstract*: In this paper, a non-linear mathematical model is proposed with the thought of treatment to depict the spread of infectious illness and assessed with three contamination stages. We talk about the dynamical behaviour and analytical study of the framework for the mathematical model which shows that it has two non-negative equilibrium points i.e., disease-free equilibrium (DFE) and interior(endemic) equilibrium. The outcomes show that the dynamical behaviour of the model is totally determined by the basic reproduction number. For the basic reproduction number $R_0 < 1$, the disease-free equilibrium is locally as well as globally asymptotically stable under a particular parameter set. In case $R_0 > 1$, the model at the interior equilibrium is locally as well as globally asymptotically stable. Finally, numerical solutions of the model corroborate the analytical results and facilitate a sensitivity analysis of the model parameters.

Keywords: Epidemic model, Three stages of treatment, Basic reproduction number, Global stability, Local stability, Sensitivity Analysis.

I. INTRODUCTION

Epidemiology, the study of disease transmission is viewed as an essential investigation of general wellbeing. It is a strategy for causal thinking dependent on creating and testing theories relating to the event and anticipation of grimness and mortality. Epidemiology is the investigation of the dispersion and determinants of health-related states or occasions in indicated populations and the utilization of this examination to the control of medical issues. At first, the terms were connected to make reference to just examination of irresistible sicknesses. In analyzing the allocation of illness, it is important to differentiate between domination and occurrence.

A mathematical model is an imaginary microworld comprising of substances carrying on as indicated by exactly determined standards. Mathematics gives us a language for defining these principles of conduct in a concise and unambiguous way, in this manner driving and helping us to clearly express our presumptions. In this way, inside the setting of the model, we can make forecasts of things to come of our fictional universe and furthermore ponder how these expectations change as the tenets administering the elements depicted by the models are varied. Numerical demonstrating assumes a critical job to comprehend the study of disease transmission of an irresistible ailment considering the primary components administering the advancement of an illness, for example, transmission and recuperation rate. Mathematical models are being utilized to foresee how the infections will spread over some undefined time frame. As of late, numerous mathematicians have been made to create realistic mathematical models for exploring the transmission dynamics of irresistible sicknesses, and the asymptotic practices of these epidemic models are considered [1, 2, 3, 4]. Many mathematical models have been proposed to study the infectious illness (which spread individual to individual), for example, Swine influenza, smallpox, conjunctivitis and HIV/AIDS and so on [5, 6]. Donahue et al. given some in vitro exploratory proof of the stage-subordinate hindrance of HIV-1 by antiretroviral drugs. They found in single-round contaminations in cell culture, the expansion of an integrase inhibitor at different occasions after disease brought about viral restraint equivalent to or more prominent than that accomplished by the expansion of an RT inhibitor [5, 7].

One of the fundamental issue in the investigation of the conduct of the pandemic model in the analysis of steady states and their stability [8]. At the point when the number of inhabitants in every compartment does not show any structure (as age, space and so forth.) and no defer procedure is considered, the time advancement of such compartments is portrayed by ordinary differential conditions (ODEs) [9]. In the research literature, it was much of the time expected that the ailment brooding is unimportant [1, 2, 3, 10, 11, 12].

In this paper, we proposed an epidemic model of disease dynamics with three phases of treatment. For this, first, we get equilibrium point and afterwards determine the basic reproduction number and the stability condition for disease-free equilibrium and endemic equilibrium.

Manuscript received on January 02, 2020.
Revised Manuscript received on January 15, 2020.
Manuscript published on January 30, 2020.
* Correspondence Author
Smriti Agrawal, Amity School Of Applied Sciences, Amity University, Lucknow, Uttar Pradesh 226028, India. E-mail: smriti.agrawal3@student.amity.edu.
Akanksha Dubey, Amity School Of Applied Sciences, Amity University, Lucknow, Uttar Pradesh 226028, India. E-mail: akankshadubey061@gmail.com.
Nimisha Mishra*, Amity School Of Applied Sciences, Amity University, Lucknow, Uttar Pradesh 226028, India. E-mail: nmishra1@lko.amity.edu.
Joydip Dhar, ABV - Indian Institute of Information Technology and Management, Gwalior, Madhya Pradesh 474010, India. E-mail: jdhar@iiitm.ac.in

We likewise examine the impact of treatment on disease dynamics for each stage. At the point when the treatment is 100 per cent and not 100 per cent powerful individually, we plot the graph for each stage. We get the slope of stages for all cases. As in [5, 6, 13, 14, 15].

II. FORMULATION OF MATHEMATICAL MODEL

In this section, we formulate dynamics of a disease model with three stages. The total population is divided into five subclasses i.e. susceptible S(t), first infected individual I_1(t), second infected individual I_2(t), third infected individual I_3(t) and recovered R(t). The total population is denoted by N(t). We assume that the total population is constant. The schematic diagram is given in figure(1).

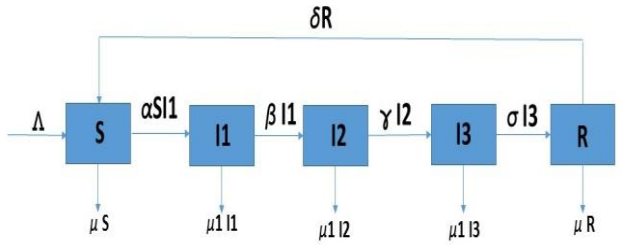

Figure 1: Schematic diagram of disease model with three stages.

The model is given as follows:

$$\frac{dS}{dt} = \Lambda - \alpha S I_1 - \mu S + \delta R, \quad (1)$$

$$\frac{dI_1}{dt} = \alpha S I_1 - \mu_1 I_1 - \beta I_1, \quad (2)$$

$$\frac{dI_2}{dt} = \beta I_1 - \mu_1 I_2 - \gamma I_2, \quad (3)$$

$$\frac{dI_3}{dt} = \gamma I_2 - \mu_1 I_3 - \sigma I_3, \quad (4)$$

$$\frac{dR}{dt} = \sigma I_3 - \mu R - \delta R. \quad (5)$$

with initial conditions:

$$S(0) = S^0 > 0,\ I_1(0) = I_1^0 > 0,\ I_2(0) = I_2^0 > 0,\ I_3(0) = I_3^0 > 0,\ R(0) = R^0 > 0;$$

where $N = S + I_1 + I_2 + I_3 + R$, is the total population at time t. The descriptions of all parameters are summarized in Table 1.

Table 1: Definitions of parameters for the system (1)-(5)

Parameter	Description
Λ	Growth Rate
α	Infection Rate
μ	Death rate of uninfected individuals
μ_1	Death rate of infected individuals
β	Transition rate of infected class from first stage to second stage
γ	Transition rate of infected class from second stage to third stage
δ	Transfer rate from recovered to susceptible individuals
σ	Recovery rate for third infection class

III. ANALYSIS OF THE MODEL

In this part, we have analyzed boundedness, R_0 the basic reproduction number, equilibrium points for all the feasible states, local and global stability for both the states (disease-free and endemic).

A. Boundedness

Since the total number of population is N. Therefore

$$N = S + I_1 + I_2 + I_3 + R,$$

The above equation can be write as,

$$\Rightarrow \frac{dN}{dt} = \Lambda - \mu(S + R) - \mu_1(I_1 + I_2 + I_3). \quad (6)$$

Let $x = min(\mu, \mu_1)$,

$$\frac{dN}{dt} \leq \Lambda - xN. \quad (7)$$

If $t \to \infty$ then $0 \leq N \leq \frac{\Lambda}{x}$.

Hence total dynamics of the system is bounded.

In the following sections, we will study the dynamical behavior of the system (1)-(5).

B. Disease-free Equilibrium

The system (1)-(5) always has the disease free equilibrium, $E_0 = (S_0, 0,0,0,0)$ where, $S_0 = \frac{\Lambda}{\mu}$ which presents the level of susceptible population in the absence of infection.

C. Basic Reproduction Number

The basic reproduction number is defined as an average number of secondary infection generates when a single infection is introduced into a completely susceptible population. The basic reproduction number, sometimes called basic reproductive rate or basic reproductive ratio, is one of the most useful threshold parameters which mathematically characterizes the spreading of infectious diseases. This metric is useful because it helps to determine whether or not an infectious disease will spread through the population. We calculate the basic reproduction number similarly as in [6] Let $y = (E,\ I_1, I_2, I_3)$, then from model (1)-(5), it follows:

$$\frac{dy}{dt} = F - V,$$

where,

$$F = \begin{bmatrix} \alpha S_0 I_1 \\ 0 \\ 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} (\mu_1 + \beta) I_1 \\ -\beta I_1 + (\mu_1 + \gamma) I_2 \\ -\gamma I_2 + (\mu_1 + \sigma) I_3 \end{bmatrix}.$$

we get,

$$F = Jacobian\ of\ F\ at\ DFE = \begin{bmatrix} g\alpha S^0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$and\ V = Jacobian\ of\ V\ at\ DFE = \begin{bmatrix} (\mu_1 + \beta) & 0 & 0 \\ -\beta & (\mu_1 + \gamma) & 0 \\ 0 & -\gamma & (\mu_1 + \sigma) \end{bmatrix}.$$

Hence, next generation matrix for the model is

$$K = \mathrm{FV}^{-1} = \begin{bmatrix} \frac{\alpha S^0}{(\mu_1+\beta)} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Again, the spectral radius R_0 of the matrix $K = \mathrm{FV}^{-1}$, is the basic reproduction number of the model, i.e., $R_0 = \rho(\mathrm{FV}^{-1})$, hence

$$R_0 = \frac{\alpha S^0}{(\mu_1+\beta)} = \frac{\Lambda}{\mu}\frac{\alpha}{(\mu_1+\beta)}. \quad (8)$$

D. Interior Equilibrium Points

The system (1)-(5) also has an interior equilibrium called endemic equilibrium given by.

Where,

$$S^* = \frac{\mu R_0}{\Lambda}$$
$$I_2^* = \frac{\beta}{(\mu_1+\gamma)} I_1^*,$$
$$I_3^* = \frac{\beta\gamma}{(\mu_1+\gamma)(\mu_1+\sigma)} I_1^*,$$
$$R^* = \frac{\beta\gamma\sigma}{(\mu_1+\gamma)(\mu_1+\sigma)(\mu+\delta)} I_1^*,$$
$$I_1^* = \frac{(\Lambda S_0)-(\mu R_0)}{(\alpha R_0)-\frac{\delta\sigma\gamma\beta S_0}{(\mu_1+\gamma)(\mu_1+\sigma)(\mu+\delta)}}.$$

where, $S_0 = \frac{\Lambda}{\mu}$ and $R_0 = \frac{\Lambda\alpha}{\mu(\mu_1+\beta)}$

The endemic equilibrium point exists iff $R_0 > 1$.

E. Local Stability Analysis

In this section, we explore the local asymptotic stability of disease-free and endemic equilibrium. Since the rate of change of total population size, $N(t)$ satisfies the equation $\frac{dN}{dt} = \Lambda - \mu N$ (where, Λ is growth rate and μ is natural death rate) and $N(t) \to \frac{\Lambda}{\mu}$, as $t \to \infty$.We can obtain analytical results by considering the limiting system of (1)-(5) in which the total population is assumed to be constant $N = N^0 = \frac{\Lambda}{\mu}$.

Then, the reduced limiting dynamical system is given by

$$\frac{dS}{dt} = \Lambda(1+\frac{\delta}{\mu}) - \alpha S I_1 - (\mu+\delta)S - \delta(I_1+I_2+I_3), \quad (9)$$
$$\frac{dI_1}{dt} = \alpha S I_1 - \mu_1 I_1 - \beta I_1, \quad (10)$$
$$\frac{dI_2}{dt} = \beta I_1 - \mu_1 I_2 - \gamma I_2, \quad (11)$$
$$\frac{dI_3}{dt} = \gamma I_2 - \mu_1 I_3 - \sigma I_3. \quad (12)$$

With initial conditions:

$S(0) = S^0 > 0,\ I_1(0) = I_1^0 > 0,\ I_2(0) = I_2^0 > 0,\ I_3(0) = I_3^0 > 0.$

The local stability for both the equilibria are established as follows,

a) For Disease-free Equilibrium

The variational matrix at disease free equilibrium point is given by

$$J_0 = \begin{bmatrix} -(\mu+\delta) & -(\alpha S^0+\delta) & -\delta & -\delta \\ 0 & (\alpha S^0-\mu_1-\beta) & 0 & 0 \\ 0 & \beta & -(\mu_1+\gamma) & 0 \\ 0 & 0 & \gamma & -(\mu_1+\sigma) \end{bmatrix}.$$

The characteristic equation of J_0 is given by

$$-(\lambda_1+(\mu+\delta))[((\alpha S^0-\mu_1-\beta)-\lambda_2)(-(\mu_1+\gamma)-\lambda_3)(-(\mu_1+\sigma)-\lambda_4)] = 0.$$

i.e.

$\lambda_1 = -(\mu+\delta),\ \lambda_3 = -(\mu_1+\gamma),\ \lambda_4 = -(\mu_1+\sigma),$ $\lambda_2 = (\alpha S^0-\mu_1-\beta)$ (which is under condition).

Therefore, $\alpha S^0-\mu_1-\beta < 0$ and we also have $R_0 = \frac{\alpha S_0}{\mu(\mu_1+\beta)}$ i.e, $R_0 < 1$. Hence, if $R_0 < 1$, then the disease-free equilibrium is locally asymptotically stable, and if $R_0 > 1$, then it is unstable.

b) For Endemic Equilibrium

The variational matrix at endemic equilibrium point is given by

$$J = \begin{bmatrix} -\alpha I_1^* - (\mu+\delta) - \lambda_1 & -(\alpha S^*+\delta) & -\delta & -\delta \\ \alpha I_1^* & -\lambda_2 & 0 & 0 \\ 0 & \beta & -(\mu_1+\gamma)-\lambda_3 & 0 \\ 0 & 0 & \gamma & -(\mu_1+\sigma)-\lambda_4 \end{bmatrix}$$

The characteristic equation of J is given by $P(\lambda) = \lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0,$

Where,

$$A_1 = ((\alpha I_1^* + \mu + \delta) + (2\mu_1 + \gamma + \sigma)),$$

$$A_2 = ((2\mu_1+\gamma+\sigma) + \mu_1(\mu_1+\gamma+\sigma) + \gamma\sigma + \alpha I_1^*(\alpha S^* + \delta)),$$

$$A_3 = (\mu_1(\mu_1+\gamma+\sigma)(\alpha I_1^* + \mu + \delta) + \gamma\sigma(\alpha I_1^* + \mu + \delta) + \alpha I_1^*(\alpha S^* + \delta)(2\mu_1+\gamma+\sigma) + \beta\alpha\delta I_1^*),$$

$$A_4 = (\alpha I_1^*(\alpha S^* + \delta)\mu_1(\mu_1+\gamma+\sigma) + \gamma\sigma\alpha I_1^*(\alpha S^* + \delta) + \beta\alpha\delta I_1^*(\mu_1+\gamma+\sigma)).$$

Hence, by Routh-Hurwitz criterion [16] the endemic equilibrium point $\bar{E}$ is locally asymptotically stable, Otherwise it is unstable

F. Global Stability Analysis

a) For Disease-free Equilibrium

Let $X = (S)$ and $Z = (E,\ I_1, I_2, I_3)$, and

$Q_0 = (X^0,\ 0), where \quad X^0 = \frac{\Lambda}{\mu}.$

(Since, $\frac{dX}{dt} = F(X,\ Z), \frac{dZ}{dt} = G(X,\ Z),\quad G(X,\ 0) = 0.$

Therefore,

$$\frac{dX}{dt} = F(X,\ Z) = \Lambda(1+\frac{\delta}{\mu}) - \alpha S I_1 - (\mu+\delta)S - \delta(I_1 + I_2 + I_3),$$

At $S = S^0,\ G(X,\ 0) = 0$ and

$$\frac{dX}{dt} = F(X,\ 0) = \Lambda(1+\frac{\delta}{\mu}) - (\mu+\delta)X.$$

As $t \to \infty$, $X \to X^0$. Hence, $X = X^0 (= S^0)$ is g.a.s.

Now,

$$G(X,\ Z) = \begin{bmatrix} -(\alpha S^0-\mu_1-\beta) & 0 & 0 \\ \beta & -(\mu_1+\gamma) & 0 \\ 0 & -\gamma & -(\mu_1+\sigma) \end{bmatrix}\begin{bmatrix} I_1 \\ I_2 \\ I_3 \end{bmatrix},$$

$$\begin{bmatrix} \alpha S^0 I_1 - \alpha S I_1 \\ 0 \\ 0 \end{bmatrix} = BZ -$$

Where,

$$B = \begin{bmatrix} -(\alpha S^0 - \mu_1 - \beta) & 0 & 0 \\ \beta & -(\mu_1 + \gamma) & 0 \\ 0 & -\gamma & -(\mu_1 + \sigma) \end{bmatrix} \quad and \quad \hat{G}(X, Z) = \begin{bmatrix} \alpha S^0 I_1 - \alpha S I_1 \\ 0 \\ 0 \end{bmatrix}.$$

Since $S^0 \geq S$, we have $\alpha S^0 I_1 \geq \alpha S I_1$. Hence $\hat{G}(X, Z) \geq 0$, Clearly, B is an M-matrix, hence above conditions (H1) and (H2) are satisfied and the disease-free equilibrium E_0 is globally asymptotically stable, if $R_0 < 1$.

b) For Endemic Equilibrium

To prove this result, the jacobian matrix'J' for the reduced system (9-12) is given below:

$$J = \begin{bmatrix} -\alpha I_1^* - (\mu + \delta) & -(\alpha S^* + \delta) & -\delta & -\delta \\ \alpha I_1^* & 0 & 0 & 0 \\ 0 & \beta & -(\mu_1 + \gamma) & 0 \\ 0 & 0 & \gamma & -(\mu_1 + \sigma) \end{bmatrix}.$$

Now the second additive matrix of 'J'is given by

$$J^{[2]} = \begin{bmatrix} J_{11}^{[2]} & 0 & 0 & \delta & \delta & 0 \\ \beta & J_{22}^{[2]} & 0 & -(\alpha S + \delta) & 0 & \delta \\ 0 & \gamma & J_{33}^{[2]} & 0 & -(\alpha S + \delta) & -\delta \\ 0 & \alpha I_1 & 0 & J_{44}^{[2]} & 0 & 0 \\ 0 & 0 & \alpha I_1 & \gamma & J_{55}^{[2]} & 0 \\ 0 & 0 & 0 & 0 & \beta & J_{66}^{[2]} \end{bmatrix}$$

Where,

$J_{11}^{[2]} = -(\alpha I_1 + \mu + \delta), J_{22}^{[2]} = -(\alpha I_1 + \mu + \delta + \mu_1 + \gamma),$

$J_{33}^{[2]} = -(\alpha I_1 + \mu + \delta + \mu_1 + \sigma), J_{44}^{[2]} = -(\mu_1 + \gamma),$

$J_{55}^{[2]} = -(\mu_1 + \sigma), J_{66}^{[2]} = -(2\mu_1 + \gamma + \sigma).$

We consider the function,

$$P = P(I_1, I_2, I_3) = diag\left(\frac{1}{I_1}, \frac{1}{I_1}, \frac{1}{I_1}, \frac{1}{I_2}, \frac{1}{I_3}, \frac{1}{I_3}\right)$$

So that

$$P_f P^{-1} = diag\left(\frac{\dot{I}_1}{I_1}, \frac{\dot{I}_1}{I_1}, \frac{\dot{I}_1}{I_1}, \frac{\dot{I}_2}{I_2}, \frac{\dot{I}_3}{I_3}, \frac{\dot{I}_3}{I_3}\right).$$

Then,

$B = P_f P^{-1} + P J^{[2]} P^{-1}$

$$B = \begin{bmatrix} J_{11}^{[2]} \frac{\dot{I}_1}{I_1} & 0 & 0 & \delta \frac{I_2}{I_1} & \delta \frac{I_3}{I_1} & 0 \\ \beta & J_{22}^{[2]} \frac{\dot{I}_1}{I_1} & 0 & -(\alpha S + \delta) \frac{I_2}{I_1} & 0 & \delta \frac{I_3}{I_1} \\ 0 & \gamma & J_{33}^{[2]} \frac{\dot{I}_1}{I_1} & 0 & -(\alpha S + \delta) \frac{I_3}{I_1} & -\delta \frac{I_3}{I_1} \\ 0 & \alpha I_1 \frac{I_1}{I_2} & 0 & J_{44}^{[2]} \frac{\dot{I}_2}{I_2} & 0 & 0 \\ 0 & 0 & \alpha I_1 \frac{I_1}{I_3} & \gamma \frac{I_2}{I_3} & J_{55}^{[2]} \frac{\dot{I}_3}{I_3} & 0 \\ 0 & 0 & 0 & 0 & \beta & J_{66}^{[2]} \frac{\dot{I}_3}{I_3} \end{bmatrix}$$

Let,

$$B = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix}$$

Where,

$$B_{11} = \begin{bmatrix} -(\alpha I_1 + \mu + \delta) \frac{\dot{I}_1}{I_1} & 0 & 0 \\ \beta & -(\alpha I_1 + \mu + \delta + \mu_1 + \gamma) \frac{\dot{I}_1}{I_1} & 0 \\ 0 & \gamma & -(\alpha I_1 + \mu + \delta + \mu_1 + \sigma) \frac{\dot{I}_1}{I_1} \end{bmatrix}$$

$$B_{12} = \begin{bmatrix} \delta \frac{I_2}{I_1} & \delta \frac{I_2}{I_1} & 0 \\ -(\alpha S + \delta) \frac{I_2}{I_1} & 0 & \delta \frac{I_3}{I_1} \\ 0 & -(\alpha S + \delta) \frac{I_3}{I_1} & -\delta \frac{I_3}{I_1} \end{bmatrix}$$

$$B_{21} = \begin{bmatrix} 0 & \alpha I_1 \frac{I_1}{I_2} & 0 \\ 0 & 0 & \alpha I_1 \frac{I_1}{I_3} \\ 0 & 0 & 0 \end{bmatrix};$$

$$B_{22} = \begin{bmatrix} -(\mu_1 + \gamma) \frac{\dot{I}_1}{I_1} & 0 & 0 \\ \gamma \frac{I_2}{I_3} & -(\mu_1 + \sigma) \frac{\dot{I}_3}{I_3} & 0 \\ 0 & \beta & -(2\mu_1 + \gamma + \sigma) \frac{\dot{I}_3}{I_3} \end{bmatrix}.$$

Now consider the norm in R^3 as, $|(u_1, u_2, u_3)| = max\{|u_1|, |u_2| + |u_3|\}$, where (u_1, u_2, u_3) denotes vector in R^3 and denote by μ the Lozinskiĭ measure [17] with respect to this norm. It follows: $\mu(B) \leq \sup\{g_1, g_2\} = \sup\{|B_{11}| + |B_{12}|, |B_{22}| + |B_{21}|\}$, where $|B_{21}|, |B_{12}|$ are matrix norms with respect to the L^1 vector norm and μ_1 denotes the Lozinskiĭ measure [17] with respect to the L^1 norm.

Then, $g_1 = |B_{11}| + |B_{12}|$

$= (\alpha I_1 + \mu + \delta)(\alpha I_1 + \mu + \delta + \mu_1 + \gamma)(\alpha I_1 + \mu + \delta + \mu_1 + \sigma)$

$((\beta + \mu_1)^3(1 - R_0)),$

Again, $g_2 = |B_{21}| + |B_{22}|$

$= (\mu_1 + \gamma)((\mu_1 + \gamma) - \beta \frac{I_1}{I_2})(\mu_1 + \sigma)(\gamma \frac{I_2}{I_3}) - (\mu_1 + \sigma))^2(2\mu_1 + \gamma + \sigma),$

$\mu(B) \leq \sup\{g_1, g_2\} = (\alpha I_1 + \mu + \delta)(\alpha I_1 + \mu + \delta + \mu + \gamma_1)(\alpha I_1 + \mu + \delta + \mu_1 + \sigma)((\beta + \mu_1)^3(1 - R_0)).$

Therefore $\mu(B) < 0$ iff $R_0 > 1$. Hence, if $R_0 > 1$, the endemic equilibrium is globally asymptotically stable.

IV. NUMERICAL SIMULATION

In this Section, we provide numerical simulations to illustrate previously established results [6] with the parameter values shown in Table 2.

Table 2: Parameter values used in the simulation for the system (1)-(5)

Parameter	Value	Dimension
Growth rate of susceptible (Λ)	variable	days
Death Rate of uninfected individuals ($1/\mu$)	0.002	days

Death Rate of infected individuals(μ_1)	0.001	Days
Transition rate of infected class from first stage to second stage(β)	0.1	days
Transition rate of infected class from second stage to third stage(γ)	0.3	days
Recovery rate for third infection class(σ)	0.2	days
Transfer rate from recovered to susceptible individuals (δ)	0.1	days
Infection rate (α)	variable	days

The set of parameter values which is given in table(2), we observe the behavior of the system for different values of the growth rate Λ and infection rateα Figures (2) and (3).

(a) For growth rate $\Lambda = 1000$ and infection rate$\alpha = 0.9 \times 10^{-7}$. We obtain the effective reproduction number $R_0 = 0.88 < 1$. Therefore,the disease free equilibrium $(1.0 \times 10^{-9}, 0,0,0)$ is globally asymptotically stable.

(b) For growth rate $\Lambda = 1200$ and infection rate $\alpha = 0.2 \times 10^{-6}$. We obtain the effective reproduction number $R_0 = 2.53 > 1$. Therefore,the endemic equilibrium $(510000,245137,81171.3,120551)$ is globally asymptotically stable.

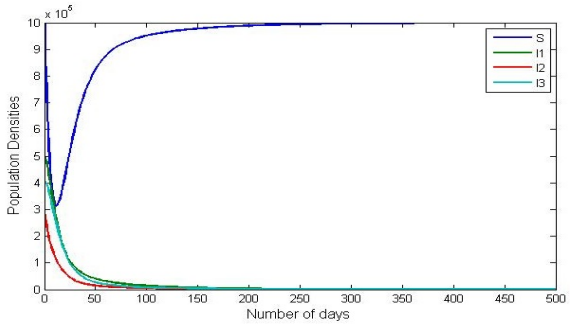

Figure 2: population densities at infection rate $\alpha = 0.9 \times 10^{-7}$and growth rate $\Lambda = 1000$.

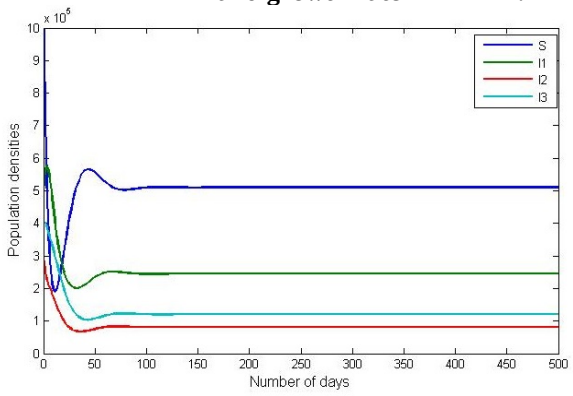

Figure 3: population densities at infection rate $\alpha = 0.2 \times 10^{-6}$and growth rate $\Lambda = 1200$.

V. SENSITIVITY ANALYSIS

In this section, sensitivity analysis of the effective reproduction number has been carried out using the normalized forward sensitivity index. The effective reproduction number estimates the average number of secondary cases per infectious case in a population made up of both susceptible and non-susceptible hosts. It can be thought of as the number of secondary infections produced by a typical infective. Sensitivity analysis tells the importance of each parameter in the infectious disease dynamics. Since there are usually errors in data collection and presumed parameter values, sensitivity analysis is commonly used to determine the robustness of model predictions on the parameter values. It is used to discover parameters that have a high impact on effective reproduction number R_0. Disease transmission is directly related to the effective reproduction number, and the disease prevalence is directly related to the endemic equilibrium point $\bar{E}$, specifically to the magnitude of I_1^*. Since we have the explicit expressions for R_0, here we derive analytical expressions for its sensitivity index of R_0 on each parameter. The effective reproduction number R_V is a function of eight parameters $\Lambda, \mu, \beta, \alpha, \gamma, \sigma, \delta$ and μ_1. The normalized sensitivity indices for eight parameters are obtained as

$$\Upsilon_{\Lambda}^{R_0} = \frac{\partial R_0}{\partial \Lambda}\frac{\Lambda}{R_0} = 1; \quad \Upsilon_{\mu}^{R_0} = \frac{\partial R_0}{\partial \mu}\frac{\mu}{R_0} = -1;$$

$$\Upsilon_{\beta}^{R_0} = \frac{\partial R_0}{\partial \beta}\frac{\beta}{R_0} = -\frac{\beta}{\mu_1 + \beta}; \quad \Upsilon_{\alpha}^{R_0} = \frac{\partial R_0}{\partial \alpha}\frac{\alpha}{R_0} = 1;$$

$$\Upsilon_{\gamma}^{R_0} = \frac{\partial R_0}{\partial \gamma}\frac{\gamma}{R_0} = 0; \quad \Upsilon_{\sigma}^{R_0} = \frac{\partial R_0}{\partial \sigma}\frac{\sigma}{R_0} = 0;$$

$$\Upsilon_{\delta}^{R_0} = \frac{\partial R_0}{\partial \delta}\frac{\delta}{R_0} = 0; \quad \Upsilon_{\mu_1}^{R_0} = \frac{\partial R_0}{\partial \mu_1}\frac{\mu_1}{R_V} = -\frac{\mu_1}{\mu_1 + \beta};$$

Using parametric values of Table (2), the sensitivity indices of effective reproduction number R_0 for eight different parameters are shown in Table (3):

Table 3: The sensitivity indices, $\Upsilon_{y_j}^{R_0} = \frac{\partial R_0}{\partial y_j} \times \frac{y_j}{R_0}$, of the effective reproduction number R_V to the parameters, y_j for parameter values given in Table (2) at $\alpha = 0.2 \times 10^{-6}$.

Parameter (y_j)	Sensitivity index of R_0 w.r.t. y_j ($\Upsilon_{y_j}^{R_0}$)
Λ	1.000
μ	-1.000
β	-0.980392
α	1.000
δ	+0.000
σ	0.000
γ	0.000
μ_1	-0.0196078

By using parametric values of Table(2), the sensitivity indices of reproduction number for eight different parameters are shown in Table(3). We observe that Λ and α are highly sensitive, μ and β are moderately sensitive and μ_1 is less sensitive to effective reproduction number.

Similarly, we can calculate the sensitivity indices of endemic equilibrium point R_0 for eight different parameters using parametric values of Table(2).

VI. DYNAMICS OF A DISEASE MODEL IN THREE STAGE WITH TREATMENT

In the previous section, we study the dynamics of a disease model in three stages without treatment. Now, we will add some treatments in this model. The analysis is performed with the assumption that drug treatment is 100 percent effective and the target cell count remains unchanged during treatment. [5]

A. Mathematical formulation of the model

Therefore, the model including treatment from different drugs classes is given as follows:

$$\frac{dS}{dt} = \Lambda - \alpha S(1-\xi_1)I_1 - \mu S + \delta R, \quad (13)$$

$$\frac{dI_1}{dt} = \alpha S(1-\xi_1)I_1 - \mu_1 I_1 - \beta(1-\xi_2)I_1, \quad (14)$$

$$\frac{dI_2}{dt} = \beta(1-\xi_2)I_1 - \mu_1 I_2 - \gamma(1-\xi_3)I_2, \quad (15)$$

$$\frac{dI_3}{dt} = \gamma(1-\xi_3)I_2 - \mu_1 I_3 - \sigma(1-\xi_4)I_3, \quad (16)$$

$$\frac{dR}{dt} = \sigma(1-\xi_4)I_3 - \mu R - \delta R. \quad (17)$$

with initial conditions:

$$S(0) = S^0 > 0,\ I_1(0) = I_1^0 > 0,\ I_2(0) = I_2^0 > 0,\ I_3(0) = I_3^0 > 0,\ R(0) = R^0 > 0;$$

where $N = S + I_1 + I_2 + I_3 + R$, is the total population at time t. The descriptions of all parameters are summarized in Table (4).

Table 4: Definitions of parameters for the system (13)-(17)

Parameter	Description
Λ	Growth Rate
α	Infection Rate
μ	Death rate of uninfected individuals
μ_1	Death rate of infected individuals
β	Transition rate of infected class from first stage to second stage
γ	Transition rate of infected class from second stage to third stage
δ	Transfer rate from recovered to susceptible individuals
σ	Recovery rate for third infection class
ξ_1	The effect of treatment in first stage
ξ_2	The effect of treatment in second stage
ξ_3	The effect of treatment in third stage

a) The Basic Reproduction Number

We derive the basic reproductive number using the spectral radius of the next generator operator of system (13)-(17) as follows: The system (13)-(17) has a disease free equilibrium $E_0 = (S^0, 0,0,0)$ where, $S^0 = \frac{\Lambda}{\mu}$. Let $x = (E,\ I_1, I_2, I_3)$, then from model(13)-(17), it follows:

$$\frac{dx}{dt} = F - V,$$

Where,

$$F = \begin{bmatrix} \alpha S_0(1-\xi_1)I_1 \\ 0 \\ 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} (\mu_1 + (1-\xi_2)\beta)I_1 \\ -\beta(1-\xi_2)I_1 + (\mu_1 + (1-\xi_3)\gamma)I_2 \\ -\gamma(1-\xi_3)I_2 + (\mu_1 + (1-\xi_4)\sigma)I_3 \end{bmatrix}.$$

We get,

$$F = Jacobian\ of\ F\ at\ DFE = \begin{bmatrix} (1-\xi_1)\alpha S^0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$and\ V = Jacobian\ of\ V\ at\ DFE = \begin{bmatrix} (\mu_1 + (1-\xi_2)\beta) & 0 & 0 \\ -(1-\xi_2)\beta & (\mu_1 + (1-\xi_3)\gamma) & 0 \\ 0 & -(1-\xi_3)\gamma & (\mu_1 + (1-\xi_4)\sigma) \end{bmatrix}.$$

Hence, next generation matrix for the model is

$$K = \mathrm{FV}^{-1} = \begin{bmatrix} \frac{\alpha(1-\xi_1)S^0}{(\mu_1+\beta)} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Again, the spectral radius R_0 of the matrix $K = \mathrm{FV}^{-1}$, is the effective reproduction number of the model, i.e., $R_0 = \rho(\mathrm{FV}^{-1})$. Hence,

$$R_0 = \frac{\alpha(1-\xi_1)S^0}{(\mu_1+\beta)} = \frac{\Lambda}{\mu}\frac{\alpha(1-\xi_1)}{(\mu_1+\beta)}$$

In the case of disease-free equilibrium, the basic reproduction number $R_0 < 1$ shows that disease-free equilibrium is stable. Similarly, The local stability and global stability of this system is calculated in the same way as the dynamics of disease model is calculated for without treatment. Now we only discuss the effect of treatment in each stages:

b) Effect of treatment

Assuming the treatments are 100percent effective. We find that the population densities undergoes an exponentially increase since treatment initiation.When the first infection stage is 100 percent effective(i.e.$\xi_1 = 1, \xi_2 = \xi_3 = \xi_4 = 0$), the slope of decline in disease is the minimum value of $(\mu_1 + \beta), (\mu_1 + \gamma)$ and $(\mu_1 + \sigma)$. We assume that the death rate of infected class increases as the infection increases $(\mu_1 = 0.002)$. We also choose small values of transition rates between stages$(\beta = 0.1, \gamma = 0.3, \sigma = 0.2)$as used in [1]. With these parametric values, the slope of the decline in disease under. $\xi_1 = 1, \xi_2 = \xi_3 = \xi_4 = 0$ is $(\mu_1 + \beta)$. Similarly, when $\xi_2 = 1$, the slope of decline in disease is the minimum value of $(\mu_1 + \gamma)$ and $(\mu_1 + \sigma)$, which is $(\mu_1 + \gamma)$. When$\xi_3 = 1$, the slope of decline in disease is $(\mu_1 + \sigma)$. This verifies that as drugs act in the later stage of infection the disease experiences a more rapid decline. When a perfect combination therapy is used($\xi_1 = \xi_2 = \xi_3 = \xi_4 = 1$, the decline in disease overlaps the decline when the latest infection stage is completely blocked as shown in figure (4, 5, 6 and 7) respectively.

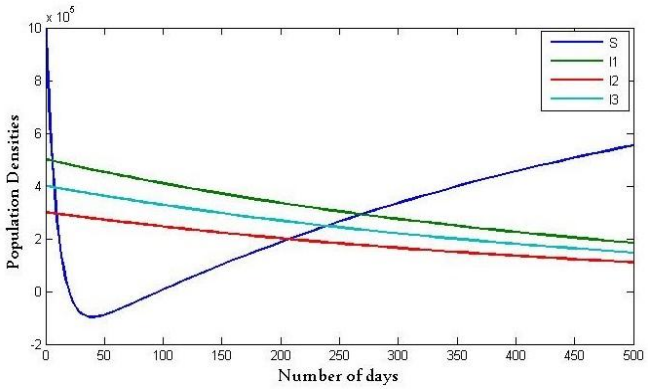

Figure 4: population densities when treatment is 100percent effective in all stages (i.e.$\xi_1 = \xi_2 = \xi_3 = \xi_4 = 1$).

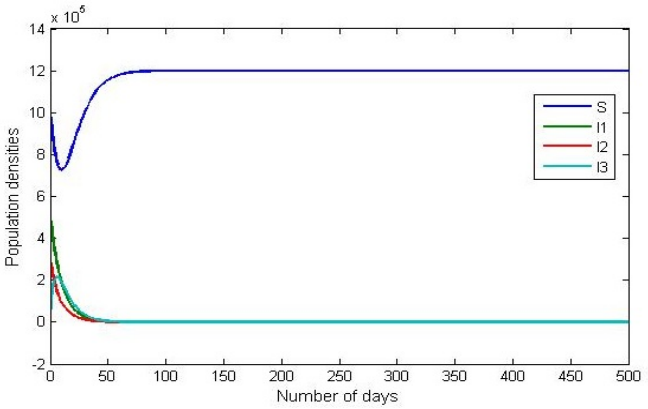

Figure 5: population densities when treatment is 100percent effective in first stages (i.e.$\xi_1 = 1, \xi_2 = \xi_3 = \xi_4 = 0$).

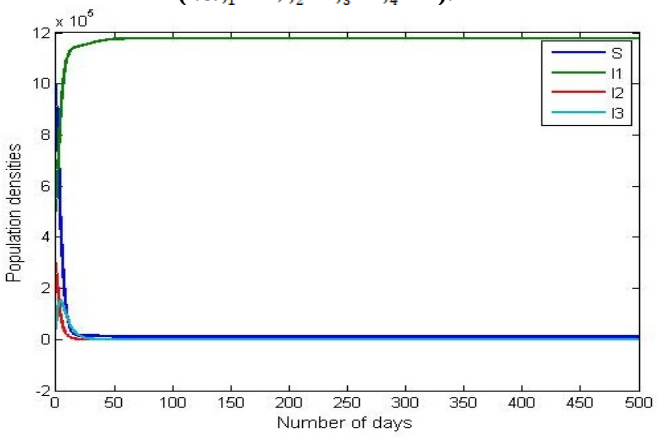

Figure 6: population densities when treatment is 100percent effective in second stages(i.e.$\xi_2 = 1, \xi_1 = \xi_3 = \xi_4 = 0$).

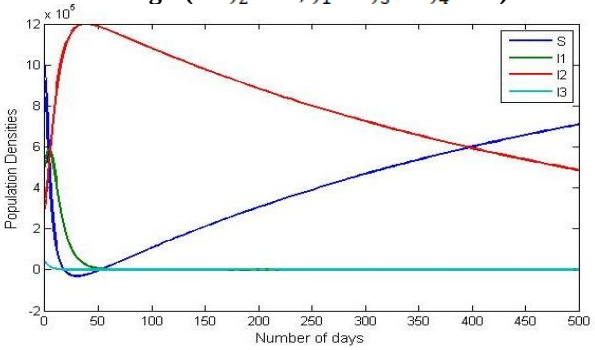

Figure 7: population densities when treatment is 100percent effective in third stages(i.e.$\xi_3 = 1, \xi_2 = \xi_1 = \xi_4 = 0$).

VII. RESULTS

The examination of the proposed model demonstrate that there exist just two non-negative equilibrium point; the disease-free equilibrium $E_0(\frac{\Lambda}{\mu})$ for example at the point when there is no disease (as$I_i = 0$, where i=1, 2, 3) and the endemic equilibrium $\bar{E}(S^*, I_1^*, I_2^*, I_3^*, R^*)$ i.e., when the infection is available in the network. The local and global dynamics of this model has likewise been considered. The disease-free equilibrium is locally and globally asymptotically stable when the basic reproduction number $R_0 < 1$ and the endemic equilibrium is locally and globally asymptotically stable when the basic reproduction number $R_0 > 1$.

VIII. CONCLUSION

In this paper, mathematical models of spreading of infectious illness are formulated evaluating the effect of treatment. For numerical accommodation, it is accepted that the population is in a homogenous domain. Further, the population in every compartment does not show any structure (as space, area, age, and so on.) with momentary moving starting with one compartment then onto the next, the time advancement of such compartments is portrayed by the arrangement of ordinary differential conditions. The obtained invulnerability (either by treatment or exhaustive recuperation from disease) should be brief so people who recovered from contamination (or who achieved treatment) can wind up powerless again after some time. Further, we talked about the dynamics of a disease model in three phases with and without treatment.

This work gives a quantitative and methodical examination of the impact of various medications on the disease dynamics utilizing a multi-organize demonstrate. These models are for the most part utilized for the treatment of viral illnesses. These two mathematical models in three phases of infection with and without treatment can help us for the analysis of different sorts of infectious illnesses like Swine Flu, HIV/AIDS, Smallpox, Conjunctivitis and distinctive kinds of Cancers.

ACKNOWLEDGMENT

I am very much thankful to my guide Dr. Joydip Dhar, Dr. Nimisha Mishra and my colleague Akanksha Dubey for their constant and continuous guidance whenever required.

REFERENCES

1. J. Dhar, A. Sharma, The role if the incubation period in a disease model, Appl. Math. E-Notes 9 146-153 (2009).
2. J. Dhar, A. Sharma, The role of virus infection in phytoplankton dynamics with the inclusion of incubation class, Nonlinear Anal. Hybrid Syst. 4 (1) 9-15 (2010).
3. G.P.Sahu, J. Dhar, Analysis of an SVEIS epidemic model with partial temporary immunity and saturation incidence rate, Appl. Math. Model. 36 (3) 908-923 (2012).
4. X. Zhou, J. Cui, Analysis of stability and bifurcation for an SEIV epidemic model with vaccination and nonlinear incidence rate, Nonlinear Dynam. 63 (4) 639-653 (2011).
5. Xia Wang, Xinyu Song, Sanyi Tang, Libin Rong, Dynamics of an HIV model with multiple infection stages and Treatment with different drug classes, Society for Mathematical Biology 78 (2) 322-349 (2016).

6. Govind Prasad Sahu, Joydip Dhar, Dynamics of an SEQIHRS epidemic model with media coverage, quarantine and isolation in a community with pre-existing immunity, Journal of mathematical analysis and applications 421 (2) 1651-1672 (2015).
7. Donahue DA, Sloan RD,Kuhl BD,Bar-Magen T, Schader SM, Wainberg MA, Stage-dependent inhibition of HIV-1 replication by antiretroviral drugs in cell culture, Antimicrob Agents Chemother 54 (3) 1047–1054 (2010).
8. Y. Kyrychko, K. Blyuss, Global properties of a Delayed SIR model with temporary immunity and nonlinear incidence rate, Nonlinear Anal. Real World Appl. 6 (3) 495-507 (2005).
9. B. Buonomo, D. Lacitignola, On the dynamics of an SEIR epidemic model with a convex incidence rate, Ric Mat. 57 (2) 261-281 (2008).
10. R. Xu, Z. Ma, Global stability of a delayed SEIRS epidemic model with saturation incidence rate, Nonlinear Dyn. 61 (1-2) 229-239 (2010).
11. K. L. Cooke, P. Van Den Driessche, Analysis of an SEIRS epidemic model with two delays, J. Math. Biol. 35 (2) 240-260 (1996).
12. H. Hethcote, P. Driessche, An SIS epidemic model with variable population size and a delay, J. Math. Biol. 34 (2) 177-194 (1995).
13. Laetitia Laguzet, Gabriel Turinici, Individual Vaccination as Nash Equilibrium in a SIR Model with Application to the 2009-2010 Influenza A (H1N1) Epidemic in France, Society for Mathematical Biology 77 (10) 1955-1984 (2015).
14. Pauline Van Den Driessche, Reproduction numbers of infectious disease models, Infectious disease modelling 29 (2) (3) 288-303 (2017).
15. A. Huppert, G. Katriel, Mathematical modelling and prediction in infectious disease epidemiology, Clin Microbiol Infect 19 (11) 999-1005 (2013).
16. J.D. Murray, Mathematical Biology, Vol II, Springer, Berlin (2003).
17. R. H. Martin, Logarithmic norms and projections applied to linear differential systems, Journal of Mathematical Analysis and Applications 45 (2) 432-454 (1974).

AUTHORS PROFILE

I, Smriti Agrawal, have done my B.Sc. Degree from Dr. R. M. L. Awadh University, Faizabad, Uttar Pradesh, India in the year 2012 and M.Sc. Degree from Amity University New Campus, Lucknow, Uttar Pradesh, India in the year 2017, during M.Sc. I have done a dissertation project from ABV-IIITM, Gwalior, Madhya Pradesh, India under the guidance of Joydip Dhar. And now I m pursuing Ph.D. (in mathematics) from Amity University New Campus, Lucknow, Uttar Pradesh, India.
In this period, I have attended many national and international conferences/ workshops/ seminars.

Akanksha Dubey, is my batchmate. She has done her B.Sc. Degree from Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, Uttar Pradesh, India in the year 2015 and M.Sc. Degree from Amity University New Campus, Lucknow, Uttar Pradesh, India in the year 2017 during M.Sc. she has done a dissertation project from ABV-IIITM, Gwalior, Madhya Pradesh, India under the guidance of Joydip Dhar. And now she is preparing for competitive exams in Delhi, India.
In this period, she has attended many national and international conferences/ workshops/ seminars.

Dr. Nimisha Mishra is our alumni. After pursuing her B. Sc. Degree from our institute, she has done **M. Sc. and Ph. D. Mathematics** from **Lucknow University** in the year 2008. In between she also cleared **CSIR-NET** exam in 2003.
She also teaches here in the year 2004 for two months, and then she joined AIET Lucknow. In the year 2005 she starts teaching in evening classes at Lucknow University and done her research work. In 2007 after submitting thesis she joined MPEC Kanpur. After one year in 2008 she joined Amity University Lucknow campus and still teaching there. So, with this she has a vast teaching experience of **15 years**.
In this period, she has attended many national and international conferences/ workshops/ seminars/ FDP's. She has published many papers in reputed journals. She has also organised several national/ international conferences and events at her university. She is also member of several committees at her place such as **IQAC, PLACEMENT, course advisory** etc.
Besides teaching she is **good mentor & guide** for the students.

Dr. Joydip Dhar is an Associate Professor in the area of Applied Sciences (Mathematics) of the Institute. Dr. Dhar has done his PhD from IIT, Kanpur in 1997 after completing his M.Sc. (Mathematics) from Visva-Bharati University, Santiniketan. He has been associated with the teaching profession and research for the past 14 years and has also published about 60 papers in his areas of interest and proficiency. Under his guidance 2 Ph.D., 8 M.Phil., 9 M.Tech. and 8 M.B.A. theses completed. Currently 6 Ph.D., 4 M.Tech., 7 M.B.A. students are pursuing their thesis. He is a life member of many professional societies ISTE, IMS, ISMMACS and annual member of American Mathematical Society (AMS). Under his mentorship a team of three students of ABV-IIITM, Gwalior after winning ACM-ICPC IIT Kanpur chapter represented India to participated in the prestigious ACM-ICPC world finals at Stockholm, Sweden from 16-22 April, 2009. He has conducted National Conference on "Mathematical Modelling and Simulation" from 9-11 January, 2009, AICTE-ISTE sponsored, short term course on "Modelling, Simulation of Engineering and Environmental Systems" from 15-19 March, 2004 and MHRD sponsored, short term course on "Modelling, Simulation in Science and Engineering" from 08-12, 2009. His current area of research is Mathematical Modelling and Simulation of Environmental, Managerial and Engineering systems.