DETERMINISTIC AND CTMC STOCHASTIC MODELS FOR ZIKA VIRUS TRANSMISSION

Motivation*:*

Transmission of Zika virus is one of the most widespread mosquito-borne diseases. It is transmitted to humans by many Aedes-type mosquitoes, primarily the Aedes aegypti mosquitoes. An infected pregnant woman can become a source of transmission of virus to her baby during pregnancy and can result in serious birth defects, including microcephaly. The outbreak emerged in 2014 in Brazil and the emergence still persists and continues to be the major cause of mortality in many subtropical and tropical countries.

Importance of Topic:

The outbreak in 2016 showed that Zikas easily missed symptoms may give no indication of its potentially serious complications. There is, currently, no treatment for Zika infection through travel to the mosquito-borne regions and sexual transmission continue to be the primary arena where the infection can be controlled. Women of childbearing age, who contract the virus, are at risk of giving birth to children with severe health problems including microcephaly, eye problems (including vision loss), epilepsy, nervous system defects, and hearing defects. Of 1450 children born to infected mothers, 1 in 7 had a birth defect associated with the virus or a neurological abnormality possibly linked to the virus

Introduction*:*

Transmission of Zika virus is the cause for one of the most widespread mosquito-borne diseases. Aedes-aegypti mosquito is the major contributor for the spread among the Aedes-type mosquitos.

We consider a sample space of a population of n healthy humans. In this case, there is no disease and hence no outbreak of any infectious disease since everyone is healthy.

Consider a situation where a small subset of the population is infected by a virus. Now, the rest of the population comes under the category of "susceptible" since they can catch the disease from the infected person/s.

One after other susceptible humans become infected humans at a rate. We assume that once the disease has prevailed in a body, it cannot affect it again because the person has either become immune to it (chickenpox) or has died from it. In both cases, the person

gets removed from the sample space of susceptible and infected humans. Everyone will either recover or die from the disease once they have caught it, and thus, it will end the pandemic in a definite time depending on the rate of spreading. There may be people who don't get sick at all.

To study this we study the dynamical system to observe how state variables change with time. We have different rates of change and increments for different variables.

State variables and Rates

- S(t): number of individuals at t who can get the disease.
- I(t): number of infected variables at t who are infected and can transmit the disease.
- R(t): number of individuals at t who are immune.

Susceptible population (S) comes in contact with infected population (I) and gets the disease.

Thus, S: S-1 and I: I+1

We need to find the probability that S comes in contact with I and gets the disease. That will be the likelihood of the state change.

S-->I bS(t)I(t) where b is the infection rate

I-->R

The rate will depend on I. Thus, the rate is rI(t) where r is the recovery rate

Assumptions:

- Each person is equally susceptible to be infected and be cured/die of that disease.
- The person cannot get that disease again.
- There aren't any new people entering or exiting the sample space.
- The death rate and the birth rate are same preserving the number of population.

Existential Approaches:

A stochastic process is defined by the probabilities with which different events happen in a small time interval. In our model, there are two possible events (production and death/removal) for each population.

For a large population size and a large number of infectious individuals, the deterministic threshold $R_O>1$ provides a good prediction of a disease outbreak. However, this prediction breaks down when the outbreak is initiated by a small number of infectious individuals. In this setting, the Markov chain (MC) models with a discrete number of individuals are more realistic than deterministic models where the number of individuals is assumed to be continuous-valued.

However, if the aim of a model is to help develop a dynamic health policy (that is a policy that can recommend switching interventions based on real-time observations about the epidemic state), it is not useful to consider models that produce epidemics with deterministic trajectories. If the epidemic trajectory could be known with certainty, it is possible to determine an optimal series of interventions at baseline and thus the motivation for dynamic decision-making is lost. Therefore, finding optimal dynamic health policies requires the use of stochastic models of infectious disease spread.

In a SIR model, people can be labeled as **Susceptible** (haven't gotten a disease yet, but aren't immune), **Infected** (they've got the disease right now), or **Recovered** (they've had the disease, but no longer have it, and can't get it because they have become immune). If they get the disease, they change states from Susceptible to Infected. If they get well, they change states from Infected to Recovered. It's impossible to change states between Susceptible and Recovered, without first going through the Infected state.

The probability of changing a state like from Susceptible to Infected is the infection rate and from Infected to Recovered is the recovery rate.

1. DETERMINISTIC MODEL:

Let ... be time dependent discrete random variables representing ... respectively. The maximum size of the population in consideration is $N_h + N_v$ (sample space), where N_h represents number of humans and N_v represents number of mosquitoes in the population.

Although infectious diseases generally spread in a stochastic fashion, deterministic models are commonly used as tools for studying epidemic behaviour. These deterministic models have been very useful in understanding the dynamics of infectious disease, estimating important epidemiologic parameters (e.g. basic reproductive numbers), and

determining targets for disease control (e.g. critical proportions of the population to immunise).

$$\dot{S}_h(t) = A_h - \rho\mu_h (I_h+R_h) - (\beta_h S_h I_v)/N_h - \mu_h R_h + \alpha R_h$$

$\dot{S}_h(t)$ → Susceptible humans (who are at risk of getting infected) over a period of time

A_h → Human recruitment rate including growing population

$\rho\mu_h (I_h+R_h)$ → Proportion of population including congenital births from infected and recovered humans

$(\beta_h S_h I_v)/N_h$ → Transmission rate of disease to the susceptible humans from infected mosquitoes

$\mu_h R_h$ → Death rate of recovered humans

αR_h → Recovered humans after a span of time

$$\dot{I}_h(t) = (\beta_h S_h I_v)/N_h - \gamma_h I_h - \mu_h I_h$$

$\dot{I}_h(t)$ → Infected humans over a period of time

$(\beta_h S_h I_v)/N_h$ → Transmission rate of disease to the susceptible humans from infected mosquitoes

$\gamma_h I_h$ → Humans having symptoms / humans during latent period

$\mu_h I_h$ → Death rate of infected humans

$$\dot{R}_h(t) = \gamma_h I_h - \mu_h R_h - \alpha R_h$$

$\dot{R}_h(t)$ → Recovered humans over a period of time

$\gamma_h I_h$ → Humans having symptoms / humans during latent period

$\mu_h R_h$ → Death rate of recovered humans

αR_h → Recovered humans after a span of time

$$\dot{I}_c(t) = \rho\mu_h (I_h+R_h) - \gamma_h I_c(t) - \mu_h I_c$$

$\dot{I}_c(t)$ → Infected congenital humans over a period of time

$\rho\mu_h$ (I_h+R_h) → Proportion of population including congenital births from infected and recovered humans

$\gamma_h I_c(t)$ → Infected congenital population in latent period

$\mu_h I_c$ → Death rate of infected congenital humans

$$\dot{R}_c(t) = \gamma_h I_c - \mu_h R_c$$

$\dot{R}_c(t)$ → Recovered congenital humans over a period of time

$\gamma_h I_c$ → Infected congenital population in latent period

$\mu_h I_c$ → Death rate of infected congenital humans

$$\dot{S}_v(t) = A_v - \beta_v S_v(I_h+I_c)/N_h - \mu_v S_v$$

$\dot{S}_v(t)$ → Susceptible mosquitoes who are at risk of getting infected over a period of time

A_v → Mosquito recruitment rate including growing population

$\beta_v S_v(I_{h+}I_c)/N_h$ → Transmission rate of disease from susceptible mosquitoes to infected and infected congenital humans

$\mu_v S_v$ → Death rate of susceptible mosquitoes population

$$\dot{I}_v(t) = \beta_v S_v(I_h+I_c)/N_h - \mu_v I_v$$

$\dot{I}_v(t)$ → Infected mosquitoes over a period of time

$\beta_v S_v(I_{h+}I_c)/N_h$ → Transmission rate of disease from susceptible mosquitoes to infected and infected congenital humans

$\mu_v I_v$ → Death rate of infected mosquitoes population

BASIC REPRODUCTION NUMBER:-

$$R_O = \sqrt{\frac{\beta_h \widehat{\beta_v} (\gamma_h+\mu_h+p\mu_h)}{\mu_v(\gamma_h+\mu_h)^2}}$$

R_O is the reproduction number which indicates the passing of the disease to the next generation. The secondary infections affecting a population at a disease-free endemic

point (DFE) can show the rate of spreading or extinction of the disease. R_O is calculated from the J matrix formed after linearising the differential equations of the random variables of infectious indicators (I_h, I_c, I_v). Finding the next generation matrix of the matrices: new infections and transmission rates, we can get R_O from the spectral radius of (FV^(-1)) called as K.Here R_O is associated with disease transmission by infected humans as well as the infection of susceptible humans by infected mosquitoes.

2. STOCHASTIC CTMC MODEL

When the number of infectious people is small, the deterministic approach does not agree with the stochastic MC Model, like it did for R_O. If $R_O > 1$, there is a possibility in the MC model that infectious individuals die or recover before an outbreak occurs.

For this case we use the branching process to study the outbreak assuming susceptible humans and mosquitoes at DFE. The three infection variables are involved in the process to generate three probability generating functions, since they are the only source of infection.

We use the multi-type Galton-Watson branching process (GWbp) to determine disease invasion and extinction probabilities.

$$G_i(s1, s2, ..., sn) = \Sigma^{\infty}_{kn=0}\Sigma^{\infty}_{kn-1=0.....}\Sigma^{\infty}_{k1=0}P_i(k_1, k_2, ..., k_n)\, s1^{k1}\, s2^{k2}...sn^{kn}$$

where $P_i(k1, ..., kn)$ is the probability that one infected individual of type i gives birth to k_j individuals of type j.

For the branching process approximation this model, assumed that infected humans (I_h) as x1, infected congenital humans (I_c) as x2, and infected mosquitoes (I_v) as x3.

For one Zika infected human, there are four possible events: infection of a mosquito, infection of a congenital human, recovery of the infectious individual, or death of the infectious individual. One infected human dies or recovers with probability $\frac{\mu_h + \gamma_h}{\mu_h + \gamma_h + \beta_v + p\mu_h}$ and infects a mosquito with probability $\frac{\beta_v}{\mu_h + \gamma_h + \beta_v + p\mu_h}$ and infects a congenital human with the probability $\frac{p\mu_h}{\mu_h + \gamma_h + \beta_v + p\mu_h}$.

Thus, the offspring of pgf for Ic, given $I_h(0) = 1$, $I_v(0) = 0$, and $I_v(0) = 0$ is

$$f_1(x_1, x_2, x_3) = \frac{\mu_h + \gamma_h + \beta_v x_1 x_3 + p\mu_h x_1 x_3}{\mu_h + \gamma_h + \beta_v + p\mu_h}$$

For an infected congenital human, there are three possible events: infection of a mosquito, recovery of the infectious individual, or death of the infectious individual. One infected congenital human dies or recovers with probability $\frac{\mu_h + \gamma_h}{\mu_h + \gamma_h + \beta_v}$ and infects a susceptible mosquito with the probability .

Thus, the offspring of pgf for Ic, given $I_h(0) = 0$, $I_c(0) = 1$, and $I_v(0) = 0$ is

$$f_2(x_1, x_2, x_3) = \frac{\mu_h + \gamma_h + \beta_v x_2 x_3}{\mu_h + \gamma_h + \beta_v}$$

For an infected mosquito, there are two possible events: death of the mosquito or infection of a susceptible human. The term $\frac{\mu_v}{\mu_v + \beta_h}$ represents the probability that the infected human dies before causing a secondary infection. And the term $\frac{\beta_h}{\mu_h + \beta_h}$ represents the probability of a susceptible human to become infected due to coming in contact with an infected mosquito.

thus, The offspring of pgf for Iv, given that $I_h(0) = 0$, $I_c(0) = 0$, and $I_v(0) = 1$, is

$$f_3(x_1, x_2, x_3) = \frac{\mu_v + \beta_h x_1 x_3}{\mu_v + \beta_h}$$

The expectation matrix M = [m_{kj}] of the offspring pgfs is a n X n matrix whose entry m_{kj} gives the expected number of infectious offspring in patch k produced by an infectious individual in patch j, where

$$m_{kj} = \frac{\partial f_j}{\partial x_k}$$

From that expectation matrix, we get the characteristic equation and thus, find the Stochastic Threshold which is called Spectral Radius of this matrix defined by $\rho(M)$. It is calculated by finding the eigenvalues of the matrix.

Relation Between basic reproduction number R0 & Stochastic threshold of matrix M :

If $\rho(M) <= 1$ implies $Ro <= 1$, then it is called critical and subcritical process.

Probability of extinction in this case is:

$$lim_{t \to \infty} Prob(I(t) = 0) = 1$$

If $\rho(M) > 1$ implies $Ro > 1$, then it is called supercritical process.

Probability of extinction in this case is:

$$lim_{t\to\infty} Prob(I(t) = 0) = q1^{h0} q2^{c0} q3^{v0}$$

for fix point $(q1, q2, q3) \to (0, 1)^3$ of the offspring pgfs and

h0 is the number of infected humans at time t=0

c0 is the number of infected congenital humans at time t=0

v0 is the number of infected mosquitoes at time t=0

q1 is the probability of disease extinction for infected humans population.

The expression for q1 has a biological interpretation. Beginning from one infected human, there is no outbreak if the infectious human recovers or dies or if there is no successful transmission to a susceptible mosquito and congenital human.

q2 is the probability of disease extinction for infected congenital humans population.

It has a biological interpretation. Beginning from one congenital infected human, there is no outbreak if the infected congenital human recovers or dies or if there is no successful transmission to a susceptible mosquito.

q3 is the probability of disease extinction for infected mosquitoes population.

It has a biological interpretation. Beginning from one infected mosquito, there is no outbreak if the infected mosquito dies or if there is no successful transmission to a susceptible human.

3. STOCHASTIC DTMC MODEL

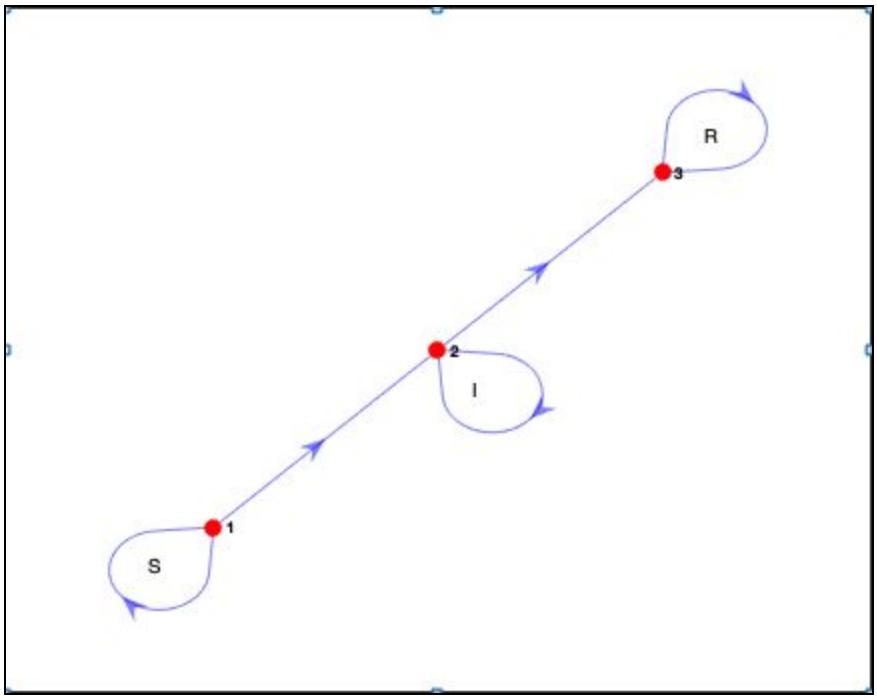
In the SIR epidemic models, the individuals conditions are classified into three categories: susceptible (S), infectious (I) and recovered (R). The number of susceptible, infected and recovered individuals are random events that depend on time so they follow the stochastic process. The number of susceptible, infected and recovered individuals at time t + 1 depends only on the individuals at time t, following the discrete time Markov process. It can be described as an epidemic model of discrete time Markov chains (DTMC) SIR.

Assumptions on the model:

- Total population size N is constant
- The birth rate that equals to the death rate
- Homogeneously populated
- The individuals born are susceptible individuals.

In the SIR model, the individuals change state from S to I to R, each with a transition rate or a transition probability. From the data of Zika outbreak in Brazil in 2016, with some arbitrary error and assumptions we can make a transition matrix to get a state transition diagram.

State Diagram:



From the Figure 7 we can see the trend of the outbreak over a fixed time. At initial time t=0, the entire population is counted as susceptible (S(t)). As the infection spreads, the susceptible individuals change their state to infected, thus the number of infected individuals (I(t)) rises. The rise in the number of infected individuals is hindered as the population starts recovering or dying. Hence, the number of recovered individuals (R(t)) rises steadily once I(t) falls.

CONCLUSION

Three different approaches have been used namely, the deterministic model and 2 stochastic models, CTMC(Continuous Time Markov Chain) and DTMC(Discrete Time Markov Chain). The results we obtained from the three approaches are evidently interchangeable. We have reproduced the graphs from the deterministic model from the base article referenced below[1]. The basic reproduction number obtained from the deterministic model is

$$R_O = \sqrt{\frac{\beta_h \widehat{\beta_v} (\gamma_h+\mu_h+p\mu_h)}{\mu_v(\gamma_h+\mu_h)^2}}$$

The threshold obtained from the deterministic model is synonymous, that is, $\rho(M) <1(=1,>1)$ when $R_O <1(=1,>1)$. The probability of disease extinction can be derived as

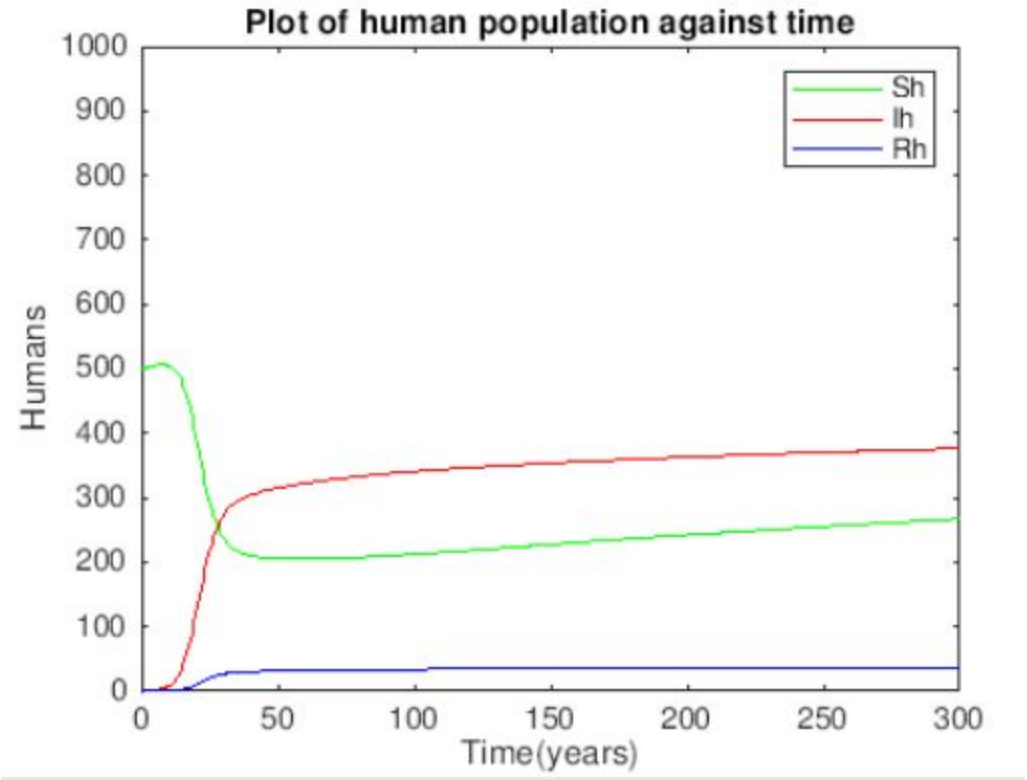
$$1 - q_1^{h_o} q_2^{c_o} q_3^{v_o}$$

using branching process approximation of the non-linear CTMC model near the disease-free equilibrium.

Our analytical and numerical results showed that both deterministic and stochastic models predict disease extinction when $R_O<1$. However, the predictions by these models are different when $R_O>1$. In this case, deterministic model predicts with certainty disease outbreak while the stochastic model has a probability of disease extinction at the beginning of an infection. Hence, with stochastic models, it is possible to attain a disease-free equilibrium even when $R_O>1$. Also, we noticed that initial conditions do not affect the deterministic threshold while the stochastic thresholds are affected. Thus, the dynamics of the stochastic model are highly dependent on the initial conditions and should not be ignored.The points q1,q2,q3 are the parameters for determining the probability of extinction when $R_O>1$, or when R_O for stochastic and deterministic does not match the conclusion.

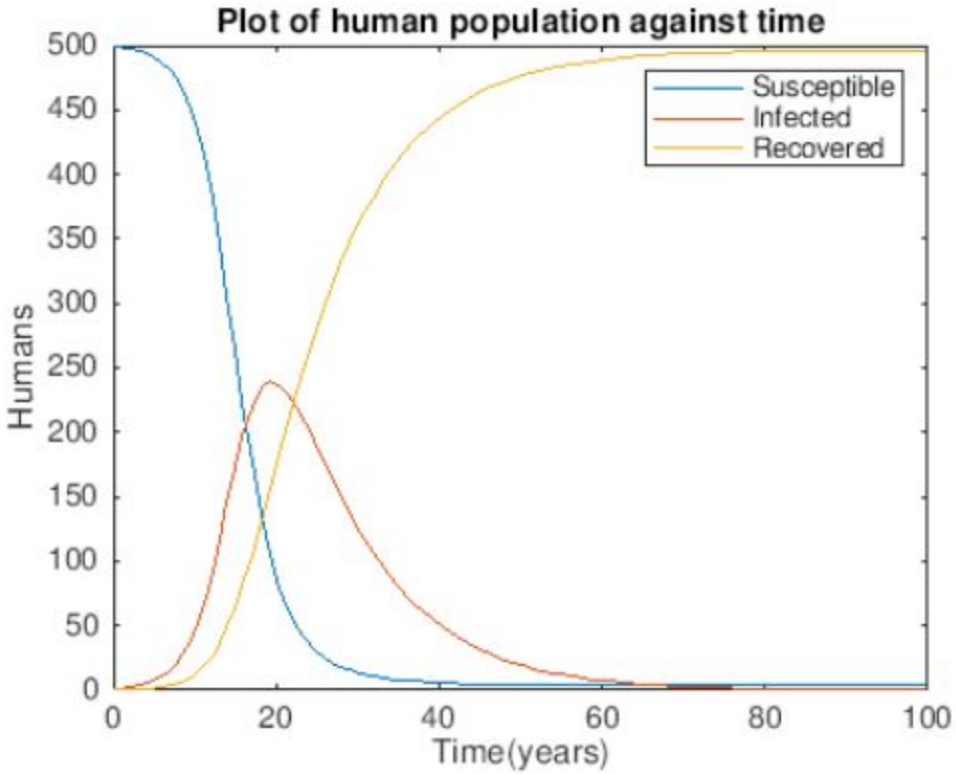
NUMERICAL SIMULATIONS WITH INFERENCES:

Figure 1:



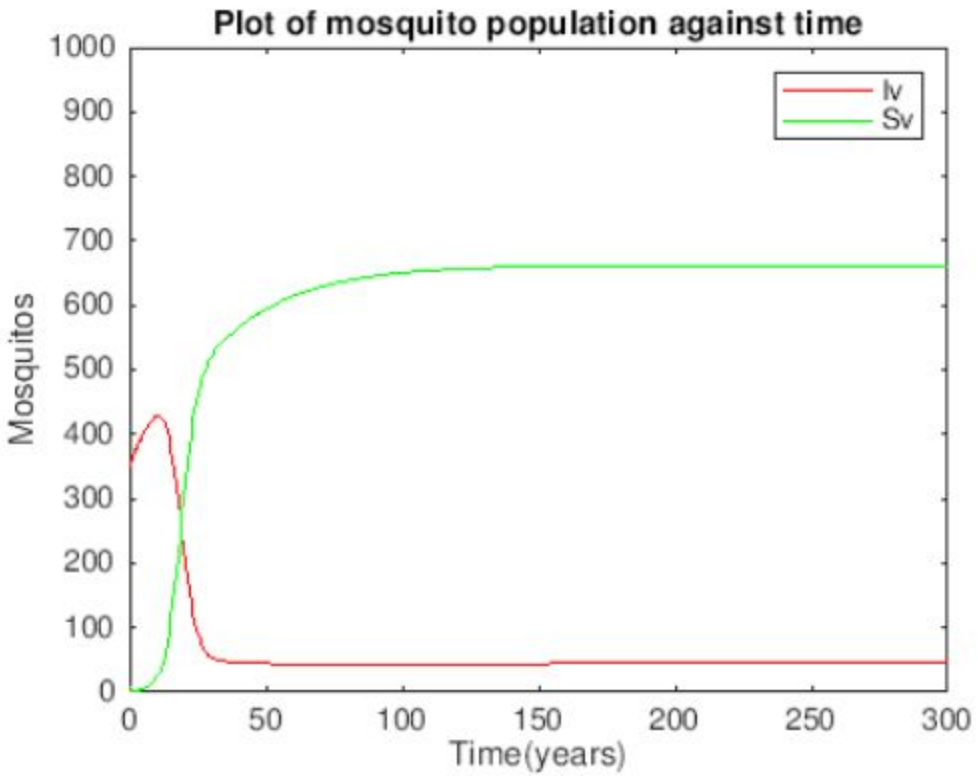
Deterministic simulation: Ah=2.73, Av=23.33, β_h =0.15, β_v =0.3, γ_h =0.1, μ_h =0.0027, μ_v =0.033, $\propto$ =1

Figure 2:



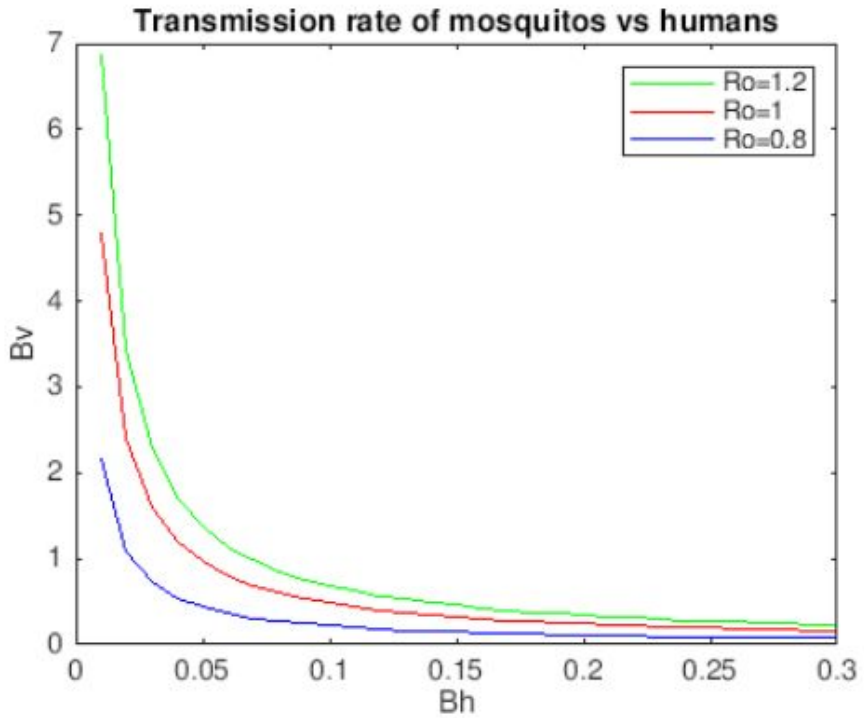
Deterministic Simulation: $\beta_h = e^{-3}$, $\gamma_h = e^{-1}$, Initial $S_h = 499$, $I_h = 1$, $R_h = 0$, $N_h = 500$

Figure 3:



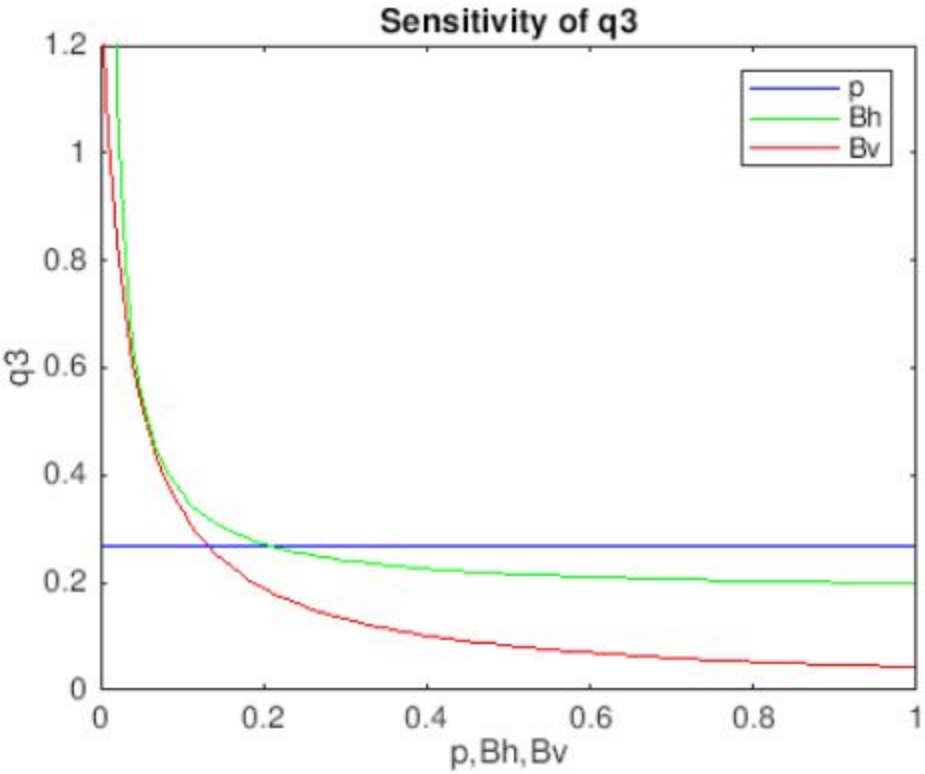
Deterministic Simulation: Ah=2.73, Av=23.33, β_h =0.15, β_v =0.3, γ_h =0.1, μ_h =0.0027, μ_v =0.033, $\propto$ =1

Figure 4:



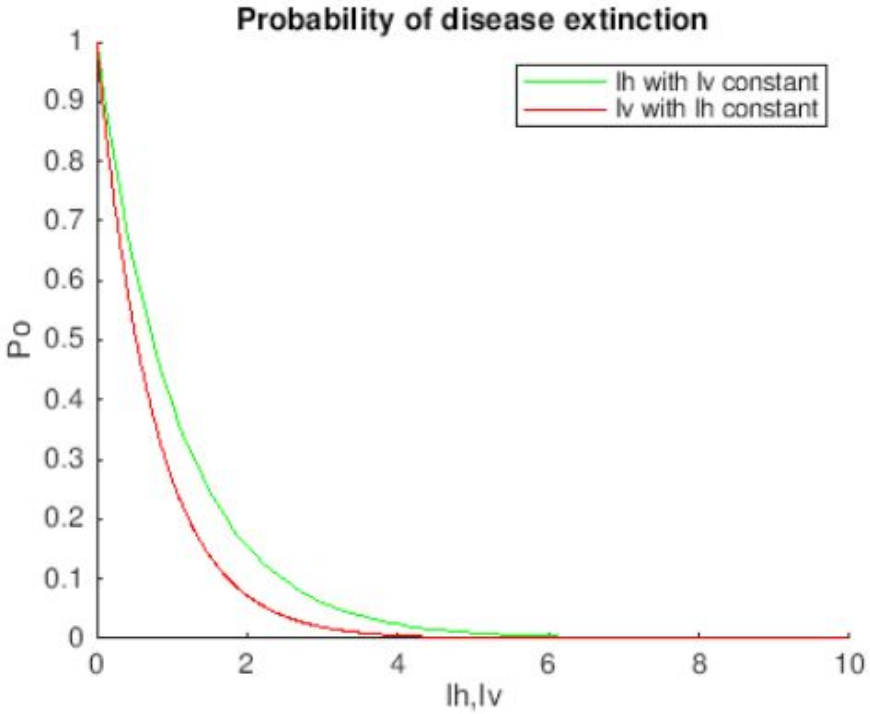
Level set of R_o : Ah=2.73, Av=23.33, β_h =0.15, β_v = 0.3, γ_h =0.1, μ_h =0.0027, μ_v =0.033, p= 0.5

Figure 5:



Sensitivity of q3: Ah=2.73, Av=23.33, β_h =0.15, β_v =0.3, γ_h =0.1, μ_h =0.0027, μ_v =0.033, p= 0.5

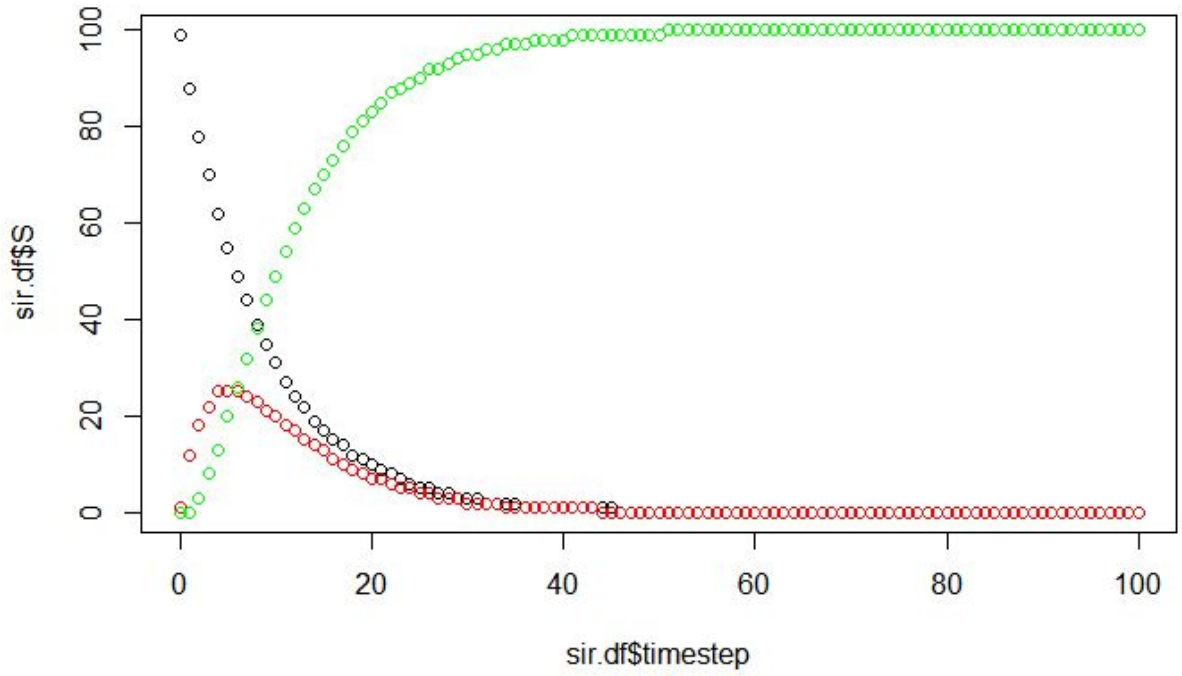
Figure 6:



Probability of extinction: Ro >1 : For I_h *plot* : $I_v = 0$, $I_c = 0$ and

For I_v *plot* : $I_v = 0$, $I_v = 0$

Figure 7:



REFERENCES*:*

1. R. Yaesoubi and T. Cohen, "Generalized Markov Models of Infectious Disease Spread: A Novel Framework for Developing Dynamic Health Policies," *European journal of operational research*, 16-Dec-2011.

2. Mbogo, R. Waema, Livingstone, Odhiambo, and J. W., "A Stochastic Model for Malaria Transmission Dynamics," *Journal of Applied Mathematics*, 11-Feb-2018.

3. Allen L J S 2008 An Introduction to Stochastic Epidemic Models (Texas: Texas Tech University)

4. Allen L J S 2003 An Introduction to Stochastic Processes with Applications to Biology (New Jersey, Upper Saddla River: Prentice Hall)

5. *SIR models of epidemics*. http://www.biosym.uzh.ch/modules/models/ETHZ/SIR-Epidemics/sir.xhtml.

6.Parinya Suparit, Anuwat Wiratsudakul, and Charin Modchang, "A mathematical model for Zika virus transmission dynamics with a time-dependent mosquito biting rate," *Theoretical Biology and Medical Modelling*, 01-Aug-2018.

7. "marya (view profile)," *How to plot with various initial conditions? - MATLAB Answers - MATLAB Central*.

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