Study of Vaccination as a Control Strategy for Swine Influenza

PROJECT REPORT

Submitted in partial fulfillment of the requirements
of EEE F422

BITS Pilani
K K Birla Goa Campus

by

Roshan Nair - 2015B4A30344G

Gaurav Patil - 2015A4PS0319G

Under the supervision of

Dr. NS Manjarekar

and

Mr. Vivek Chandran

Contents

List of Figures

Acknowledgement

We would like to express out gratitude to Dr.Manjarekar and Mr.Vivek Chandran for designing this project component that greatly supplements our learning. The literature survey, mathematical modelling and implementation involved has pushed us to correlate theoretical concepts and get a flavor of the application of essential control theory to other domains. We would like to acknowledge the guidance given by Mr.Vivek in routine discussions. Lastly, we would like to acknowledge the use of the student license of MATLAB R2018a.

Abstract

In 2009, there was a major outbreak of Swine Flu(H1N1, Swine Influenza) in India. When the disease was monitored for nearly a year(August, 2010), there were over 30 thousand diagnosed cases of H1N1 and over 2500 deaths. At the time of the outbreak the only known drug that was effective for Swine Flu was Tamiflu, which wasn't available in general medical stores. It was only months later that a fairly generic version of the drug was made available to the public. There was no efficient strategy used for dealing with the outbreak. The lack of preparedness and lack of data to base strategies for the control of such pandemics clearly caused substantial deaths. The mathematical modeling of diseases and analysis of various control strategies are therefore of utmost importance for a faster and more accurate handling of pandemics. In this paper we use existing epidemiological models to study the effect of vaccinations as a viable control strategy

Introduction

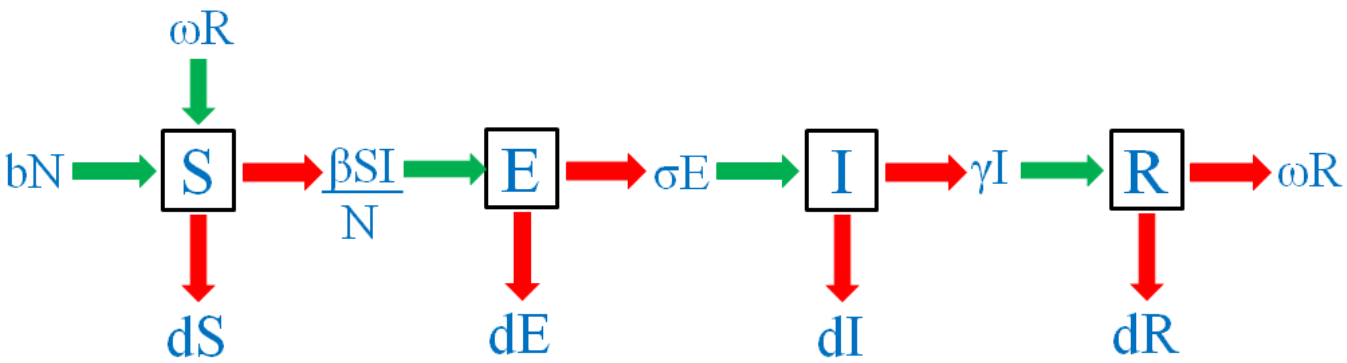
Epidemiological Models date back to the late 1920s where Kermack and McKendrick used such models to study the plague. From there, the various generalizations of epidemic models have enabled us to represent most epidemics with a great deal of accuracy. We use the common SEIR epidemic model [1] to model the effects of H1N1. The model is further used along with specific control law in the form of vaccinations[2] to study its effect. We aim to show in this project that using vaccinations will lead to a decrease in the peak number of infected people and thereby help stabilize the epidemic a lot faster. The rest of this report is organised as follows: We first introduce the model without vaccinations and briefly discuss the stability about the two important equilibrium points. We present the simulink implementation of this system and the various graphs we generated from this model. The second part of the paper will be a repeat of this process with the inclusion of vaccinations. The final part will essentially be the observations and concluding remarks.

1 Model without Vaccinations

1.1 Assumptions Made

1. Population is not constant. We take different values of birth rate(b) and death rate(d) to analyze a more realistic situation of the disease dynamics.
2. The death rate due to disease has not been explicitly modelled. The death rate due to Swine Influenza is quite small in comparison to the natural death rate.
3. We initially assume everyone is Susceptible and as time progresses, it is from this susceptible population that exposed and Infected populations arise.
4. In theory the value of w when there is no vaccination should be zero. For the solving the system numerically taking a negligible value of w in fact yields little to no difference in the solution and for ease of computation we assume it to be zero. However, for mathematical completeness we acknowledge that some individuals might have some kind of immunity to the disease inherently and take a negligible value of w for stability considerations.
5. We study this for an initial population of 1 million. Given that the dynamics are dependent on this initial condition, changing this as per requirement will give us the required dynamics.

1.2 Flowchart of the Model



1.3 Mathematical Model

The SEIR model with non constant population gives the most general understanding of disease dynamics. S represents the Susceptible population, E represents the Exposed population, I the infected population and R the recovered population. N is the total population at a given time. S,E,I,R and N vary with time and system is best represented by the following equations:

$$S' = bN - \beta\frac{SI}{N} - dS + wR$$

$$E' = \beta\frac{SI}{N} - \sigma E - dE$$

$$I' = \sigma E - \gamma I - dI$$

$$R' = \gamma I - dR - wR$$

b	Natural Birth Rate	5.48e-5
d	Natural Death Rate	5e-5
w	Rate at which Immunity is lost	≈ 0
β	Transmission Rate from class S to I	0.65
γ	Recovery rate	1/7
σ	Transmission Rate from class E to I	0.95

Table 1: Constants used for Swine Flu [3]

S(0)	9.8e05
E(0)	1.5e04
I(0)	5e03
R(0)	0

Table 2: Initial Conditions used

1.4 Stability Considerations

We study the stability about two equilibrium points that are extremely important for any disease dynamics model. The first is the Disease free equilibrium, where the populations of E, I and R are 0 and $S = \frac{bN}{d}$. The second equilibrium point is termed as the endemic equilibrium point. Both equilibirum points are the solutions we get from setting S', E', I' and R' to 0 simultaneously.

1.4.1 Stability of the Disease Free Equilibrium(DFE)

DFE=$E_0 = (\frac{bN}{d}, 0, 0, 0)$

Now to study the stability of the system at the DFE, we first linearize the system about the DFE. On linearizing the system (Using the Jacobian) and then evaluating the Jacobian at the DFE we in face obtain the A matrix of the corresponding linear system. Proceding with the standard theory of linear systems, we we can show that this A matrix fact all negative eigenlaues we can conclude that the DFE is a stable equilibrium point.

$$J(S,E,I,R) = \begin{pmatrix} \frac{-\beta I}{N} - d & 0 & \frac{-\beta S}{N} & w \\ \frac{\beta I}{N} & -\sigma - d & \frac{\beta S}{N} & 0 \\ 0 & \sigma & -\gamma - d & 0 \\ 0 & 0 & \gamma & -d - w \end{pmatrix}$$

Now we evaluate this at the DFE for the corresponding linear matrix A.

$$J(DFE) = \begin{pmatrix} -d & 0 & \frac{-\beta b}{d} & w \\ 0 & -\sigma - d & \frac{\beta b}{d} & 0 \\ 0 & \sigma & -\sigma - d & 0 \\ 0 & 0 & \gamma & d - w \end{pmatrix}$$

We further simplify this matrix by taking $\frac{\beta b}{d}$ as l, $\sigma + d$ as f, $\gamma + d$ as g and $d + w$ as h. We now obtain:

$$A = \begin{pmatrix} -d & 0 & -l & w \\ 0 & -f & l & 0 \\ 0 & \sigma & -g & 0 \\ 0 & 0 & \gamma & -h \end{pmatrix}$$

The final step in concluding on the stability of the DFE we have to find the eigenvalues. We do so, by equating the characteristic equation of A.
On doing this we obatin the following eigenvalues:

$\lambda_1 = -d$, $\lambda_2 = -h$, $\lambda_3 = \frac{1}{2} \times (-f - g - \sqrt{f^2 - 2fg + g^2 + 4l\sigma})$ and $\lambda_4 = \frac{1}{2} \times (-f - g + \sqrt{f^2 - 2fg + g^2 + 4l\sigma})$

As all the constants, as mentioned before, are positive values it follows directly that λ_1, λ_2 and λ_3 are indeed negative non-zero quantities. If we can now comment on λ_4 we can conclude on the stability of the DFE.

We take λ_4 and add and subtract $2fg$ inside the square-root. We get $\lambda_4 = \frac{1}{2} \times (-f - g + \sqrt{f^2 + 2fg + g^2 - 4fg + 4l\sigma})$.
Simply completing the square inside the square root we can observe that if $-4fg + 4l\sigma$ is less than 0 we in fact have that $\lambda_4 < 0$ thereby guaranteeing stability of the DFE. Now, $-4fg + 4l\sigma < 0$ in actuality is a valid assumption and the ratio we so obtain $\frac{\beta b \sigma}{d(\sigma+d)(\gamma+d)}$ is termed as the basic reproduction number. The basic reproduction number R_0 for a disease free equilibrium point is by definition a positive value lesser than 1.
So we have now proven that the DFE is a stable equilibrium point for the system.

NOTE:

1. Basic Reproduction Number:

   The basic reproduction number can be thought off as the transmission potential of a disease. It is characterized as the number of secondary infections produced by a typical infection in a population that is totally susceptible. It is generally denoted by R_0. For a disease to actually exist of even cause infections $R_0 > 1$. Quite clearly this is so because if one infected individual gives rise to multiple infected individuals the disease spreads. It is instructive to note that as this basic reproduction number gets higher the disease is rather rapidly spreading.
   When the Basic Reproduction number is less than unity we can infer that all individuals are just susceptible and no infection actually exists. This is much like the DFE and therefore the simplifying assumption we made to derive stability checks out.

2. Effective Reproduction Number:

   In reality assuming that the entire initial population is susceptible is unrealistic. This is so because some proportion of the people have some kind of immunity to the disease. Further, given the dynamic nature of the population itself having R_0 to be the deciding factor for a disease spreading is unrealistic. SO we use effective reproduction number as the main factor. Again, it is important to note that at the DFE it is alright to take basic Reproduction number and proceed with the stability analysis as at the DFE the infectious population is in fact 0.
   Now we define $R_{eff} = p \times R_0$, where p is some proportion that is less than 1. Here we emphasize that only if $R_{eff} > 1$ at the Endemic Equilibrium will the disease spread.

1.4.2 Stability of the Endemic Equilibrium point

To study the stability of the above model we first make a simple transformation for ease of calculation.
We use the transform $sN = S$, $eN = E$, $iN = I$ and $rN = R$. This transformation can be thought off as a conversion from absolute numbers of Susceptible, Exposed, infected and Recovered populations to that of proportions.
Now, it is important to note that on using this transformation we can't simply write $S' = Ns'$. Working with a non-constant population, we must include its effect in this transformation.
Therefore, it is correct to write $S' = s'N + sN' = s'N + (b - d)N$. Similar results follow for E,I,R.

Applying this to the original system, we get

$s' = b - \beta si - bs + wr$

$e' = \beta si - \sigma e - be$

$i' = \sigma e - \gamma i - bi$

$r' = \gamma i - wr - br$

We further simplify this model by clubbing together some parameters. We note that as all the constants are in fact positive values, this clubbing together doesn't make a huge difference for the analysis. We take $f = b + \sigma$, $g = \gamma + b$ and $h = w + b$ and rewrite the system as follows

$s' = b - \beta si - bs + wr$

$e' = \beta si - fe$

$i' = \sigma e - gi$

$r' = \gamma i - hr$

Similar to the case of studying the stability of the DFE we first find the Jacobian and evaluate the Jacobian at the Endemic Equilibrium point. We first find the equilibrium point by equating s', e', i' and r' to 0 simultaneously.

The Endemic equilibrium point (EE) of the transformed system is
$s^* = \frac{fg}{\beta\sigma}$
$e^* = \frac{-bfg^2h + bgh\beta\sigma}{\beta\sigma(fgh - w\gamma\sigma)}$
$i^* = \frac{-bfgh + bh\beta\sigma}{\beta(fgh - w\gamma\sigma)}$
$r^* = \frac{-bfg\gamma + b\beta\gamma\sigma}{\beta(fgh - w\gamma\sigma)}$

It can clearly be seen that s^* is a positive value. We now proceed to show that e^*, $i*$ and r^* are positive. We do this in order to simplify the process of commenting on the stability.

We first start by looking at the term $(fgh - w\gamma\sigma)$. Expanding f, g and h we have:
$(\sigma + b)(\gamma + b)(w + b) - w\gamma\sigma$
On expanding the terms in the bracket we obtain $(...positiveterms...) + w\gamma\sigma - w\gamma\sigma$ which is clearly positive.
We now look at the numerator in i^*. We have $bh\beta\sigma - bfgh$. We simplify this as follows in order to comment on the sign of the numerator.

$bh \times (\beta\sigma - fg) = (bhfg) \times (\frac{\beta\sigma}{fg} - 1) = (bhfg) \times (R_0 \frac{d}{b} - 1)$
Here we note that as mentioned in the NOTE of Section 3.4.1 that $R_0 \times p$, where $p < 1$ is the effective reproduction number. In our scenario, $R_0 \times \frac{d}{b}$ is the effective reproduction number, R_{eff}. As mentioned earlier, we need that $R_{eff} > 1$ for the disease to propagate. Under this assumption we have that the numerator of $i^* > 0$. Having already shown the numerator is positive we can conclude that i^* is indeed a positive value.

Using this knowledge we can very easily show that e^* and r^* are also positive values. The reader's attention is directed towards Appendix A for more detail on the same.

Now that we have that all the arguments of the EE are positive we proceed to discuss the stability at the EE. We proceed without substituting the actual values of the EE into the Jacobian. We instead leave the s,e,i,r terms as us but keep in mind that they are indeed positive values. We do this in order to simplify the mathematical expressions we have to deal with.

We also note that as the Jacobian Matrix is a complex at the EE we refrain from explicitly finding the eigenvalues. We instead resort to finding the characteristic equation and using Descartes' Rule of Sign Changes criteria to deduce stabil-

ity.
We first calculate the Jacobian of the most simplified system obtained in this section.

$$J(s,e,i,r) = \begin{pmatrix} -\beta i & 0 & -\beta s & w \\ \beta i & -f & \beta s & 0 \\ 0 & \sigma & -g & 0 \\ 0 & 0 & \gamma & -h \end{pmatrix}$$

The linearized matrix A at EE is just J(s,e,i,r) evaluated at the EE. We now obtain the characteristic equation for J(EE) as follows:

$-iw\beta\gamma\sigma + (-h-\lambda) \times [(-g-\lambda) \times (bf + b\lambda + f\lambda + \lambda^2 + fi\beta + i\beta\lambda) - (-bs\beta - s\lambda\beta)\sigma] = 0$

This characteristic equation of the system linearized about the EE in fact has all negative roots [Appendix A] and we thereby conclude that the system is stable at the EE as well.

1.5 Simulink Implementation with Graphs

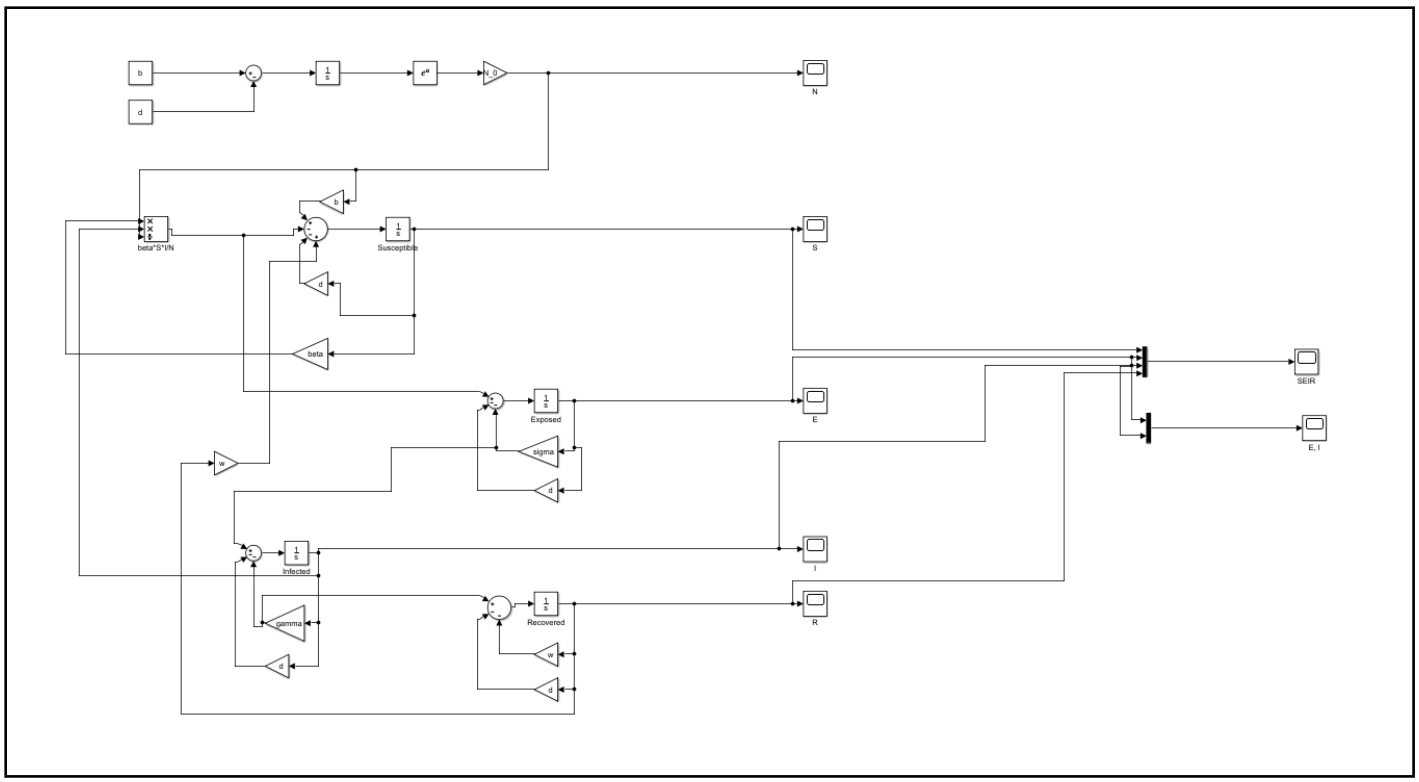


Figure 1: Block Diagram representation of SEIR Model (Without Control)

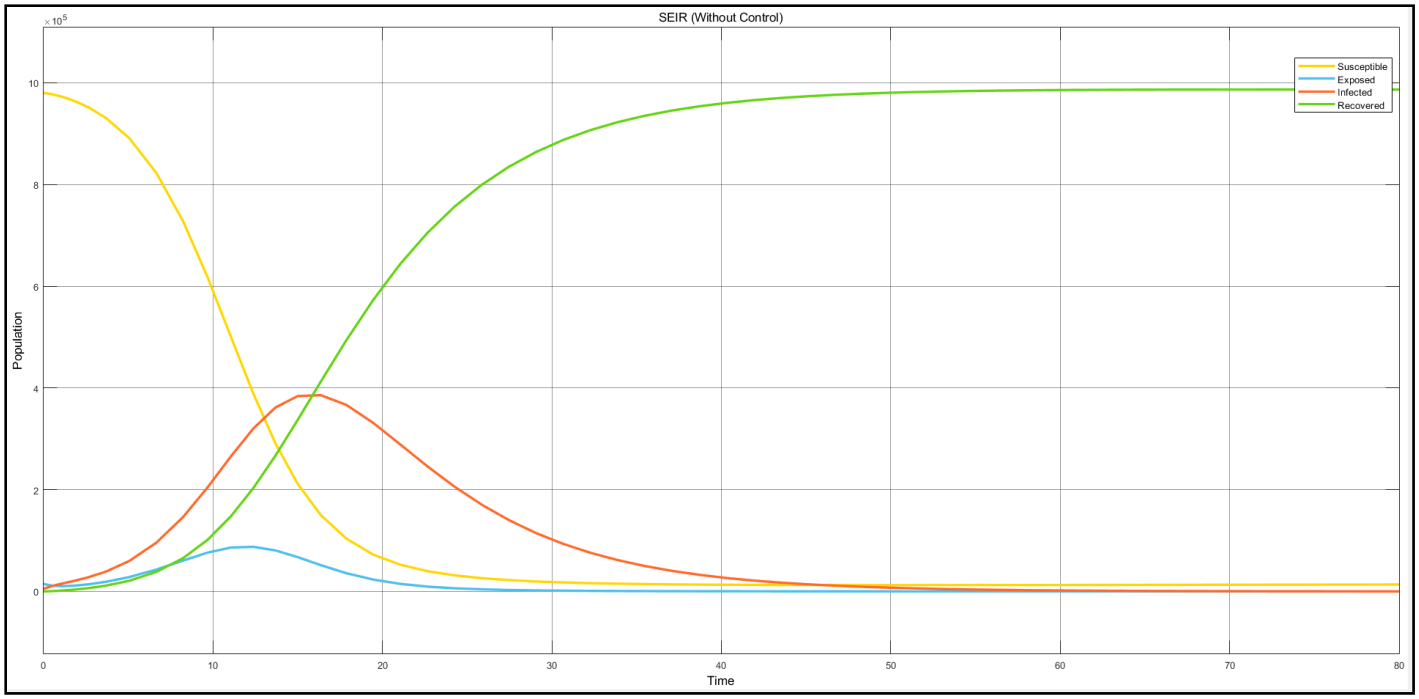


Figure 2: SEIR Dynamics (Without Control)

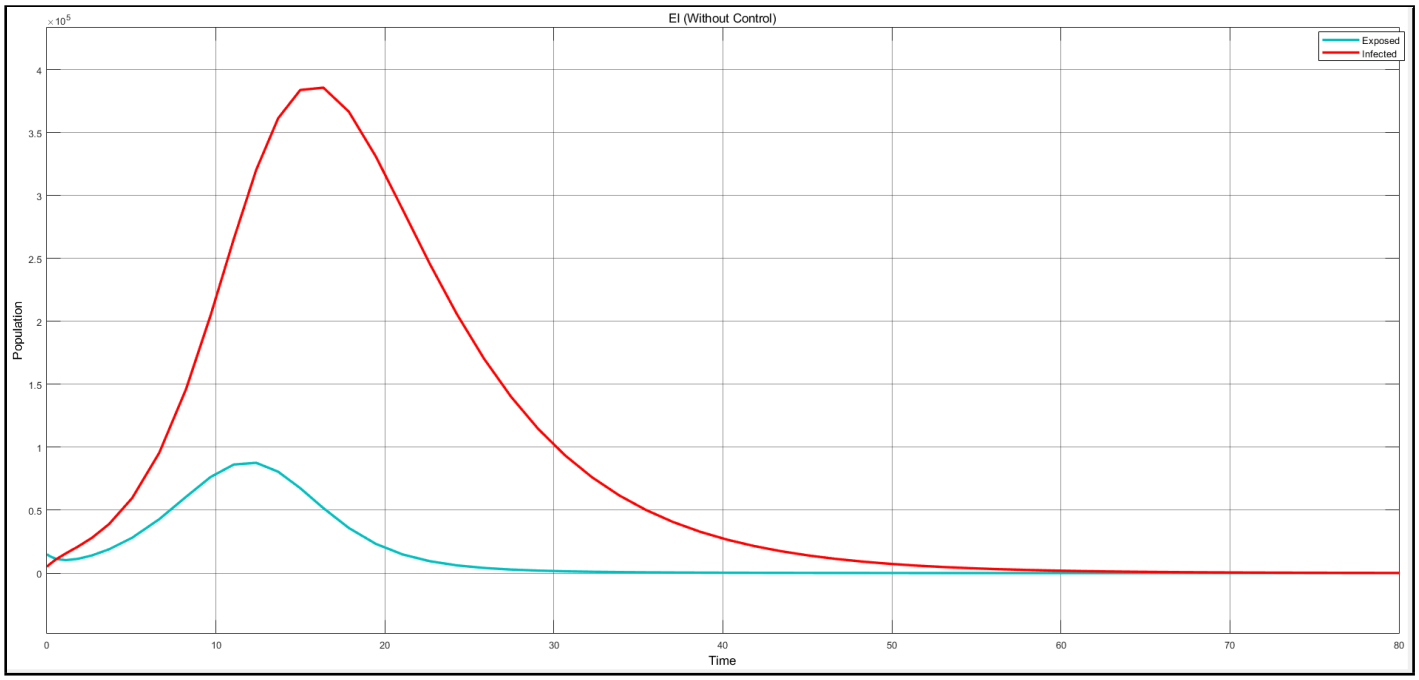


Figure 3: Dynamics of Exposed and Infected Populations (Without Control))

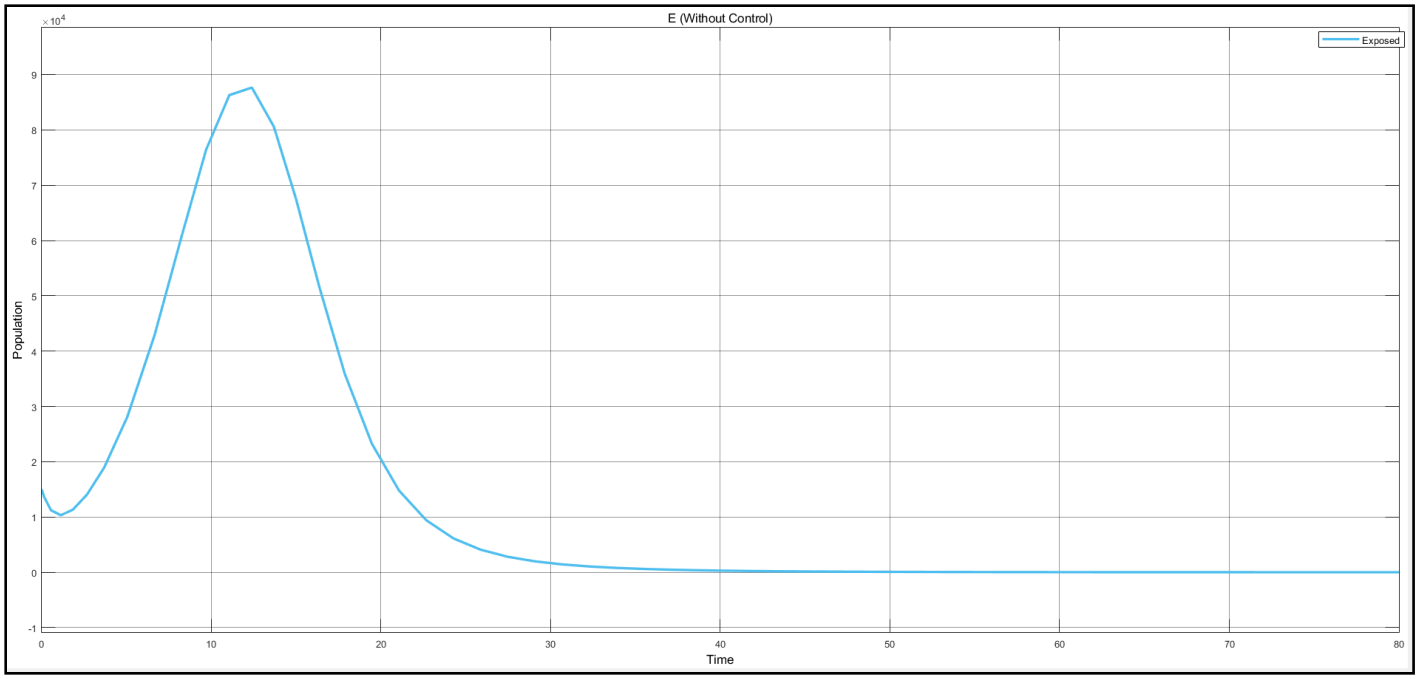


Figure 4: Dynamics of Exposed Population (Without Control))

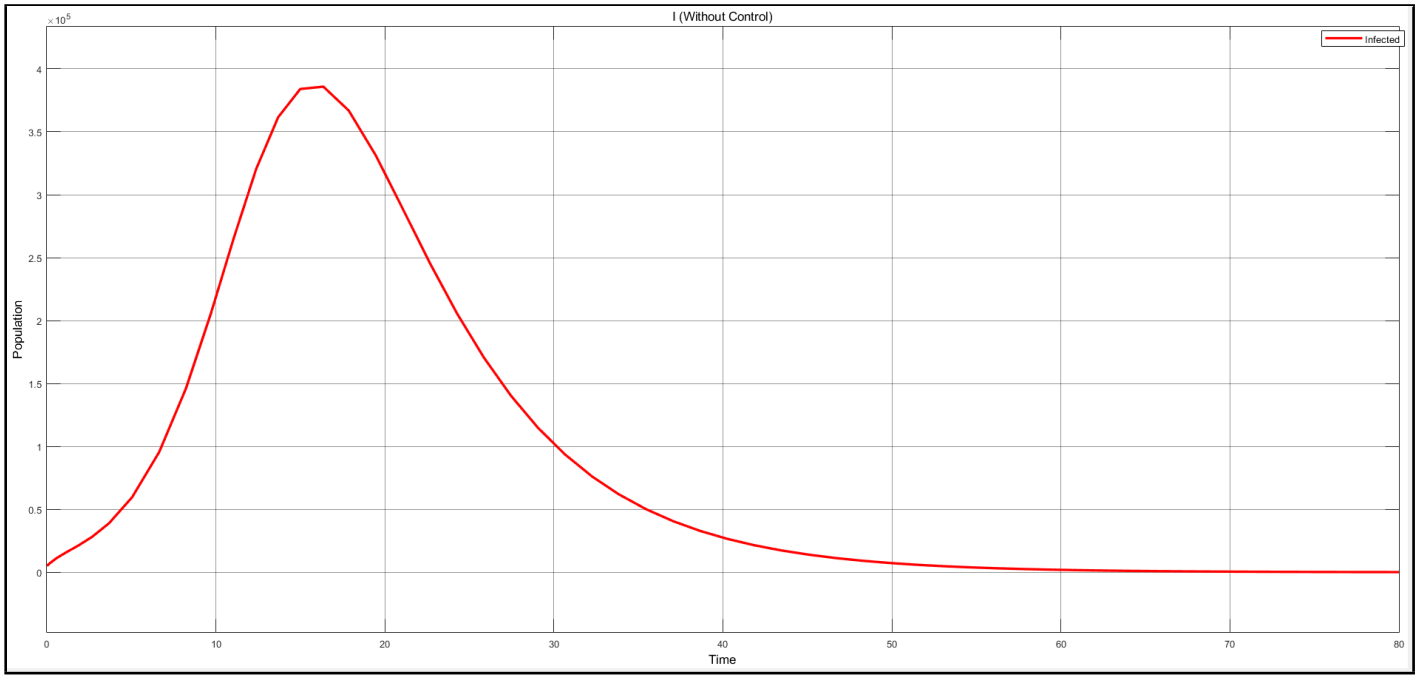


Figure 5: Dynamics of Infected Population (Without Control))

2 Model with Vaccination Control Law

2.1 Assumptions made

The same assumptions made for the model without vaccinations hold even for this case. We however add a few additional notes for completeness and discuss the control law we use for the system and its main use.

NOTES:

1. Till now we considered the system in the form $X' = F(X)$, where X is the state vector. $X \in R^4$ and we take $X = (S, E, I, R)$. We showed in the previous sections that this system is in fact stable. So that begs the question, Why do we need a control law?
2. The use of control laws varies from problem to problem. Here, we use a Vaccination Control Law and form a closed-loop system to show that the infected population and Exposed population can in fact be controlled very efficiently. We note that this control law is taken from [2].
3. The control law we use is as follows:
$$V(t) = \frac{1}{bN} \times [wR(t) + (g - \frac{\beta I(t)}{N})S(t) + bN]$$
Here the parameter g can be thought of as the vaccination parameter that can be varied to obtain a different vaccination law. The mathematical derivation of the control can be seen clearly in [2] and is in fact quite intuitive.
4. Vaccination Control parameter g:
Increasing the value of g, as is clear, increases the Vaccination proportion. But, it is imperative to note that a random high value of g is practically impossible to achieve. This is so because of the limited resources we have for Vaccinations and money to produce the vaccinations.
5. We now have the freedom to think of w as a more well-defined parameter in the model. It can now we understood as the rate at which immunity is lost by some people. This immunity was a rather ambiguous term in the previous model, but here it clearly takes the role as the effect of vaccinations.

2.2 Mathematical Model

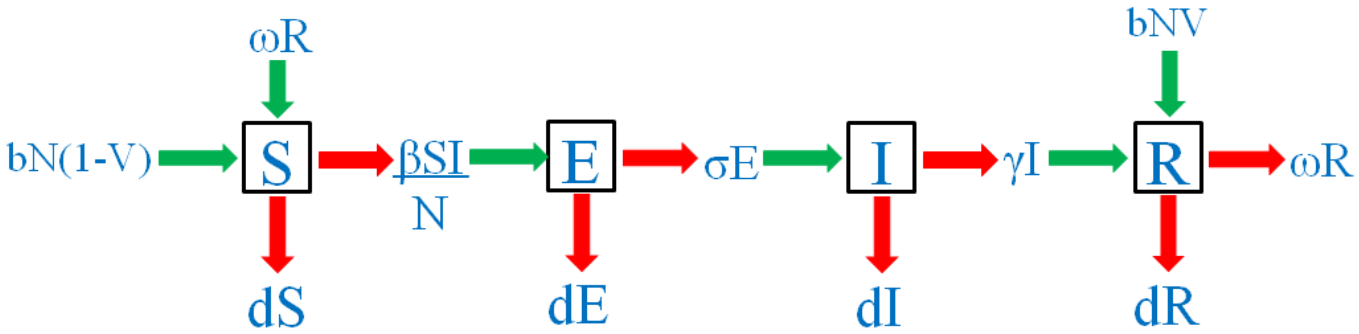
We now add the closed-loop vaccination control law to the initial compartmental model and obtain the following system:

$S' = bN(1 - V) - \beta\frac{SI}{N} - dS + wR$

$E' = \beta\frac{SI}{N} - \sigma E - dE$

$I' = \sigma E - \gamma I - dI$

$R' = \gamma I - dR - wR + bNV$



We note here that w is in fact non-zero because of the consideration of vaccinations. We repeat here that vaccinations last only for a certain period of time after which an individual loses immunity. The rate at which this immunity is lost is characterized by w.

2.3 Stability Considerations

The stability considerations for the system with Vaccinations is not as straightforward as the stability analysis of the system with no control. We restrict the stability considerations to graphically convincing ourselves that the S,E,I and R trajectories in fact converge to a finite value in a finite interval of time. Readers with interest can look at stability considerations with a similar model in [2].

2.4 Simulink Implementation with Graphs

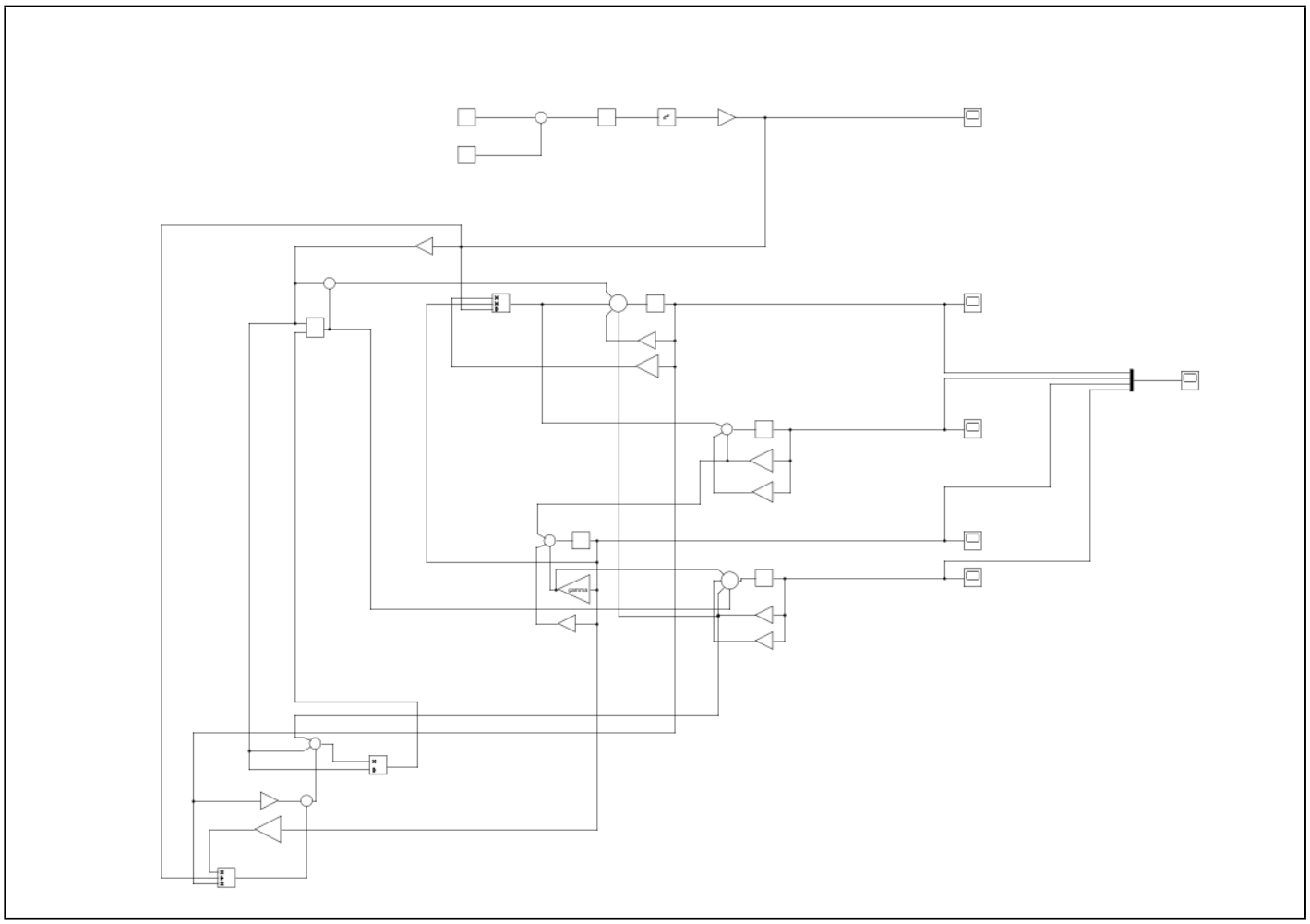


Figure 6: Block Diagram representation of SEIR Model (With Vaccination Control Law)

Since the compartmental SEIR model is inherently stable, our objective with using a control strategy would be to inhibit the spread of the disease within a smaller population and in lesser time.

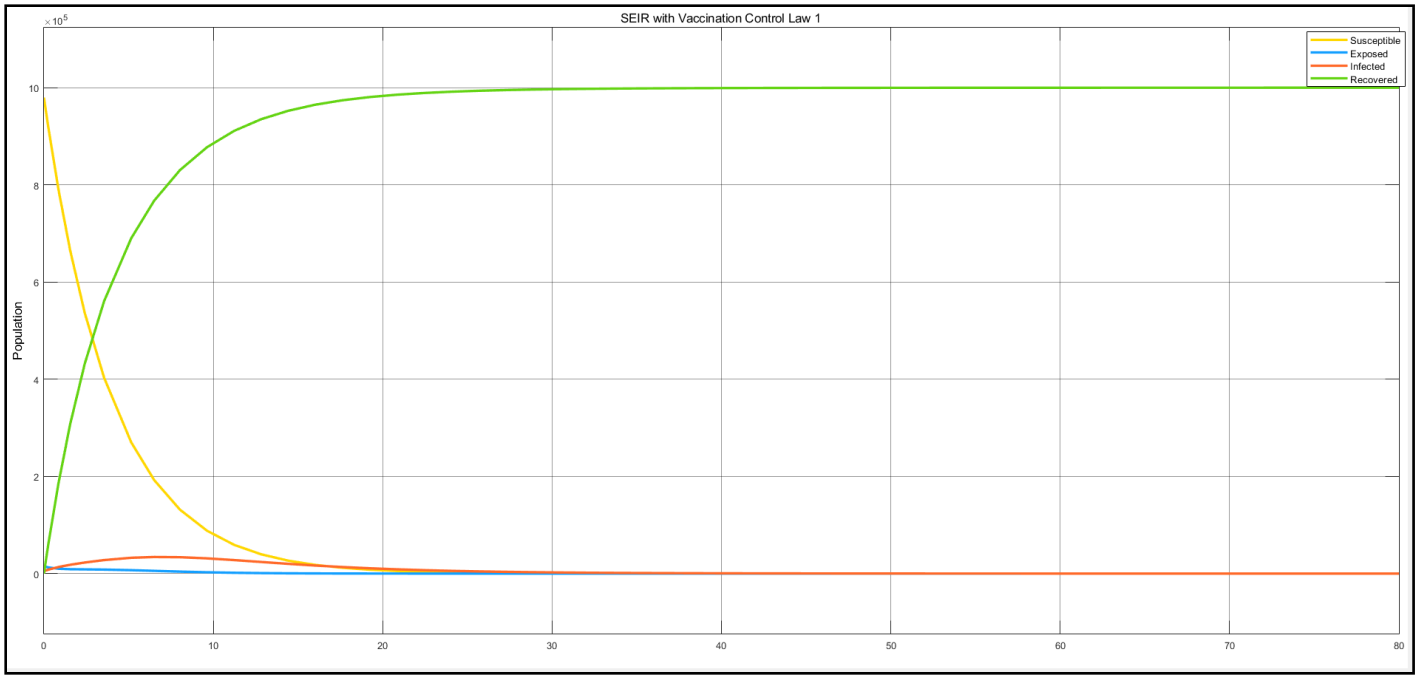


Figure 7: SEIR Dynamics (With Vaccination Control Law)

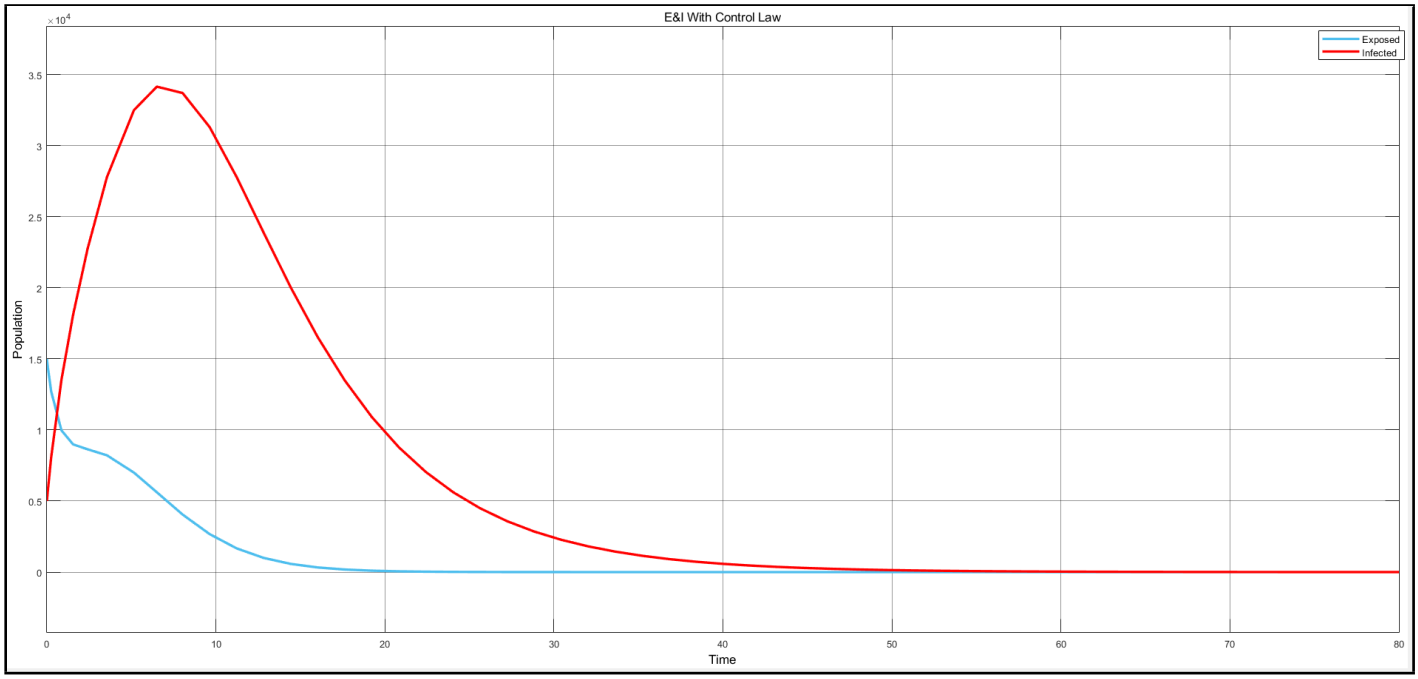


Figure 8: Dynamics of Exposed and Infected Populations (With Vaccination Control Law)

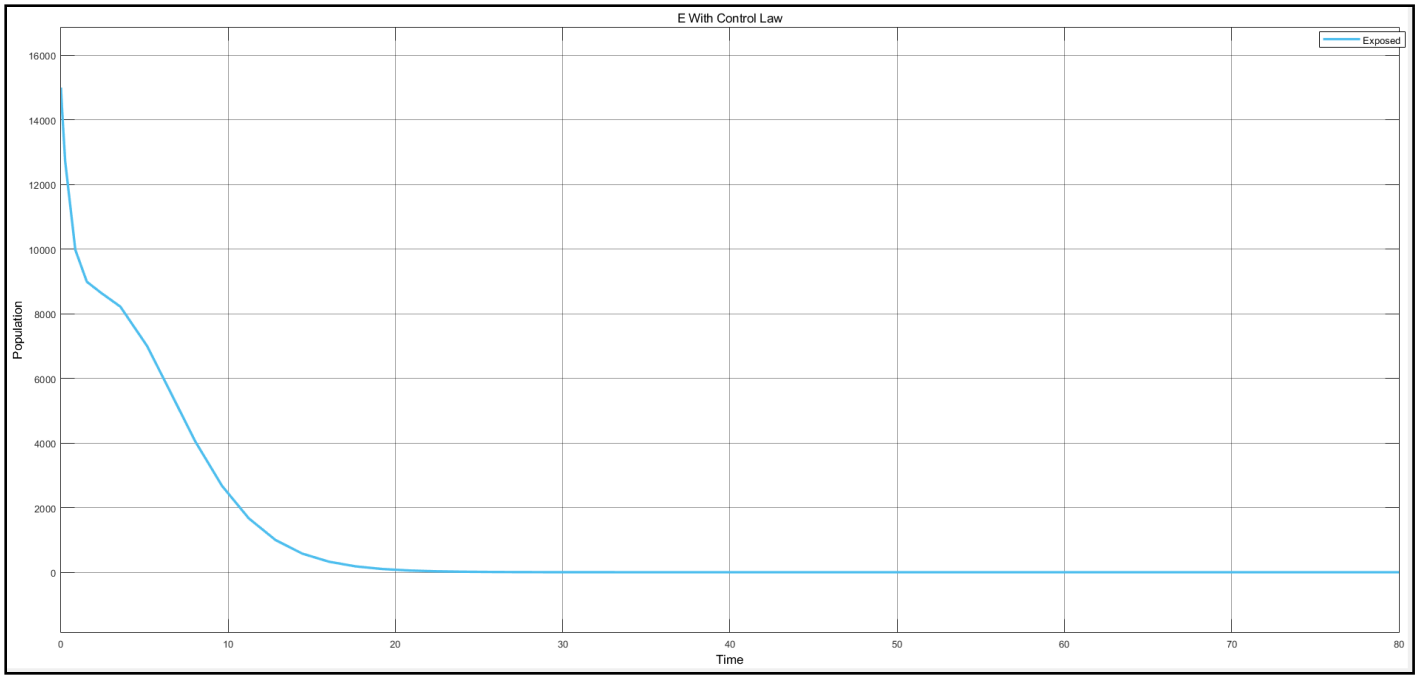


Figure 9: Dynamics of Exposed population (With Vaccination Control Law)

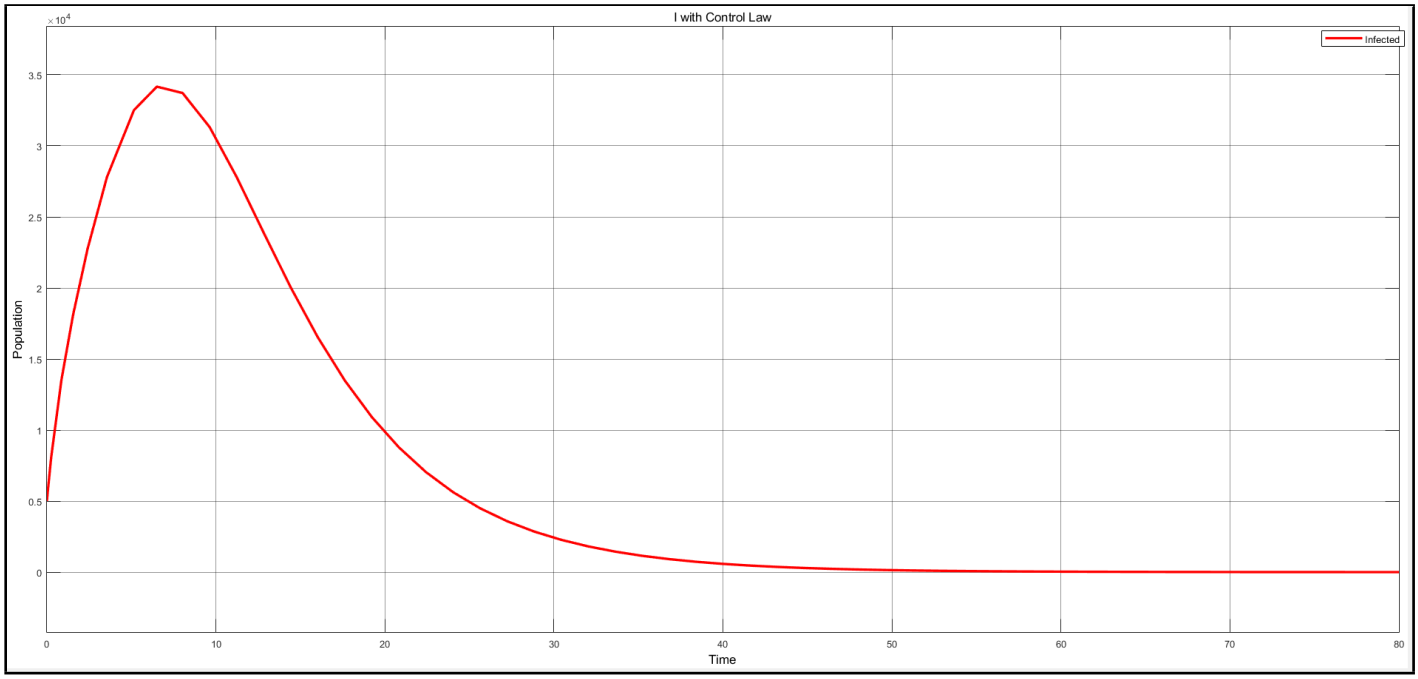


Figure 10: Dynamics of Infected population (With Vaccination Control Law)

3 Observations

1. Figure 2 shows the behaviour of the disease in a population without the use of control. The decay of of SEI plots and simultaneous growth of R plot allow us to infer that the SEIR model used is inherently stable.

2. Figure 3 shows a comparison between E and I plots that gives us details of their respective points of maximum instability and time-growth. Additionally, we observe that the rate of change of I exceeds that of E, which implies that it would be harder to tackle the spread of such a potent disease beyond the E compartment. Control Strategies should be aimed at mitigating spread among other compartments.

3. Figure 7 shows the disease dynamics with control strategies deployed. We observe that disease dynamics among E and I compartments have been subdued (rder of 10) within a shorter time frame (¡10 days). The consequences of this control are a) Reduced stress on healthcare infrastructure due to quicker inhibition of the disease b) Reduced lifespan of disease pathogen within a population leading to lesser room for mutation of disease. Mutation poses a great threat to the effectiveness of the control strategy since it leads to unaccounted changes in the constants used.

4. Figure 8 shows a comparison in the E-I dynamics under vaccination. We observe that the rates of decay of E and I show a similarity, which is a positive change since this targets the transmission of the disease at the site where its effects are contracted.

APPENDIX A

1. Sign of the Endemic Equilibrium Point

   Having already shown that i^* is a positive value, we now proceed to comment on e^* and r^*. The numerator of i^* and r^* are the same and therefore we immediately have that r^* is in fact a positive value. Now, the numerator of e^* is simply $g\times$ numerator of i^*. Therefore again we have that e^* is also a positive value.

2. Stability Considerations of the EE

   As obtained earlier the characteristic equation for the system linearized about the EE is as follows:

   $$-iw\beta\gamma\sigma + (-h-\lambda)\times[(-g-\lambda)\times(bf+b\lambda+f\lambda+\lambda^2+fi\beta+i\beta\lambda)-(-bs\beta-s\lambda\beta)\sigma] = 0$$

   We now expand this entirely to obtain:

   $$\lambda^4+\lambda^3(b+f+g+h+\beta i)+\lambda^2(bf+bg+fg+bh+fh+gh+fi\beta+gi\beta+hi\beta-s\beta\sigma)$$

   $$+\lambda(bfg+bfh+bgh+fgh+fgi\beta+fhi\beta+ghi\beta-bs\beta\sigma-hs\beta\sigma)+(bfgh+fghi\beta-bhs\beta\sigma-iw\beta\gamma\sigma)=0$$

   Now, instead of finding the roots of this equation and then commenting on whether these roots are negative or not we use Descartes' rule of sign change to obtain the number of negative roots.

   In order to use Descartes' rule we first have to definitely know the sign of the coefficients in the characteristic equation. We see by inspection that the coefficients of λ^4 and λ^3 have a positive file.
   We observe in the coefficient of λ^2 that we have a term $fg-s\beta\sigma$. We are evaluating the characteristic equation at the EE and therefore $fg-s\beta\sigma$ is in fact $fg-s^*\beta\sigma=0$. The remaining terms in the coefficient of λ^2 are positive and therefore we conclude that the coefficient is positive. Now, we group similar terms in the coefficient of λ^1 and λ^0 are positive.

   With the knowledge that all the coefficients of the characteristic equation are poitive we procees to apply Descartes' Rule of sign change. Let us call the characteristic equation $h(\lambda)=0$

   We use this rule in two steps.

   (a) We evaluate $h(\lambda)=0$ at $\lambda=+1$ and count the number of sign changes between consecutive coefficient. The number of changes will give us the number of positive roots.
   We notice here because all coefficients are positive, the series of signs on substituting +1 is as follows:
   + + + + +
   As there are no sign changes we conclude that there are no positive roots for the characteristic equation.

   (b) Now we evaluate $h(\lambda)=0$ at $\lambda=-1$ and again count the number of sign changes.
   Remembering that all coefficient are positive values the series of signs are as follows:
   + - + - +
   There are clearly 4 sign changes and this means there are at least 4 negative real roots for the characteristic equation.
   No as the equation is of fourth order and the coefficients are all real we now the maximun number or roots are 4. Therefore, all roots of the characteristic equation are negative.

   We have thus shown that the eigenvalues are in fact all negative, thereby guaranteeing stability at the EE.

REFERENCES

[1] Marek B. Trawicki, Deterministic Seirs Epidemic Model for Modeling Vital Dynamics, Vaccinations, and Temporary Immunity, Mathematics 2017, 5, 7; doi:10.3390/math5010007

[2] M. De la Sen, S. Alonso-Quesada, Vaccination strategies based on feedback control techniques for a general SEIR-epidemic model, Applied Mathematics and Computation 218 (2011) 3888–3904

[3] Xuhui Tan, Lingling Yuan, Jingjing Zhou, Yinan Zheng, Fen Yang, Modeling the initial transmission dynamics of influenza A H1N1 in Guangdong Province, China, International Journal of Infectious Diseases 17 (2013) e479-e484

[4] Sarah A. Al-Sheikh, Modeling and Analysis of an SEIR Epidemic Model with a Limited Resource for Treatment, Global Journal of Science Frontier Research Mathematics and Decision Sciences, Volume 12 Issue 14, 2012