Math 636 - Mathematical Modeling

Discrete SIR Models
Influenza

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Outline

Influenza

Influenza

- Influenza or flu is a viral infection transmitted by air
- Seasonal disease causing respiratory problems in humans and animals
- Annually results in an average of 30,000 deaths primarily among young and old
- Pandemic in 1918 – Perhaps worst natural disaster in human history
  - Resulted in 50-100 million people (3-5% of world population
  - Peak deaths were from young adults
  - Created a ***cytokine storm*** (overreaction in immune system)
  - Uncertainty on reasons for why this pandemic was particularly bad
  - Caused by **H1N1 influenza virus**

Influenza

Influenza

- There are two primary types, **A** and **B**, of influenza
- ***Flu season*** usually starts in Fall continuing through winter
- Virus mutates regularly, creating new strains each year
- Influenza is an RNA virus with 11 genes
- Common symptoms are high fever, runny nose, sore throat, muscle and/or head aches, coughing, and tired feeling though 33% with flu are asymptomatic
- Symptoms appear 2 days after exposure and last about one week
- Considered an airborne disease, spread by coughing, but contact with infected surfaces can transmit the disease
- Limited available treatments, but vaccines are effective

Influenza Virus

Influenza Vaccine

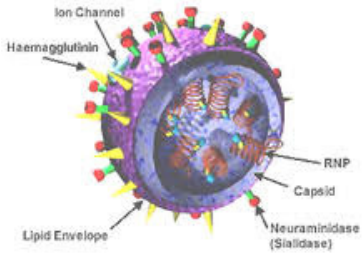
Influenza has high ***mutation*** rate.

WHO and **CDC** predict likely strains for each flu season (from around the world)

Requires 6 months to develop

Still uses hen eggs for millions of doses

Flu Vaccine is usually effective 2 weeks after vaccination



Influenza Case Study

Type A Influenza (H3N2) cases from **CDC** 2004-2005
Infected cases from 157,759 samples tested from people with flu-like symptoms

n (wk)	I_n	n (wk)	I_n	n (wk)	I_n	n (wk)	I_n
0	3	13	675	25	164	37	1
1	2	14	580	26	94	38	6
2	7	15	844	27	37	39	0
3	12	16	974	28	26	40	0
4	9	17	1096	29	15	41	1
5	10	18	1354	30	8	42	0
6	27	19	1335	31	5	43	0
7	21	20	1109	32	3	44	0
8	36	21	936	33	1	45	1
9	63	22	627	34	2	46	0
10	108	23	476	35	0	47	3
11	255	24	295	36	2	48	0
12	472						

$n = 0$ is last week in September, beginning of the flu season

SIR - Influenza Model 1

SIR Model: Influenza is a disease that satisfies conditions for an SIR model.

- Population is divided into susceptible, infected, and recovered (or removed) individuals.
- New strains of influenza make most people susceptible (S_n) at the beginning of an outbreak.
- Exposed individuals become infected (I_n) – contact with sputum of infected individuals.
- Individuals, who recover, enter the recovered group (R_n).
- Recovered individuals have immunity preventing reinfection.
- Influenza needs to mutate to be able to attack humans in the next year, as the available susceptibles is small after a influenza outbreak.

SIR - Influenza Model 2

SIR Model: Influenza is a rapidly spreading, mostly non-fatal disease.

Assume that the human population is constant N for the duration of the model simulation,

$$N = S_n + I_n + R_n \qquad \text{or} \qquad R_n = N - S_n - I_n,$$

so births and deaths are ignored.

A ***discrete model*** is presented for the weekly evolution of the disease.

- New infecteds, I_{n+1}, result from contact between the susceptibles, S_n, and infecteds, I_n, with contact rate β/N.
- Infecteds are cured at a rate proportional to the number of infecteds, γI_n, which become recovered, R_n.

SIR - Influenza Model 3

SIR Model for Influenza: The assumptions on contact and cure rates give the ***SIR model***, with the constant population assumption, $N = S_n + I_n + R_n$:

$$\begin{aligned} S_{n+1} &= S_n - \frac{\beta}{N} S_n I_n, \\ I_{n+1} &= I_n + \frac{\beta}{N} S_n I_n - \gamma I_n, \\ R_{n+1} &= R_n + \gamma I_n. \end{aligned}$$

Note that the first two equations have no dependence on R_n.

The term $\frac{\beta}{N} S_n$ represents the proportion of contacts by an infected individual that result in the infection of a susceptible individual.

The parameter γ is the probability that an infected person recovers (enters class R of the SIR model).

The ratio $\frac{1}{\gamma}$ is the average length of the infectious period of the disease.

SIR Model Simulation

Simulation of SIR Model for Influenza: A least squares best fit to the infected population, I_n, is fit to the CDC data for the 2004-2005 flu season.

$$\begin{aligned} S_{n+1} &= S_n - \frac{\beta}{N} S_n I_n, \\ I_{n+1} &= I_n + \frac{\beta}{N} S_n I_n - \gamma I_n. \end{aligned}$$

The model is initialized with $N = 157,759$, $S_0 = 157,756$, and $I_0 = 3$ and run for $n = 48$ weeks.

The ***SSE*** is minimized giving

$$\beta = 3.9928 \qquad \text{and} \qquad \gamma = 3.5170,$$

where $SSE = 155,083$.

SIR - Parameter Fit

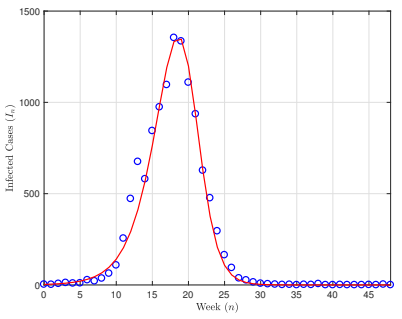
```
1  function J = lst_sir(p,idata)
2  %Least Squares best fit of SIR model
3  K = length(idata);
4  N = 157759;
5  Sn(1) = [157756];
6  In(1) = [3];
7  for i = 2:K
8      Sn(i) = Sn(i-1) - p(1)*Sn(i-1)*In(i-1)/N;
9      In(i) = In(i-1) + p(1)*Sn(i-1)*In(i-1)/N - ...
           p(2)*In(i-1);
10 end
11 err = idata - In;
12 J = err*err';
13 end
```

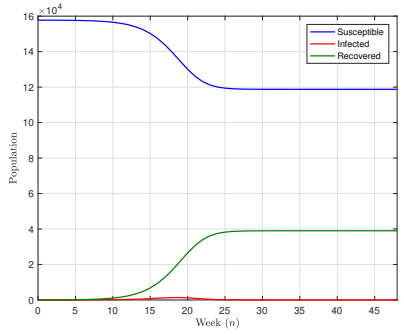
The best-fitting model to the infected population, `idata`, uses the nonlinear solver:

`p1=fminsearch(@lst_sir,p0,[],idata)`

SIR - Influenza Model

The graphs below show the fit to the CDC data and the behavior of the model





As the data shows there is a peak in the disease, then it dies off almost as rapidly as it starts.

The simulation shows that over 48 weeks about 39,000 cases of flu occur, which is about 24.7% of the population.

Basic Reproduction Ratio, R_0

Epidemiologists often examine the ***Basic Reproduction Ratio,*** R_0,

$$R_0 = \frac{\beta}{\gamma}.$$

This provides a measure of how rapidly a disease will spread and how much of the population will be affected by a particular disease.

The parameter, β, reflects the average number of susceptible contacts an infected individual will have during the infection.

The parameter, γ, reflects the average length of time an infected individual remains infective.

This time is $\frac{1}{\gamma}$, which is about 1.99 days for our case.

For the CDC case study of the 2004-2005 flu season, our best fitting model gives:

$$R_0 = \frac{3.9928}{3.5170} = 1.135.$$

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Basic Reproduction Ratio, R_0

The studies of Sir Ronald Ross around 1900 demonstrated the important concept that extinction of malaria would not require elimination of all mosquitoes.

This is the importance of R_0.

- If R_0 is greater than **1**, then more people are getting the disease than are recovering from it, so the disease spreads.
- However, if $R_0 < 1$, then there is an exponential decay of the disease, causing the disease to die out.
- The larger the value of R_0, the more infectious the disease.
- In the case of ***influenza***, R_0 is only a bit more than **1**, which is why survival of the influenza virus depends on its high mutation rate

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Controlling Influenza

CDC is interested in minimizing the impact of ***influenza*** – Examine **3** different controls.

- **Flu Vaccine**
  - Vaccines lower the pool of susceptibles, S_0
  - Vaccines take susceptibles and move them to recovered, so S_0 individuals $\rightarrow R_0$.
- **Quarantine** or **Education of public**
  - Both methods reduce the contact of susceptibles.
  - These methods lower the value of β.
- **Oseltamivir** or **Tamiflu**
  - This drug shortens the time with the symptoms of flu, so decreases the period of infectivity.
  - This is modeled by increasing the value of γ.

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Flu Vaccine

Flu Vaccine: Assume that 5% of the population receive vaccination that immediately transfer individuals from S_0 to R_0.

Thus, begin the model with

$$S_0 = 0.95N - I_0 \qquad \text{and} \qquad R_0 = 0.05N.$$

For the simulation, assume that β and γ remain the same.

The simulation shows that over 48 weeks about 22,298 cases of flu occur, which is about 14.1% of the population.

This is about 57.2% of the number infections from the original model simulation.

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Quarantine or Education of public

Quarantine or **Education of public**: Assume that the contact rate decreases by 5% or $\beta = 3.7931$.

The model simulation remains the same as the original simulation, except the value value of β is reduced.

The simulation shows that over 48 weeks about 23,468 cases of flu occur, which is about 14.9% of the population.

This is about 60.2% of the number infections from the original model simulation.

Oseltamivir or Tamiflu

Oseltamivir or **Tamiflu**: Assume that Tamiflu is given within 24 hours of symptoms occurring for flu.

Assume that this decreases the time of infectiousness by about 5%, which is reflected by increasing γ by 5%.

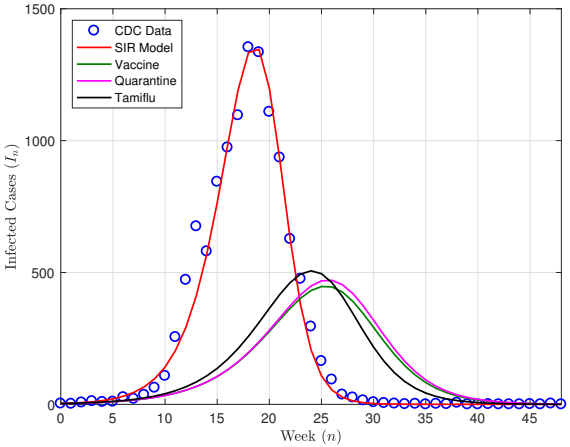
The model simulation remains the same as the original simulation, except the value of γ is increased with β and initial conditions the same.

The simulation shows that over 48 weeks about 24,305 cases of flu occur, which is about 15.4% of the population.

This is about 62.3% of the number infections from the original model simulation.

Graph of Influenza Cases with Treatments

By making variations of only 5% in either the initial susceptibles (vaccination) or either the parameter for contact, β, or flu duration, γ, results in about 60% of the number of cases, which is seen in the graph below:



Modeling Influenza Treatments

The modeling shows that each of the treatments are roughly the same in decreasing the spread of influenza.

- The model presented is a simple well-mixed compartmental model, which allows a comparative study of possible treatments.
  - Because the treatments produce similar outcomes, the best course of action would depend on costs or the practicality of the approach
- One should discuss the strengths and weaknesses of this model.
- What other diseases fit this type of model?
- Does this model help with strategies for elimination of more serious diseases?

Equilibria 1

The SIR model (with constant population N) satisfies the equations:

$$\begin{aligned} S_{n+1} &= S_n - \frac{\beta}{N} S_n I_n, \\ I_{n+1} &= I_n + \frac{\beta}{N} S_n I_n - \gamma I_n. \end{aligned}$$

By setting $S_{n+1} = S_n = S_e$ and $I_{n+1} = I_n = I_e$, the first equation satisfies:

$$S_e = S_e - \frac{\beta}{N} S_e I_e, \quad \text{or} \quad \frac{\beta}{N} S_e I_e = 0,$$

which gives $S_e = 0$ or $I_e = 0$.

The second equation satisfies:

$$I_e = I_e + \frac{\beta}{N} S_e I_e - \gamma I_e, \quad \text{or} \quad \frac{\beta}{N} S_e I_e = \gamma I_e.$$

Equilibria 2

From the second equation:

$$\frac{\beta}{N} S_e I_e = \gamma I_e,$$

so if $S_e = 0$, then necessarily $I_e = 0$. However, if $I_e = 0$, then S_e could be anything.

It follows that the equilibria are:

$$I_e = 0 \qquad \text{and} \qquad 0 \le S_e \le N.$$

Thus, the infectious population must fall to **zero**, while the susceptible population could be anything. The remainder of the population is in the recovered group of individuals.

Linearizing about the Equilibria

The system:

$$\begin{pmatrix} S_{n+1} \\ I_{n+1} \end{pmatrix} = \begin{pmatrix} F(S_n, I_n) \\ G(S_n, I_n) \end{pmatrix} = \begin{pmatrix} S_n - \frac{\beta}{N} S_n I_n \\ (1-\gamma) I_n + \frac{\beta}{N} S_n I_n \end{pmatrix},$$

is linearized using the Jacobian matrix, which satisfies:

$$J(S_n, I_n) = \begin{pmatrix} \frac{\partial F}{\partial S_n} & \frac{\partial F}{\partial I_n} \\ \frac{\partial G}{\partial S_n} & \frac{\partial G}{\partial I_n} \end{pmatrix} = \begin{pmatrix} 1 - \frac{\beta}{N} I_n & -\frac{\beta}{N} S_n \\ \frac{\beta}{N} I_n & 1 - \gamma + \frac{\beta}{N} S_n \end{pmatrix}.$$

At the equilibrium, $(S_e, 0)$, the linearized discrete system satisfies:

$$\begin{pmatrix} S_{n+1} \\ I_{n+1} \end{pmatrix} = \begin{pmatrix} 1 & -\frac{\beta}{N} S_e \\ 0 & 1 - \gamma + \frac{\beta}{N} S_e \end{pmatrix} \begin{pmatrix} S_n \\ I_n \end{pmatrix}.$$

This matrix is an upper triangular, so the eigenvalues are $\lambda_1 = 1$ and $\lambda_2 = 1 - \gamma + \frac{\beta}{N} S_e$.

Linearizing about the Equilibria

The equilibrium is unstable, and the ***influenza*** spreads if $\lambda_2 > 1$ or

$$1 - \gamma + \frac{\beta}{N} S_e > 1 \qquad \text{or} \qquad \beta \frac{S_e}{N} > \gamma.$$

This is equivalent to

$$\frac{N}{S_e} < \frac{\beta}{\gamma} \equiv R_0.$$

Recall the disease spreads when $R_0 > 1$, so if $S_0 \approx N$, the inequality above implies that the disease will spread.

However, as S_n gets smaller with more people getting immunity, then the inequality reverses with

$$\frac{N}{S_n} > \frac{\beta}{\gamma},$$

so $\lambda_2 < 1$, which results in the disease dying out.