Mathematical Models in Epidemiology

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Model

- Fashion model
- Toy Model of a train
- Road Map
- Globe
- Prototype of a car

What do they do?
-they represent something else.

What is a Model?

"Model is an object or a concept that is used to represent something else in a form we can comprehend."

Note:
A sense of purpose is intrinsic in a model.

Modeling is the process of building (developing) model.

A model can be a

- Scaled model
- Pictorial model
- Conceptual model
- Symbolic model

Mathematical Model is a symbolic model where the language is in terms of mathematical symbols/concepts.

Modeling Process

This requires translation of real world problem as a real world model with a specific goal.

A model retains only those features/ characteristics which are relevant and significant from the point of view of goal.

Then real world model is translated in the language one can conceive of (Mathematics here).

A model is said to be adequate/ satisfactory if it is adequate for goals in the mind of modeler.

Is Mathematics Useful?

For Hardy, the most beautiful mathematics was that which had no practical applications in the outside world .
Its (pure mathematics) very "uselessness" on the whole meant that it could not be misused to cause harm.
Little did he know that number theory figures prominently in public-key cryptography.

Where as according to Galileo Galilei (1564-1642) the universe cannot be read until we have learned the language and become familiar with the characters in which it is written. It is written in mathematical language, and the letters are triangles, circles and other geometrical figures, without which means it is humanly impossible to comprehend a single word.

Why is Mathematics Ubiquitous ?

It allows description, analysis, and prediction (simulation) of quantitative systems

It exposes structures patterns of nature

It leverages wisdom, through abstraction

It gives expression to physical laws: Newtons laws, Maxwells equations, Schrodingers equation, Einsteins relativity, etc.

It provides a lingua franca for scientific people across all cultures and eras.

Why this emphasis?

Mathematics is fundamentally entrenched in the world

Advent of computers has made a significant change in problem solving.

It is integral to many different disciplines

Many new areas are utilizing mathematic tools, e.g social sciences, biology, chemistry, natural sciences, etc.

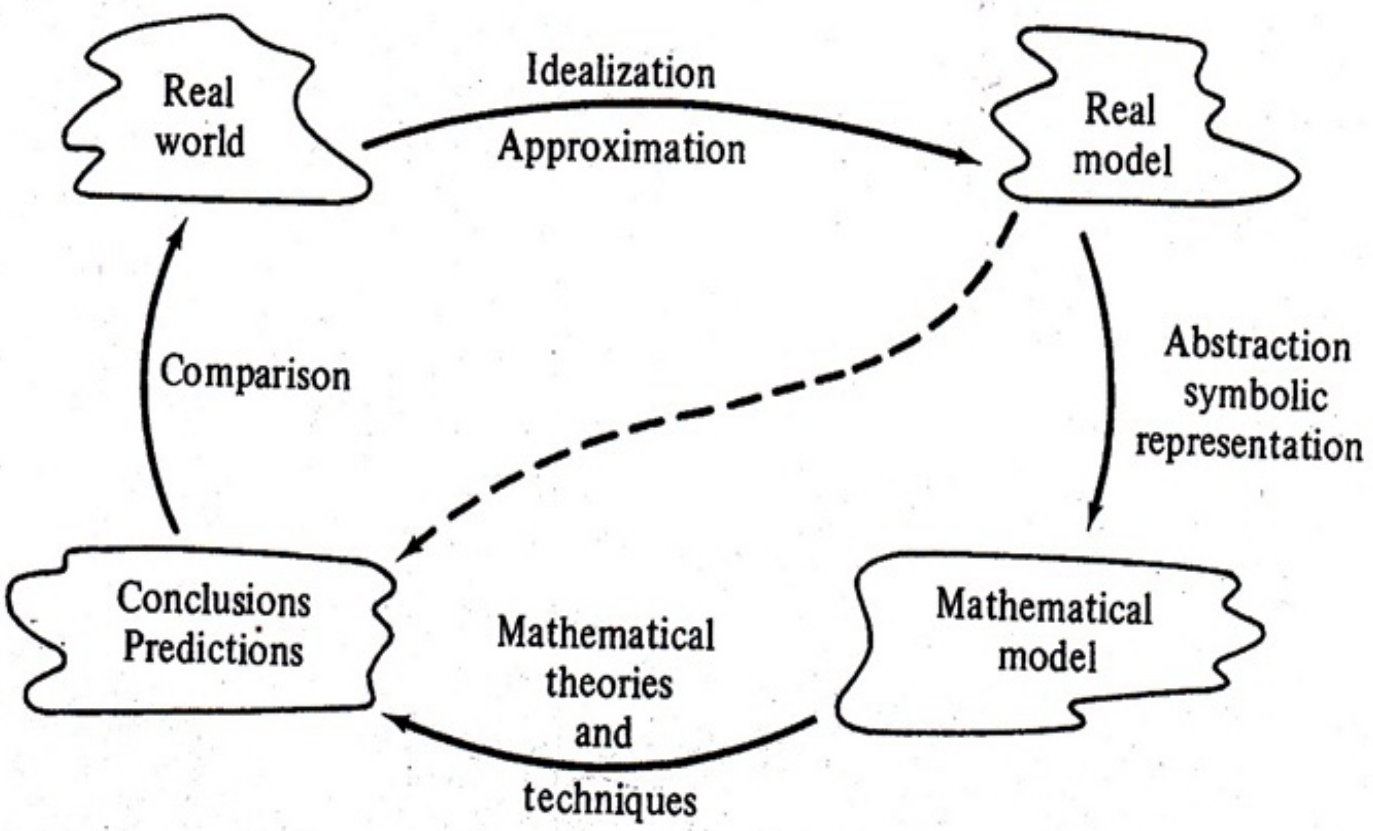
Why Mathematical Models ?

A mathematical model has a number of advantages over the other models.

- it may not always be possible to conduct experimentation with scaled down models.

- to gain new understanding about some phenomenon,
- to obtain the response behaviour of a system
- to design a complicated piece of equipment,
- to optimize some performance
- to make prediction about the system

How to use Mathematics



Step 1: Definition of Problem

-Define the problem clearly and unambiguously.

- The problem is then transformed into a system with a goal of study.

- This may require prior knowledge about the real world associated with the problem,

- If the prior knowledge is not sufficient, then one has to design an experiment to obtain new/additional knowledge

Step 2: Real World Model

Step 1 leads to an initial description of the problem based on prior knowledge of its behaviour.

This step is a process of simplification and idealization keeping in view the goal of the study. It leads to a real world model.

It is a crucial step in model building and requires a deep understanding of the physical aspects of the system.

Step 3: Mathematical Model

At this stage the real world model is related to a mathematical formulation

It involves two stages, firstly selection of a suitable mathematical formulation, and then the variables of the formulation are related with the relevant features of the system.

The abstract formulation is clothed in terms of physical features to give mathematical model.

This step requires a strong interaction between the physical features of the system and the abstract mathematical formulation.

Step 4: Analysis

Once mathematical model is obtained, its relationship with the physical world are temporarily discarded and the mathematical formulation is solved/ analyzed using mathematical tools. This is done purely according to the rules of mathematics.

At this step, one needs to assign numerical values to various parameters of the model to obtain the model behaviour. This is done by parameter estimation using given data.

Step 5: Validation

In this step, the formulation is interpreted back in terms of the physical features of the problem to yield the behaviour of the mathematical model.

The behaviour of mathematical model is then compared with that of given problem in terms of the data of real world to determine if the two are in reasonable agreement or not, according to some predefined criterion.

This is called validation.

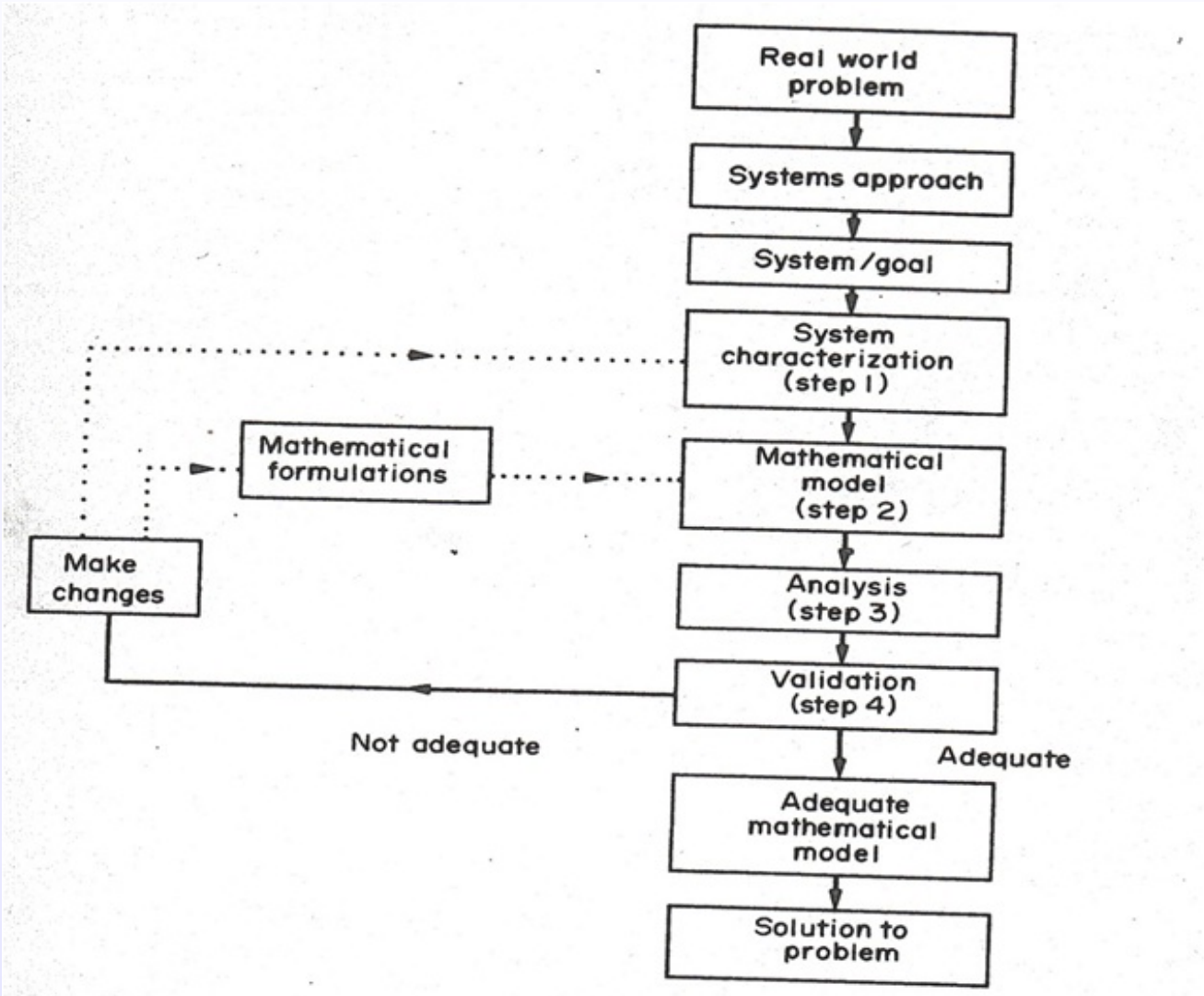
Step 6: Adequate Model

If the model passes the test of validation it is called an adequate model and process comes to an end.

Otherwise, one needs to back track and make changes either in the description of the system (Step 2) or in the mathematical formulation itself (Step 3), and the process starts from there again.

It is a sequential feed back procedure which requires interdisciplinary approach.

Flow Chart for Modeling



Pitfalls of Modeling:

A word of caution.

It should be noted that mathematical model is only a model and not the real world problem by itself.

There could be pitfalls in the mathematical model and this could be because an error at any of the above steps.

Therefore, care should be taken in using the results of the mathematical model.

Epidemiology: It is a discipline, which deals with the study of infectious diseases in a population. It is concerned with all aspects of epidemic, e.g. spread, control, vaccination strategy etc.

Disease is 'a condition of the body or some of its part in which its functions are disturbed causing a departure of from normal state of health'.

Non-infectious Disease

Infectious Disease

Acute (Fast Infectious): Stay for a short period (days/weeks) e.g. Influenza, Chickenpox etc.

Chronic Infectious Disease: Stay for longer period (month/year) e.g. hepatitis.

To study the spread of an infectious disease, we divide the human population in various classes depending on the level of pathogen.

Susceptible - when there is no pathogen present in the host (individual), then the host belongs the susceptible class.

Infected / Exposed - Once the pathogen of the disease is transmitted to a susceptible host, it becomes infected with micro-parasites. In certain cases the level of pathogen in the early phase may remain low enough to infect another susceptible. Such a individual though infected cannot infect others. This is known as exposed class.

Infectious - Once the pathogen level in the host grows such that it starts causing infection then the host belongs to infectious class.

Recovered - if the immune system clears the parasite, host is no longer infectious and is recovered and belongs to recovered class.

$$S(Susceptible) \longrightarrow E(Exposed) \longrightarrow I(Infected) \longrightarrow R(Recovered)$$

In general the spread of an infectious disease depends upon: Susceptible population, Exposed population, Infective population, Immune population, and the mode of transmission. However in many infectious diseases the exposed class is ignored.

At time t the number of individuals in the susceptible class are denoted by $X(t)$, in exposed class be $\bar{Y}(t)$ in infected class by $Y(t)$ and in the recovered class by $Z(t)$.

If N is the total population then $N = X + \bar{Y} + Y + Z$.
In many studies the researchers have considered the fraction of population as given by
$S = X/N$, $E = \bar{Y}/N$, $I = Y/N$ and $R = Z/N$.
Here we shall see some simple mathematical models without considering the mode of transmission.
Hence it is a Black Box approach.

Assumptions

We shall make some general assumptions, which are common to all the models and then look at some simple models before taking specific problems.

- The disease is transmitted by contact (direct or indirect) between an infected individual and a susceptible individual.
- There is no latent period for the disease, i.e., the disease is transmitted instantaneously when the contact takes place.
- All susceptible individuals are equally susceptible and all infected ones are equally infectious.
- The population size is large enough to take care of the fluctuations in the spread of the disease, so a deterministic model is considered.
- The population, under consideration is closed, i.e. has a fixed size.

S-I Model

• If B is the average contact number with susceptible which leads to new infection per unit time per infective, then

$$Y(t+\Delta t) = Y(t) + BY(t)\Delta t$$

which in the limit $\Delta t \to 0$ gives $\frac{dY}{dt} = BY(t)$. Hence $Y \to \infty$ as $t \to \infty$. Thus the model is not appropriate for a chronic disease.

• It is observed that B depends upon the susceptible population. So, define $\beta =$ average number of contact between susceptible and infective which leads to new infection per unit time per susceptible per infective, then $B = \beta X(t)$, which gives,

$$\frac{dY}{dt} = \beta X(t)Y(t) = \beta(N-Y)Y.$$

where $N = X + Y$ is the total population, which is fixed as per the above assumption.

SIS (No Immunity) [Ross, 1916 for Malaria]

$$S \longrightarrow I \longrightarrow S(\mathbf{After\ \ recovery})$$

In the above model, it is assumed that the whole population is divided into two classes susceptible and infective; and that if one is infected then it remains in that class. However, this is not the case, as an infected person may recover from the disease.

• Recovery rate (γ) α $\frac{1}{Infectious\ \ period}$ is taken to be constant where infection period (the time spent in the infectious class) is distributed about a mean value & can be estimated from the clinical data.

Thus model is given by the following

$$\begin{cases} \frac{dS}{dt} = \gamma I - \beta SI, \\ \\ \frac{dI}{dt} = \beta SI - \gamma I, \end{cases} \tag{1}$$

$$\frac{dI}{dt} = \beta \left[(1 - \frac{1}{R_0}) - I \right] I, \quad R_0 = \frac{\beta}{\gamma}.$$

$S^* = \frac{1}{R_0}$ and $I^* = 1 - \frac{1}{R_0}$, feasible if $R_0 > 1$.

SIR Model (Kermack & McKendrick 1927)

The SIR model, considering the immunity after illness, is given by

$$\begin{cases} \frac{dS}{dt} = -\beta SI, \\ \frac{dI}{dt} = \beta SI - \gamma I, \\ \frac{dR}{dt} = \gamma I, \end{cases} \tag{2}$$

with initial conditions: $S(0) > 0$, $I(0) > 0$ & $R(0) = 0$.

- Note that if $S(0) < \frac{\gamma}{\beta}$, then initially $\frac{dI}{dt} < 0$ and the infection dies out.
- Thus, for an infection to invade, $S(0) > \frac{\gamma}{\beta}$ or if $\frac{\gamma}{\beta}$: removal rate is small enough then the disease will spread.
- The inverse of removal rate is defined as 'basic reproductive ratio' $R_0 = \frac{\beta}{\gamma}$.

Basic Reproduction Ratio

It is defined as the average number of secondary cases arising from an average primary case in an entirely susceptible population *i.e.* the rate at which new infections are produces by an infectious individual in an entirely susceptible population.

- It measures the maximum reproductive potential for an infectious disease.
- If $S(0) \approx 1$, then disease will spread if $R_0 > 1$. If the disease is transmitted to more than one host then it will spread.
- R_0 depends on disease and host population e.g.
  - $R_0 = 2.6$ for TB in cattle.
  - $R_0 = 3 - 4$ for Influenza in humans.
  - $R_0 = 3.5 - 6$ for small pox in humans.
  - $R_0 = 16 - 18$ for Measles in humans.

Note

- For an infectious disease with an average infectious period $\frac{1}{\gamma}$ and transmission rate β, $R_0 = \frac{\beta}{\gamma}$.
- For a closed population, infection with specified R_0, can invade only if threshold fraction of susceptible population is greater than $\frac{1}{R_0}$.
- Vaccination can be used to reduce the susceptible population below $\frac{1}{R_0}$.

Also we see that

$$\frac{dS}{dR} = -R_0 S \Rightarrow S(t) = S(0)e^{-R_0 R(t)}.$$

- This implies as the epidemic builds up $S(t) \downarrow$ and so $R(t) \uparrow$.
- There will always be some susceptible in the population as $S(t) > 0$.

- The epidemic breaks down when $I = 0$, we can say

$$S(\infty) = 1 - R(\infty) = S(0)e^{-R_0 R(\infty)}.$$

or

$$1 - R(\infty) - S(0)e^{-R_0 R(\infty)} = 0. \tag{3}$$

- R_∞ is the final proportion of individuals recovered $=$ total number of infected proportion.
- We can assume that for given $S(0) > R_0$, the equation (2) has a roots between 0 & 1.

$$[R_\infty = 0 \Rightarrow 1 - S_0 > 0 \quad \text{and} \quad R_\infty = 1 \Rightarrow -S(0)e^{-R_0} < 0].$$

- $$\frac{dR}{dt} = \gamma(1 - S - R) = \gamma[1 - S(0)e^{-R_0 R} - R].$$

This can be solved either numerically or approximately for small values of $R_0 R$.

SIR model with demography

Assumptions

Now we shall consider some models with demography.

- In earlier model constant population size was considered (closed population) - this is good in developed countries.
- Model with demography considers birth/death.
- New born have passive immunity and hence susceptible are added at a constant rate ν.
- Vertical transmission is ignored.
- This is an open population model i.e. N need not be constant.

$$\begin{cases} \frac{dS}{dt} = \nu - \beta SI - \mu S, \\ \frac{dI}{dt} = \beta SI - \gamma I - \mu I, \\ \frac{dR}{dt} = \gamma I - \mu R, \end{cases} \tag{4}$$

- μ is the rate at which individual suffer natural mortality i.e. $\frac{1}{\mu}$ is natural host life span.
- $R_0 = \frac{\beta}{\gamma+\mu}$.
- $\frac{1}{\gamma+\mu}$ is the average time which an individual spends in each class.

Equilibrium States

(i) $(\overline{S}, \overline{I}, \overline{R}) = (1, 0, 0)$, disease free.
(ii) $(S^*, I^*, R^*) = (\frac{1}{R_0}, \frac{\mu}{\beta}(R_0 - 1), (1 - \frac{1}{R_0})(1 - \frac{\mu}{\gamma}))$, for $\mu < \gamma$.

- Clearly, $R_0 > 1$ for endemic equilibrium.
- It can be seen that endemic equilibrium is stable if $R_0 > 1$, otherwise disease free equilibrium is stable.

- The characteristic equation for Jacobian at endemic equilibrium

$$(\lambda+\mu)[\lambda^2+\mu R_0\lambda+(\mu+\gamma)\mu(R_0-1)]=0. \tag{5}$$

$$\lambda_1=-\mu \quad \text{and} \quad \lambda_{2,3}=\frac{-\mu R_0}{2}\pm\frac{\sqrt{\mu {R_0}^2-\frac{4}{AG}}}{2},$$

where, $A=\frac{1}{\mu(R_0-1)}$, denotes mean age of infection.
$G=\frac{1}{\mu+\gamma}$: typical period of infectivity.

SIRS Model (Waning Immunity)

In many diseases the immunity is not permanent and the immune population (recovered) after loosing the immunity joins the susceptible class. This lead to the SIRS model as given below:

$$\begin{cases} \frac{dS}{dt} = \nu + \omega R - \beta SI - \mu S, \\ \frac{dI}{dt} = \beta SI - (\gamma + \mu)I, \\ \frac{dR}{dt} = \gamma I - \mu R - \omega R, \end{cases} \tag{6}$$

ω : the rate at which immunity is lost.

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

SEIR Model

Transmission of disease starts with a low number of pathogen (bacterial cells etc.) which reproduce rapidly within host.

- At this time the pathogen is present in host but can not transmit disease to other susceptible.
- Infected but not infectious $\Rightarrow E$ class.

$$\begin{cases} \frac{dS}{dt} = \nu - (\beta I + \mu)S, \\ \frac{dE}{dt} = \beta SI - (\mu + \sigma)E \\ \frac{dI}{dt} = \sigma E - (\gamma + \mu)I, \\ \frac{dR}{dt} = \gamma I - \mu R. \end{cases} \tag{7}$$

$\frac{1}{\sigma}$ gives latent period.

Carrier dependent

• Hepatitis B: where a proportion of infected persons become chronic carrier and transmit disease for a long time at low rate.

• Those infected by acutely infectious individuals and those infected by carriers are indistinguishable.

• A recently infected person is acutely infectious and then recovers completely or moves to carrier class.

$$\begin{cases} \frac{dS}{dt} = \nu - (\beta I + \epsilon\beta C)S - \mu S, \\ \frac{dI}{dt} = (\beta I + \epsilon\beta C)S - (\mu + \gamma)I \\ \frac{dC}{dt} = \gamma q I - \delta C - \mu C, \\ \frac{dR}{dt} = \gamma(1-q)I + \delta C - \mu R. \end{cases} \tag{8}$$

where ϵ is reduced transfer rate from chronic carriers.
δ is the rate at which individuals leave C class.

$$R_0 = \frac{\beta}{\mu+\gamma} + (\frac{q\gamma}{\mu+\gamma})(\frac{\epsilon\beta}{\mu+\delta}).$$

- $\frac{q\gamma}{\mu+\gamma}$: accounts for people who do not die but become carrier.

Further Considerations:

• The above models are very general in nature. It may be noted that these models follow a Black Box approach and do not consider the mechanism of transmission of a disease. In fact the structure of a disease plays an important role in the modeling.

• It may be noted that a disease can be transmitted directly or indirectly. The direct mode of transmission could be by viral agents (influenza, measles, rubella, chicken pox); by bacteria (TB, meningitis, gonorrhea). While the former ones confer immunity against re-infection, there is no such immunity in the later cases. The indirect mode of transmission could be due to vectors or carriers (malaria).

• Thus, modeling for most of the communicable diseases, require further considerations. In the following, we consider some such factors.

(1) **Heterogeneous Mixing**-Sexually transmitted diseases (STD), e.g. AIDS, the members may have different level of mixing, e.g. preference for mixing with a particular activity.
(2) **Age structured population**- Many of the diseases spread with the contact in the group of a given age structure, e.g. measles, chicken pox and other childhood diseases spread mainly by contact between children of similar age group.
(3) **The incubation period**- It was assumed that the latent period of disease is very small and that there is no incubation time for the disease to show. This is not true with disease like Typhoid. There is latent period. Such consideration will give rise to time delay models.
(4) **Variable infectivity**- In diseases like HIV/AIDS the infective members are highly infective in the initial stages of getting infection. Thereafter, the they have a relatively low infectivity for a long period before again becoming highly infective before developing full blown AIDS.

(5) **Spatial non-uniformity**- It is well known that movement of bubonic plague from place to place was carried by rats. Thus, the spatial spread becomes important in such cases, which will lead to again a system of PDEs.
(6) **Vertical Transmission**- In some diseases, the offspring of infected members may be born infective (AIDS). So the birth in infective class needs to be considered. This is called Vertical Transmission.
(7) **Models with Compartments**-In many cases the population can be placed in different compartments, where inter-compartmental interaction takes place, e.g. in Malaria.
(8) **Stochastic Models**- So far we have considered only deterministic models, and random effects have not been taken care. This is fine if the population size is large, however, for population size small the stochastic models will be required.

Spread of Malaria- Environmental Effects.

• Malaria is a parasitic disease transmitted by mosquitoes. It is caused by parasites (such as : Plasmodium (P) falciparum, P. Vivax, P. malariae and P. ovale). It spreads by bites of female mosquito of Anopheline specie. (Anopheles (An) stephensi, An. dirus, An. gambiae, An. freeborni).

• It is during the course of blood feeding that the protozoan parasites of malaria is ingested by mosquitoes and later transmitted after reproductions to humans. The phases of the cycle of malaria parasite in mosquitoes (definitive hosts) and humans (intermediate hosts) represent a complex series of processes.

• The production of malarial parasite in human host begins in liver cells and undergoes asexual multiplication in red blood cells where the merozoites are produced. These merozoites eventually lyse the infected cells and invade other erythrocytes. During this process certain merozoites develop into sexual forms- the male and female gametocytes.

• Mosquitoes become infected when they feed and ingest human blood containing mature gametocytes. In the mosquito midgut, the macro (female) - micro (male) - gametocytes shed the red blood cell membranes that surround them and develop into gametes. These gametes mature into macrogametes, which accept microgametes to become zygotes.

• The zygote then elongates to become ookinete. The ookinete penetrates the midgut epithelium and oocyst development takes place in about 24 hours after the blood meal. The length of time required to go from ookinetes to mature sporozoites in oocyst depends upon the type of malaria parasite, mosquito species, the ambient temperature, the density of infection, etc. Later, sporozoites escape from oocysts to find their way to mosquito salivary glands. Only from there the sporozoites are transmitted to human host when the female mosquito next feeds.

• It may be noted that to be a good vector the Anopheline mosquito must have appropriate environment (natural, manmade as well as physiological) so that it can survive long enough for the parasite to develop in its gut and be ready to infect humans during the next blood meal. The prevailing environment in its habitat should also be conducive for fertilization and breeding to increase its population and there by infecting more persons due to enhanced contacts.

In view of the fact that mosquito feed on water, nectars, sugar solutions, blood etc. and breed on store/ stagnant water, vegetation and grasses in water, household wastes, etc, the following factors may be important for the spread of malaria:
(i) Natural environmental and ecological factors conducive to the survival and growth of mosquito population: Examples are rain, temperature, humidity, vegetation and grasses in water, etc.
(ii) Human population density related factors (human made environment) conducive to the survival and growth of mosquito population. Examples are open drainage of sewage water, water ponds, water tanks, household wastes, hedges and damp parks, etc.
(iii) Demographic factors: Examples are growth of human population due to immigration, living conditions etc.
Although there have been several experimental studies related to surveys of malaria in different regions, there are not many mathematical models of the spread of disease considering the factors mentioned above.

SIS Model (without reservoir):

Therefore, we present here a non-linear SIS type model for malaria to study the effects of household and other environmental discharges on the ground, such as waste water, foodstuff and so on by considering with and without reservoir human population.

Assumptions

- Population size is described by a continuous function (large size).
- The mosquito population consists of Female (anopheline species) only, and follow generalized logistic models.
- Random fluctuations are neglected (deterministic model).
- Homogeneous population i.e. all individuals are identical and are equally susceptible.
- In the mosquito population all individuals are equally infective.

• Population has complete mixing, i.e. individuals should have the possibility to be present everywhere in a habitat.

• The growth rate of the mosquito population increases as the density of cumulative environmental discharges into the environment increases.

• Criss-cross interaction between female mosquitoes.
The human population density, $N_1(t)$ is divided into two classes namely, the susceptible class $X_1(t)$ and the infective class $Y_1(t)$. The mosquito population density $N_2(t)$ is also divided into the susceptible class $X_2(t)$ and the infective class $Y_2(t)$. Here the both human and mosquito population densities follow logistic growth models so that their birth and death rates are density dependent.

$$
\begin{aligned}
\dot{X}_1 &= [b_1 - ar_1\frac{N_1}{K_1}]N_1 - \beta_1 X_1 Y_2 - [d_1 + (1-a)r_1\frac{N_1}{K_1}]X_1 + \nu_1 Y_1, \\
\dot{Y}_1 &= \beta_1 X_1 Y_2 - [\nu_1 + \alpha_1 + d_1 + (1-a)r_1\frac{N_1}{K_1}]Y_1, \\
\dot{N}_1 &= r_1[1 - \frac{N_1}{K_1}]N_1 - \alpha_1 Y_1, \qquad (1) \\
\dot{X}_2 &= (b_2 - a'\frac{r_2}{K_2}N_2)N_2 - \{d_2 + (1-a')\frac{r_2}{K_2}N_2\}X_2 - \beta_2 X_2 Y_1 - \alpha_2 X_2 + \delta_2 N_2 E, \\
\dot{Y}_2 &= \beta_2 X_2 Y_1 - \{\alpha_2 + d_2 + (1-a')\frac{r_2}{K_2}N_2\}Y_2, \\
\dot{N}_2 &= r_2 N_2(1 - \frac{N_2}{K_2}) - \alpha_2 N_2 + \delta_2 N_2 E, \\
\dot{E} &= Q(N_1) - \delta_0 E, \quad 0 \leq a \leq 1, \quad 0 \leq a' \leq 1,
\end{aligned}
$$

$$X_1(0) > 0,\ Y_1(0) \geq 0,\ X_2(0) \geq 0, Y_2(0) \geq 0 \text{ and } E(0) > 0.$$

Also Q, the cummulative rate of environmental discharges is assumed to be linearly dependent upon human population density and is taken as $Q(N_1) = Q_0 + lN_1$, where Q_0 and l are constants. Here b_1 and d_1 are natural birth and death rates; $r_1 = b_1 - d_1$ is the growth rate constant; β_1 is the interaction coefficient of the susceptible human with the infective mosquito population; ν_1 is the recovery rate coefficient of the human population; α_1 is the disease related death rate constant; b_2 and d_2 are the birth and the death rate constants corresponding to the mosquito population; $r_2 = b_2 - d_2$ is the growth rate coefficient of the mosquito population; K_1 and K_2 are the carrying capacities of the human and the mosquito population in the natural environment respectively; α_2 is the death rate of mosquitoes due to control measures ($r_2 > \alpha_2$); β_2 is the interaction coefficient of susceptible mosquitoes with the infective human class; δ_2 is the growth rate coefficient of the mosquito population due to the environmental discharges of cumulative concentration E; δ_0 is its cumulative depletion rate; a and a' are constants (such that $0 \leq a \leq 1$ and $0 \leq a' \leq 1$), which governs the logistic birth and logistic death of the human and the mosquito population respectively [5]. It may be remarked here that the value of a' is very close to unity as the mosquito population is

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THANK YOU