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Contents

Glossary

Abbreviation	Meaning
LAS	Locally-asymptotically stable
GAS	Globally-asymptotically stable
DFE	Disease-free equilibrium
EEP	Endemic equilibrium point
AIDS	Acquired immune deficiency syndrome
HIV	Human immuno-deficiency virus

Introduction

Epidemiology is defined as "the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the prevention and control of health problems". Traditional epidemiological studies include quantitative and qualitative study designs. Quantitative study designs include observational and interventional methodology. Observational methods describe associations that are already present at population (descriptive) or individual (analytical) level. Although they form the mainstay of epidemiological studies, observational methods are prone to bias and confounding.

There are several modern and emerging uses of traditional epidemiological techniques in the fields of infectious disease, environmental, molecular and genetic epidemiology and we use some mathematical methods to find these techniques.

In this project, we explain the power of Lyapunov functions in determining stability of equilibria. Lyapunov functions are also basis for many other methods in analysis of dynamical system, like frequency criteria and the method of comparing with other systems. The theory of Lyapunov function is a powerful method, but finding a good Lyapunov function can often be a big scientific problem. We also explain the method of Dulac Criterion and La Salles Principal (a modification of Lyapunov functions). These methods also help us to find the stability of the solutions of epidemic models.

We arrange the project as follows:

In chapter one, we have presented some definitions and theories those are related to the project.

In chapter two, we have presented briefly about epidemiology, its history, importance and application.

In chapter three, Lyapunov Functions and La Salles Principle are discussed with examples.

In chapter four, we have discussed the method Dulac Criterion with example to find stability of epidemic models.

In chapter Five, a basic HIV Vaccine Model with Differential Infectivity and Staged-Progression (DISP) is presented using Lyapunov Function and La Salles Principle.

Chapter One: Preliminaries

The following necessary definitions and theories are useful throughout the project.

1.1Differential Equation: [3]

An equation containing the derivatives of one or more dependent variables, with respect to one or more independent variables is said to be a differential equation.

$$a\frac{d^n x}{dt^n} + b\frac{d^{n-1} x}{dt^{n-1}} + \ldots\ldots + x = 0$$

is an n^{th} order differential equation.

Differential equation is of two types:

1. **Ordinary differential equation::**
   A differential equation is called an **ordinary differential equation**, abbreviated by **ode,** if it has ordinary derivatives in it.
   Ex: $\sin(y)\frac{d^2y}{dy^2} = (1-y)\frac{dy}{dx} + y^2 e^{-5y}$
2. **Partial differential equation::**
   A differential equation is called a **partial differential equation,** abbreviated by **pde,** if it has differential derivatives in it.
   Ex: $\frac{\partial^3 u}{\partial^2 x \partial t} = 1 + \frac{\partial u}{\partial y}$

1.2Epidemic: [3]

Epidemic is the rapid and extensive spreading by an infection that affects many individuals in an area or a population at the same time. An epidemic may be restricted to one location; however, if it spreads to other countries or continents and affects a substantial number of people, it may be termed a pandemic. Epidemics of infectious disease are generally caused by a change in the ecology of the host population (e.g. increased stress or increase in the density of a vector species), a genetic change in the parasite population or the introduction of a new parasite to a host population.

1.3 Dynamical System: [3]

The dynamical system concept is a mathematical formalization for any fixed "rule" which describes the time dependence of a point's position in its ambient space. Time can be measured by integers, by real or complex numbers or can be a more general algebraic object, losing the memory of its physical origin, and the ambient space may be simply a set without the need of a smooth space-time structure defined on it.

Mathematically, a dynamical system is a manifold M called the phase (or state) space endowed with a family of smooth evolution functions Φ^t that for any element of $t \in T$, the time, map a point of the phase space back into the phase space. There are several choices for the set T. When T is taken to be the reals, the dynamical system is called a flow and if T is restricted to the non-negative reals, then the dynamical system is a semi-flow. When T is taken to be the integers, it is a cascade or a map; and the restriction to the non-negative integers is a semi-cascade.
Ex: The evolution function Φ^t is often the solution of a differential equation of motion

$$\dot{x} = v(x)$$

The equation gives the time derivative, represented by the dot, of a trajectory $x(t)$ on the phase space starting at some point x_0. The vector field $v(x)$ is a smooth function that at every point of the phase space M provides the velocity vector of the dynamical system at that point.

1.3.1 Linear Dynamical Systems: [3]

Linear dynamical systems are dynamical systems whose evaluation functions are linear. Linear dynamical systems can be solved exactly, and they have a rich set of mathematical properties. Linear systems can also be used to understand the qualitative behavior of general dynamical systems, by calculating the equilibrium points of the system and approximating it as a linear system around each such point.

Ex: In a linear dynamical system, the variation of a state vector (an N-dimensional vector denoted X) equals a constant matrix (denoted A) multiplied by x. This variation can take two forms: either as a flow, in which x varies continuously with time.

$$\frac{d}{dt}X(t) = A\,X(t)$$

or as a mapping, in which x varies in discrete steps

$$X_{m+1} = A\,X_m$$

These equations are linear in the following sense: if x(t) and y(t) are two valid solutions, then so is any linear combination of the two solutions.

Ex: $z(t) = \alpha x(t) + \beta y(t)$ where α and β are any two scalars. The matrix A need not be symmetric.

Linear dynamical systems can be solved exactly, in contrast to most nonlinear ones. Occasionally, a nonlinear system can be solved exactly by a change of variables to a linear system. Moreover, the solutions of (almost) any nonlinear system can be well-approximated by an equivalent linear system near its fixed points. Hence, understanding linear systems and their solutions is a crucial first step to understanding the more complex nonlinear systems.

1.4 Equilibrium: [3]

Equilibrium is a state of balance between opposing influences or actions that is either static or dynamic. IT is the stable condition in which forces cancel one another. An equilibrium is considered stable (asymptotic stability) if the system always returns to it after small disturbances. If the system moves away from the equilibrium after small disturbances, then the equilibrium is unstable.

1.5 Equilibrium Solution: [7]

Consider the following general autonomous system

$$\dot{x} = f(x), \qquad x \epsilon \mathbb{R}^n \tag{1.1}$$

An equilibrium solution of (1.1) is a point $\bar{x}\epsilon\mathbb{R}$ such that $f(\bar{x}) = 0$.

1.6 Stable, Asymptotically Stable & Unstable: [7]

Let $\bar{x}(t)$be any solution of (1.1). Then, $\bar{x}(t)$is stable if solutions starting "close" to $\bar{x}(t)$at a given time remain close to $\bar{x}(t)$for all later times. It is asymptotically stable if nearby solutions actually converge to $\bar{x}(t)$as $t \to \infty$. This is formally defined below:

1.6.1 Stable:: The equilibrium$\bar{x}(t)$is said to be stable if given$\epsilon > 0$thereexists a$\delta = \delta(\epsilon) > 0$such that, for any solution$y(t)$of (1.1) satisfying

$$|\bar{x}(t_0) - y(t_0)| < \delta, |\bar{x}(t_0) - y(t_0)| < \epsilon \; for \; t > t_0, t_0 \epsilon \mathbb{R}$$

1.6.2 Asymptotically Stable:: The equilibrium $\bar{x}(t)$ is said to be asymptotically stable if (i) it is stable and (ii) there exists a constant$c > 0$such thatif

$$|\bar{x}(t_0) - y(t_0)| < c$$

Then,

$$\lim_{t\to\infty}|\bar{x}(t)-y(t)|=0$$

1.6.3: Unstable:: A solution which is not stable is said to be unstable.

1.7 Invariant Set: [3]

Let us consider the autonomous system

$$\dot{x}=f(x),\ f(0)=0 \qquad (1.2)$$

A set M$\subset R^n$ is said to be

- An invariant set with respect to (1.2) if $X(0)\in M \Longrightarrow X(t)\in M, \forall t\in R$
- A positively invariant set with respect to (1.2) if $X(0)\in M \Longrightarrow X(t)\in M, \forall t\geq 0$

Chapter Two: Epidemiology

2.1 Definition of epidemiology: [3]

The word **epidemiology** comes from the Greek words **epi** meaning "on or upon", **demos** meaning "people", and **logos** meaning "the study of".
"Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations.

This definition of epidemiology includes several terms which reflect some of the important principles of the discipline which are now discussed below:

- **Distribution:** Epidemiology is concerned with the frequency and pattern of health events in a population. Frequency includes not only the number of such events in a population, but also the rate or risk of disease in the population. The rate (number of events divided by size of the population) is critical to epidemiologists because it allows valid comparisons across different populations.

- **Determinants:** Epidemiology is also used to search for causes and other factors that influence the occurrence of health-related events. Analytic epidemiology attempts to provide the '*Why'* and '*How'* of such events by comparing groups with different rates of disease occurrence and with differences in demographic characteristics, genetic or immunologic make-up, behaviors, environmental exposures and other so-called potential risk factors. Under ideal circumstances, epidemiologic findings provide sufficient evidence to direct swift and effective public health control and prevention measures.

- **Specified populations**:: Both Clinicians and Epidemiologists are concerned with disease and control of disease, but they differ greatly in how they view the patient. The clinician usually focuses on treating and caring for the individual where the epidemiologist focuses on the exposure (action or source that caused the illness), the number of other persons who may have been similarly exposed, the potential for further spread in the community and interventions to prevent additional cases or recurrences.
  Clinicians are concerned with the health of an individual; epidemiologists are concerned with the collective health of the people in a community or other area.

2.2 History of epidemiology: [3]

Although epidemiology as a discipline has blossomed since World War II, epidemiologic thinking has been traced 2500 yeas ago from Hippocrates through John Graunt, William Farr, John Snow, and others.

The Greek physician Hippocrates is known as the father of medicine. Hippocrates attempted to explain disease occurrence from a rational rather than a supernatural viewpoint. In his essay entitled "On Airs, Waters, and Places" Hippocrates suggested that environmental and host factors such as behaviors might influence the development of disease.

In the middle of the 16th century, a doctor from Verona named Girolamo Fracastoro first proposed a theory that some of very small, unseeable, particles that cause disease were alive. These particles were considered to be able to spread by air, multiply by themselves and to be destroyable by fire. In 1543 he wrote a book 'De contagione et contagiosis morbis', in which he was the first to promote personal and environmental hygenie to prevent disease.

Another early contributor to epidemiology was John Graunt, a London haberdasher and councilman who published a landmark analysis of mortality data in 1662. This publication was the first to quantify patterns of birth, death, and disease occurrence, noting disparities between males and females, high infant mortality, urban/rural differences, and seasonal variations.

2.3 Epidemiology in modern era: [3]

John Snow isknown as the father of modern Epidemiology. He was one of the first Epidemiologists who showed that cholera was water-borne. For his investigation he examined the neighbourhood, and talked to everyone he could. He was looking for an underlying theme that linked these people together. Because Snow believed that water was a source of infection for cholera, he marked the location of water pumps on his spot map, then looked for a relationship between the distribution of households with cases of cholera and the location of pumps. He noticed that more case households clustered around Pump A, the Broad Street pump, than around Pump B or C. He suspected some contamination of the water and found that all were attacked by drinking water.

In the 1930s and 1940s, epidemiologists extended their methods to noninfectious diseases. The period since World War II has seen an explosion in the development of research methods and the theoretical underpinnings of epidemiology. Epidemiology has been applied to the entire range of health-related outcomes, behaviors, and even knowledge and attitudes.

The studies by Doll and Hill linking lung cancer to smoking and the study of cardiovascular disease among residents of Framingham, Massachusetts are two examples of how pioneering researchers have applied epidemiologic methods to chronic disease .

In the 1980s, epidemiology was extended to the studies of injuries and violence. In the 1990s, the related fields of molecular and genetic epidemiology took root. Meanwhile, infectious diseases

continued to challenge epidemiologists as new infectious agents were identified like Ebola virus, Human Immunodeficiency virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS).

Now a days public health workers throughout the world accept and use epidemiology regularly to characterize the health of their communities and to solve day-to-day problems, large and small.

2.4 Importance of epidemiology: [1]

Epidemiology is the study of the origin and causes of diseases in a community. It is the scientific method of investigation problem solving used by disease detectives epidemiologists, laboratory scientists, statisticians, physicians and other health care providers, and public health professionals to get to the root of health problems and outbreaks in a community.

So, epidemiology is very important to public health because it provides a basis for developing, prioritizing and evaluating public health programs. Public health programs should be developed based on need and the epidemiologic approach is helpful in needs assessment.
Measures of morbidity, mortality, years of potential life lost, as well as other epidemiologic measures can be used to characterize the impact of public heath problems.
Finally, epidemiology can be used to evaluate the success of public health programs. Significant reduction in risk-taking behaviors, incidence of disease or mortality may all be useful measures of a program's long- term success.

The epidemiologists use what they learn to prevent s future outbreaks from occurring. They are able to stop the outbreak after gaining the information from their investigation. The investigation will improve outbreak detection and timely response and new vaccines may provide to reduce the disease in future.

2.5 Applications of epidemiology: [1]

The epidemiologists are not only concerned of an individual health, they are working to solve the problem by using data from their investigation so that the disease can not spread to everyone. That's why statistical epidemiology is applied everywhere.

- Epidemiology is applied to investigate the particular dietary component influences to find the risk of developing cancer.
- It is applied to survey a population over a wide region where the population is highly risked to be attacked by HIV.
- To create consciousness among the people about the revolution of the effectiveness and impact of a cholesterol awareness program.
- It is applied to research the future public health resource that is needed.
- To monitor the present and possible future communicable diseases in a community.

So, we can’t conclude the application of the epidemiology as it is now applied in every investigation and research based diseases to keep people cured and away of the diseases by using the data.

Chapter Three: Lyapunov Function and La Salles Invariance principle

3.1 Lyapunov function: [3]

A Lyapunov function is a scalar function $v(y)$ defined on a region D that is continuous, positive definite, $v(y) > 0$ for all $y \neq 0$, and has continuous first-order partial derivatives at every point of D. The derivative of V with respect to the system $y' = f(y)$, written as $V^*(y)$ is defined as the dot product

$$V^*(y) = \nabla V(y).f(y)$$

The existence of a Lyapunov function for which $V^*(y) \leq 0$ on some region D containing the origin, guarantees the stability of the zero solution of $y' = f(y)$, while the existence of a Lyapunov function for which $V^*(y)$ is negative definite on some region D containing the origin guarantees the asymptotical stability of the zero solution of $y' = f(y)$

3.2 Stability of Lyapunov function: [2]

Consider an autonomous nonlinear dynamical system

$$\dot{x} = f\big(x(t)\big), \;\; x(0) = x_0$$

where $x(t) \in D \subseteq \mathbb{R}$ denotes the system state vector, D an open set containing the origin, and $f: D \longrightarrow \mathbb{R}$ continuous on D. Suppose f has an equilibrium at x_e so that $f(x_e) = 0$ then,

This equilibrium is said to be Lyapunov stable, if, for every $\mathcal{E} > 0$ there exists a $\delta = \delta(\varepsilon) > 0$ such that, if $\| x(0) - x_e \| < \delta$ then for every $t \geq 0$ we have $\| x(t) - x_e \| < \varepsilon$

So, Lyapunov stability of an equilibrium means that solutions starting "close enough" to the equilibrium (within a distance δ from it) remain "close enough" forever (within a distance ε from it).

Ex:: consider the system

$\dot{x}$= -x + y + xy

$\dot{y}$ = x -y -x^2-y^3

Let, V = $x^2 + y^2$

$\dot{V} = \frac{\partial}{\partial x} V\dot{x} + \frac{\partial}{\partial y} V\dot{y}$
$=2x (-x + y + xy) + 2y(x -y -x^2-y^3)$
$= -2x^2 + 4xy -2y^2-2y^4$
$= -2(x - y)^2-2y^4$
< 0

So the origin is stable.

3.3 Lyapunovs direct method: [4,5,6]

Let $\Omega \subseteq \mathbb{R}^n$ be open and contain the origin and suppose that $f: \mathbb{R} \times \Omega \to \mathbb{R}^n$ is continuously differentiable function. Suppose that $f(t, 0) = 0$ for every $t \in \mathbb{R}$, so $x(t) \coloneqq 0$ is a solution of the equation

$$\dot{x} = f(t, x)$$

Now, a subset of Ω that contains the origin in its interior will

be called a neighborhood of 0.

Definition: Suppose that D is a neighborhood of 0 and that $W: D \to \mathbb{R}$ is

continuous and satisfies $W(0) = 0$. Then:

- If $W(x) \geq 0$ for every $x \in D$, then W is positive semidefinite.
- If $W(x) > 0$ for every $x \in D\backslash\{0\}$, then W is positive definite.
- If $W(x) \leq 0$ for every $x \in D$, then W is negetive semidefinite.
- If $W(x) < 0$ for every $x \in D\backslash\{0\}$, then W is negetive definite.

Definition: Suppose that D is a neighborhood of 0 and that $V: \mathbb{R} \times D \to \mathbb{R}$ is continuous and satisfies $V(t, 0) = 0$ for every $t \in \mathbb{R}^n$. Then:

- If there is a positive semidefinite function $W: D \to \mathbb{R}$ such that $V(t, x) \geq W(x)$ for every $(t, x) \in \mathbb{R} \times D$, then V is positive semidefinite.
- If there is a positive definite function $W: D \to \mathbb{R}$ such that $V(t, x) \geq W(x)$ for every $(t, x) \in \mathbb{R} \times D$, then V is positive definite.

- If there is a negative semidefinite function $W: D \to \mathbb{R}$ such that $V(t,x) \leq W(x)$ for every $(t,x) \in \mathbb{R} \times D$, then V is negetive semidefinite.
- If there is a positive definite function $W: D \to \mathbb{R}$ such that $V(t,x) \leq W(x)$ for every $(t,x) \in \mathbb{R} \times D$, then V is positive definite.

Theorem (Lyapunov global asymptotic stability): [2,3,4]

Consider the nonlinear system

$$\dot{x} = f(x)$$

and function $V : \mathbb{R}^n \to \mathbb{R}$.
Suppose the function V is such that

- V is positive definite
- $\dot{V}(z) < 0$ for all $z \neq 0, \dot{V}(0) = 0$

then, every trajectory of $\dot{x} = f(x)$ converges to zero as $t \to \infty$
(i.e. the system is globally asymptotically stable)
interpretation:

- V is positive definite generalized energy function
- energy is always dissipated, except at 0

Proof::

suppose trajectory $x(t)$ does not converge to zero.
$V(x(t))$ is decreasing and nonnegative, so it converges to, say ε as $t \to \infty$
Since $x(t)$ doesn't converge to 0, we must have $\varepsilon > 0$, so for all t,

$$\varepsilon \leq V(x(t)) \leq V(x(0)).$$

$$C = \{z \mid \varepsilon \leq V(z) \leq V(x(0))\}$$

is closed and bounded, hence compact. So $\dot{V}$
(assumed continuous) attains its supremum on C, i.e. $sup_{z \epsilon c} \dot{V} = -a < 0$. Since

$\dot{V}(x(t)) \leq -a$ for all t, we have

$$V\left(x(T)\right) = V\left(x(0)\right) + \int_0^T \dot{V}(x(t))\, dt \leq V(x(0)) - aT$$

which for $T > V(x(0))/a$ implies $V(x(0)) < 0$, a contradiction.
So every trajectory $x(t)$ converges to 0, i.e. $\dot{x} = f(x)$ is globally asymptotic stable.

Ex: consider the system

$$\dot{x_1} = -x1 + g(x_2)$$

$$\dot{x_2} = -x_2 + h(x_1)$$

where $|g(u)| \leq |u|/2,\ and\ |h(u)| \leq |u|/2$

Let $V = (x_1^2 + x_2^2)/2$

Now, $\dot{V} = x_1\dot{x}_1 + x_2\dot{x}_2$

$$= -x_1^2 - x_2^2 + x_1 g(x_2) + x_2 h(x_1)$$

$$\leq -x_1^2 - x_2^2 + |x_1 x_2|$$

$$\leq -(x_1^2 + x_2^2)/2$$

$$= -V$$

So we conclude that the system is globally asymptotically stable.

Theorem (Lyapunov global exponential stability): [2,3,4]

Consider the nonlinear system

$$\dot{x} = f(x)$$

suppose there is a function $V : \mathbb{R}^n \to \mathbb{R}$. and constant $\alpha > 0$ such that
• V is positive definite
• $\dot{V}(z) \leq -\alpha V(z)$ for all z
then, there is an M such that every trajectory of $\dot{x} = f(x)$ satisfies

$$\| x(t) \| \leq Me^{-\alpha t/2} \| x(0) \|$$

This is called global exponential stability.

3.4 Indirect method of Lyapunov: [10]

Consider the nonlinear system

$$\dot{x} = f(x) \qquad \text{.....(1)}$$

has an equilibrium point at $\bar{x} = 0$ (an equilibrium at any other location can be dealt with by a preliminary change of variables to move that equilibrium to the origin). Assume that

$$f(x) = Ax + h(x) ,$$

where

$$\lim_{\|x\| \to 0} \frac{\|h(x)\|}{\|x\|} = 0$$

i.e. $h(x)$ denotes terms that are higher order than linear, and A is the Jacobian matrix associated with the linearization of (1) about the equilibrium point. The linearized system is thus given by

$$\dot{x} = Ax \qquad \text{.....(2)}$$

if (2) is asymptotically stable, then in a small neighborhood around the equilibrium point, the system (1) behaves like (2) and will be stable.

Proof::

If system (2) is asymptotically stable, then for any $Q > 0$, there exists $P > 0$ such that

$$A^T P + PA = -Q$$

and $V(x) = x^T P x$ is a Lyapunov function for system (2). Consider $V(x)$ as a Lyapunov function candidate for system (1). Then

$$\dot{V}(x) = x^T (A^T P + PA)x + 2x^T P h(x)$$

$$\leq -\lambda_{min}(Q) \| x \|^2 + 2 \| x \| . \| h(x) \| . \lambda_{max}(P)$$

$$\leq -[\lambda_{min}(Q) - 2\lambda_{max}(P) . \frac{\|h(x)\|}{\|x\|}] . \| x \|^2$$

From the assumption on h, for every $\varepsilon > 0$, there exists $r > 0$

Such that $\| h(x) \| < \varepsilon \| x \|$, for all $\| x \| < r$

This implies that $\dot{V}$ is strictly negetive for all $\| x \| < r$, where r is chosen for

$$\varepsilon < \frac{\lambda_{min}(Q)}{2\lambda_{max}(P)}$$

This concludes the proof.

Ex:: The equations of motion for a pendulum with friction are

$$\dot{x_1} = x_2$$

$$\dot{x_2} = -x_2 - \sin x_1$$

The two equilibrium points of the system are at $(0,0)$ and $(\pi,0)$. The linearized system at the origin is given by

$$\dot{x_1} = x_2$$

$$\dot{x_2} = -x_2 - \sin x_1$$

$$\dot{x} = \begin{bmatrix} 0 & 1 \\ -1 & -1 \end{bmatrix} x = Ax$$

This A has all its eigenvalues in the OLHP. Hence the equilibrium point at the

origin is asymptotically stable. Note, however, that if there were no damping, then

the linearized system would be

$$\dot{x} = \begin{bmatrix} 0 & 1 \\ -1 & -1 \end{bmatrix} x$$

and the resulting matrix A has eigenvalues on the imaginary axis.

The linearization around the equilibrium point at $(\pi,0)$ is

$$\dot{z_1} = z_2$$

$$\dot{z_2} = +z_1 - z_2$$

where $z_1 = x_1 - \pi$ and $z_2 = x_2$, so these variables denote the small deviations of x_1 and x_2 from their respective equilibrium values. Hence

$$A = \begin{bmatrix} 0 & 1 \\ -1 & -1 \end{bmatrix} x = Ax \ ;$$

which has one eigenvalues in the RHP, indicating that this equilibrium point is unstable.

3.5 Introduction to La Salles Principle: [9]

In 1892 Lyapunov published his paper giving his "second method". The basic guiding principle was that we might be able to know something about the stability of the system from the form of the equations describing it. Specifically, the idea was that it would not be necessary to know the solutions of the equations involved.

Lyapunov's method is extremely valuable, since it enables us to reach conclusions about stability without obtaining explicit solutions. The disadvantage is that finding an appropriate Lyapunov function can often be very difficult.

In response to this fact, LaSalle produced an extension of Lyapunov's method in the early sixties. In this extension, LaSalle used the notion of limit sets (sets of limit points) and the notion of invariance (the property of certain sets whereby a given function takes elements in the set to elements in the set). By introducing these notions, LaSalle was able to show how Lyapunov functions could be defined less restrictively. His Invariance Principle is the invariance-and-limit sets version of Lyapunov's theorems
describing his method. LaSalle has produced both discrete and continuous
versions of his Principle.

3.6 Theorem (LaSalle's Invariance Principle): [8]

We consider the autonomous system

$$\dot{x} = \mathrm{f}(x)$$

Suppose there is a neighborhood D of 0 and a continuously differentiable (time-independent) positive definite function $V{:}D\to\mathbb{R}$ whose orbital derivative V (w.r.t. the autonomous system) is negative semidefinite. Let I be the union of all complete orbits contained in

$$\{x\epsilon\ D\ \mathrm{l}\dot{V}(x)=0\}$$

Then there is a neighborhood $\mathbf{\upsilon}$ of 0 such that for every $x_0 \epsilon\ \mathbf{\upsilon}$, $\omega\ (x_0) \subseteq I$.

Proof::

Let φ be the flow generated by the autonomous system. So 0 must be Lyapunov stable, thus we can pick a neighborhood $\mathbf{\upsilon}$ of 0 such that $\varphi(\mathrm{t}, x)\ \epsilon\ D$ for every $x_0\ \epsilon\ \mathbf{\upsilon}$ and every $t \geq 0$.

Let $x_0\ \epsilon\ \mathbf{\upsilon}$ and $y\epsilon\ \omega(x_0)$ be given. By the negative semi-definiteness of $\dot{V}$, we know that $V(\varphi(\mathrm{t}, x_0))$ is a nonincreasing function of t. By the positive definiteness of V, we know that $V(\varphi(\mathrm{t}, x_0))$ remains nonnegative, so it must approach some constant $c \geq 0$ as $\mathrm{t}\uparrow \infty$. By continuity of

V , $V(z) = c$ for every $z \in \omega(x_0)$. Since $\omega(x_0)$ is invariant, $V(\varphi(t, y)) = c$ for every $t \in \mathbb{R}$. The definition of orbital derivative then implies that $V(\varphi(t, y)) = 0$ for every $t \in \mathbb{R}$. Hence $y \in I$.

Theorem:: Let f(x) be a locally Lipschitz function defined over a domain D $\subset \mathbb{R}^n$; 0 ϵ D. Let V(x) be a continuously differentiable positive definite function defined over D such that $\dot{V}(x) \leq 0$ in D. Let S= $\{x \epsilon D \mid \dot{V}(x) = 0\}$

- If no solution can stay identically in S, other than the trivial solution $x(t) \equiv 0$,then the origin is asymptotically stable.
- Moreover if $\Gamma \subset D$ is compact and positively invariant, then it is a subset of the region of attraction.
- Furthermore if D = $\mathbb{R}^n$, and V(x) is radially unbounded, then the origin is globally asymptotically stable.

Ex::

$$\dot{x}_1 = x_2$$

$$\dot{x}_2 = -h_1(x_1) - h_2(x_2)$$

$$h_i(0)=0, \quad y h_i(y) > 0, \quad \text{for } 0 < |y| < a$$

$$V(x) = \int_0^{x_1} h_1(y)dy + \frac{1}{2}x_2^2$$

$$D = \{-a < x_1 < a, \quad -a < x_2 < a\}$$

$$\dot{V}(x) = h_1(x_1)x_2 + x_2[-h_1(x_1) - h_2(x_2)] = -x_2 h_2(x_2) \leq 0$$

$$\dot{V}(x) = 0 \implies x_2 h_2(x_2) = 0 \implies x_2 = 0$$

$$S = \{x_2 \epsilon D \mid x_2 = 0\}$$

$$\dot{x}_1 = x_2, \qquad \dot{x}_2 = -h_1(x_1) - h_2(x_2)$$

$$x_2(t) \equiv 0 \implies \dot{x}_2(t) \implies h_1\big(x_1(t)\big) \equiv 0 \implies x_1(t) \equiv 0$$

The only solution that can stay identically in S is $x(t) \equiv 0$
Thus, the origin is asymptotically stable.

Suppose $a = \infty$ and $\int_0^y h_1(z)dz \to \infty$ as $|y| \to \infty$
Then D=$\mathbb{R}^2$ and V(x)=$\int_0^{x_1} h_1(y)dy + \frac{1}{2} x_2^2$ is radially unbounded.

S=$\{x \in \mathbb{R}^2 | x_2 = 0\}$ and the only solution that can stay identically in S is $x(t) = 0$.
The origin is globally asymptotically stable.

A More Complicated Example:

The previous example is so simple that it might make one question whether the direct method is of any use on problems where stability cannot be determined by linearization *or* by inspection. Thus, let's consider something more complicated. Consider the planar system

$$\begin{cases} \dot{x} = -y - x^3 \\ y = x^5 \end{cases} \qquad \text{.....(3)}$$

The origin is a non-hyperbolic equilibrium point, with 0 being the only eigenvalue, so the principle of linearized stability is of no use. A sketch of the phase portrait indicates that orbits circle the origin in the counterclockwise direction, but it is not obvious whether they spiral in, spiral out, or move on closed curves. The simplest potential Lyapunov function that often turns out to be useful is the square of the standard Euclidean norm, which in this case is

$V = x^2 + y^2$. The orbital derivative is

$$\dot{V} = 2x\dot{x} + 2y\dot{y} = 2x^5 y - 2xy - 2x^4 \qquad \text{.....(4)}$$

For some points (x, y) near the origin (e.g., (δ, δ)) $\dot{V} < 0$, while for other points near the origin (e.g., $(\delta, -\delta)$) $\dot{V} > 0$, so this function does not seem to be of much use.

Sometimes when the square of the standard Euclidean norm doesn't work, some other homogeneous quadratic function does. Suppose we try

$V := x^2 + \alpha xy + \beta y^2$, with α *and* β to be determined. Then

$$\dot{V} = (2x + \alpha y)\dot{x} + (\alpha x + 2\beta y)\dot{y} = -(2x + \alpha y)(y + x^3) + (\alpha x + 2\beta y)x^5$$

$$= -2x^4 + \alpha x^6 - 2xy - \alpha x^3 y + 2\beta x^5 y - \alpha y^2$$

Setting (x, y)=$(\delta, -\delta^2)$ for δ positive and small, we see that $\dot{V}$ is not going to be negative semidefinite, no matter what we pick α *and* β to be.
If these quadratic functions don't work, maybe something customized for the particular equation might. We note that the right hand side of the first equation in (4) sort of suggests that x^3 and y should be treated as quantities of the same order of magnitude.

Let's try V:= $x^6 + \alpha y^2$, for some $\alpha > 0$ to be determined. Clearly, V is positive definite, and $\dot{V} = 6x^5\dot{x} + 2\alpha y\dot{y} = \dot{} (2\alpha - 6)x^5 y - 6x^8$

If $\alpha \neq 3$ then $\dot{V}$ is opposite signs for $(x, y) = (\delta, \delta)$ and for $(x, y) = (\delta, -\delta)$ when δ is small. Hence, we should set $\alpha = 3$, yielding $\dot{V} = -6x^8 \leq 0$. Thus V is positive definite and $\dot{V}$ is negative semidefinite implying that the origin is Lyapunov stable.

Now the ques arises that is the origin asymptotically stable or not. Perhaps we can make a minor modification to the preceding formula for V so as to make $\dot{V}$ strictly negative in a deleted neighborhood of the origin without destroying the positive definiteness of V. If we added a small quantity whose orbital derivative was strictly negative when $x = 0\ and\ |y|$ is small and positive, this might work. Experimentation suggests that a positive multiple of xy^3 might work, since this quantity changes from positive to negative as we cross the y-axis in the counterclockwise direction. Also, it is at least of higher order than $3y^2$ near the origin, so it has the potential of preserving the positive definiteness of V.

In fact we claim that $V \coloneqq x^6 + xy^3 + 3y^2$ is positive definite with negative definite orbital derivative near 0. A handy inequality, sometimes called "Young's inequality", that can be used in verifying this claim.

Lemma (Young's Inequality)::

If $a, b \geq 0$, then

$$ab < \frac{a^p}{p} + \frac{b^q}{q} \qquad \text{.....(5)}$$

for every pair of numbers $p, q \in (1, \infty)$ satisfying

$$\frac{1}{p} + \frac{1}{q} = 1 \qquad \text{.....(6)}$$

Proof ::

Assume that (6) holds. Clearly (5) holds if $b = 0$, so we assume that $b > 0$, and we fix it.

Define g: $[0, \infty)$ by the formula

$$g(x) \coloneqq \frac{x^p}{p} + \frac{b^q}{q} - xb$$

We note that g is continuous, and $g'(x) = x^{p-1} - b$ for every $x \epsilon (0, \infty)$.
Since $\lim_{x \downarrow 0} g'(x) = -b < 0$, $\lim_{x \uparrow \infty} g'(x) = \infty$ and g' is increasing on $(0, \infty)$, we know that g has a unique minimizer at $x_0 = b^{1/(p-1)}$. Thus for every $x \epsilon [0, \infty)$, using (4), we see that

$$g(x) \geq g(b^{1/(p-1)}) = \frac{b^{p/(p-1)}.}{p} + \frac{b^q}{q} - b^{p/(p-1)} = \left(\frac{1}{p} + \frac{1}{q} - 1\right) b^q = 0$$

In particular, $g(a) \geq 0$, so (5) holds.

Now, let $V = x^6 + xy^3 + 3y^2$. Applying Young's Inequality with $a = |x|$, $b = |y|^3$, $p = 6$, and $q = \frac{6}{5}$, we see that $|xy^3| = |x||y|^3 \leq \frac{|x|^6}{6} + \frac{5|y|^{18/5}}{6} \leq \frac{1}{6}x^6 + \frac{5}{6}y^2$ if $|y| \leq 1$,

So, $V \geq \frac{5}{6}x^6 + \frac{13}{6}y^2$

if $|y| \leq 1$, Also

$$\dot{V} = -6x^8 + y^3\dot{x} + 3xy^2\dot{y} = -6x^8 - y^3(y + x^3) + 3x^6y^2$$
$$= -6x^8 - x^3y^3 + 3x^6y^2 - y^4$$

Applying Young's inequality to the two mixed terms in this orbital derivative, we have

$$|-x^3y^3| = |x|^3|y|^3 \leq \frac{3|x|^3}{8} + \frac{5|y|^{24/5}}{8} \leq \frac{3}{8}x^8 + \frac{5}{8}y^4$$

If $|y| \leq 1$, and

$$|3x^6y^2| = 3|x|^6|y|^2 \leq 3\left[\frac{3|x|^8}{4} + \frac{|y|^8}{4}\right] = \frac{9}{4}x^8 + \frac{3}{4}y^8 \leq \frac{9}{4}x^8 + \frac{3}{64}y^4$$

$|y| \leq 1$, Thus

$$\dot{V} \leq -\frac{27}{8}x^8 - \frac{21}{64}y^4$$

If $|y| \leq \frac{1}{2}$, so, in a neighborhood of 0, V is positive definite and $\dot{V}$ is negative definite, which implies that 0 is asymptotically stable.

Chapter Four: Dulac Criterion

4.1 Dulac Criterion: [3]

Let *D* be a simply connected region of the phase plane. If there exists a continuously differentiable function $\phi(x,y)$ such that

$$\frac{\partial}{\partial x}\{\phi(x,y)f(x,y)\}+\frac{\partial}{\partial y}\{\phi(x,y)g(x,y)\}$$

is of constant sign in *D* then the dynamical system

$$\dot{x}=f(x,y)$$

$$\dot{y}=g(x,y)$$

has no closed orbits wholly contained in *D*.

4.2 Theorem (Dulac Criterion): [6]

Let $\underline{\dot{x}}$=f ($\underline{\dot{x}}$) be a continuously differentiable vector field defined on a simply connected subset R of the plane. If there exists a continuously differentiable, real valued function g ($\underline{\dot{x}}$) such that ∇. (g$\underline{\dot{x}}$) has one sign throughout R,then there are no closed orbits lying entirely in R.

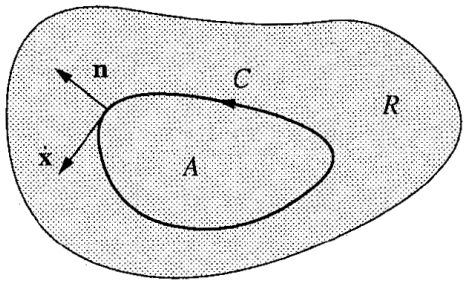

Figure 1

Proof::

Suppose there were a closed orbit C lying entirely in the region R. Let A denote the region inside C(Figure 1). Then Green's theorem yields

$$\iint \nabla.(g\dot{\underline{x}})dA = \oint g\dot{\underline{x}}.\dot{\underline{n}}\ dl$$

Where $\dot{\underline{n}}$ is the outward normal & dl is the element of the arc length along C. Looking first at the double integral on the left: it must be non zero since $\nabla.(g\dot{\underline{x}})$ has one sign in R. On the other hand, the line integral on the right equals zero since $\dot{\underline{x}}.\dot{\underline{n}}=0$ everywhere by the assumption that C is a trajectory (the tangent vector $\dot{\underline{x}}$ is orthogonal to $\dot{\underline{n}}$. This contradiction implies that no such C can exist.

Ex:: We have to show that $\dot{\underline{x}}$=y, $\dot{\underline{y}}$=-x-y+x^2+y^2 has no closed orbits.

Let us pick g=e^{-2x}

Then, $\nabla.(g\dot{\underline{x}})$ = -2e^{-2x}y +e^{-2x}(-1+2y)

$$= -e^{-2x} < 0$$

So by Dulac criterion,there are no closed orbits.

4.3 Bendixson-Dulac theorem: [3]

The Bendixson–Dulac theorem on dynamical system states that if there exists a C^1 function $\varphi(x,y)$ (called the Dulac function) such that the expression

$$\frac{\partial(\varphi f)}{\partial x}+\frac{\partial(\varphi g)}{\partial y}$$

has the same sign ($\neq 0$) almost everywhere in a simply connected region of the plane, then the plane autonomous system

$$\frac{dx}{dt}=f(x,y)$$
$$\frac{dy}{dt}=g(x,y)$$

has no periodic solutions lying entirely within the region. "Almost everywhere" means everywhere except possibly in a set of measure 0, such as a point or line.

Proof::

Without loss of generality, let there exist a function $\varphi(x, y)$ such that

$$\frac{\partial(\varphi f)}{\partial x} + \frac{\partial(\varphi g)}{\partial y} > 0$$

In simply connected region $\mathbb{R}$. . Let C be a closed trajectory of the plane autonomous system in $\mathbb{R}$. Let D be the interior of C. Then by Green's Theorem

$$\iint_D \left(\frac{\partial(\varphi f)}{\partial x} + \frac{\partial(\varphi g)}{\partial y}\right) dxdy = \oint_C -\varphi g dx + \varphi f dy$$

$$= \oint_C \varphi(-\dot{y}dx + \dot{x}dy)$$

But on C, $dx = \dot{x}dt$ and $dy = \dot{y}dt$, so the integral evaluates to 0. This is a contradiction, so there can be no such closed trajectory C.

Ex:: Consider the Lotka-Volterra system

$$x^{\cdot} = x(ax + by + c), \quad y^{\cdot} = y(dx + ey + f) \qquad \text{.....(1)}$$

where all the parameters are real numbers. By uniqueness of solutions it is clear that if it has periodic orbits then they do not intersect the coordinate axes. By making the change of variables

$x \to \pm x,\ y \to \pm y$

we can restrict our attention to the first quadrant U and prove that the system has no periodic orbit in it. To do this consider the Dulac function $D(x, y) = x^A y^B$

where the real numbers A and B have to be determined.

Then the function M appearing in

$$M(x, y) = < \nabla D(x, y), X(x, y) > + D(x, y)\ divX(x, y)$$

$$= x^A y^B((aA + dB + 2a + d)x + (bA + eB + 2e + b)y + (cA + fB + c + f)).$$

When $ae - bd \neq 0$ we can solve the linear system obtained vanishing the coefficients of x and y with unknowns A and B. Call the solution $A = \alpha$ and $B = \beta$. Then

$$M(x, y) = \frac{abf + ced - aef - ace}{ae - bd} x^\alpha y^\beta := Rx^\alpha y^\beta$$

When $R \neq 0$ we can apply the **Bendixson-Dulac Theorem** and since U is simply connected ($\ell(U) = 0$) the system has no limit cycles. When $R = 0$ then $x^A y^B$ is an integrating factor. Hence the system is integrable and its first integral is smooth in U . Thus it can not have isolated periodic orbits, i.e. it has no limit cycles. This case includes the famous Lotka-Volterra system. We recall that it has a center in U, surrounded by periodic orbits.

When $ae - bd = 0$ then either the linear system

$$ax + by + c = 0,\ dx + ey + f = 0,$$

with unknowns x and y has no solutions or its solutions are either the full plane or a whole line. In the first case the only critical points of system (1) are on the axes, so the system can not have periodic orbits. Otherwise it is either the trivial system

$x' = 0,\ y' = 0$ or is a reparameterization of the simple system $\dot{x} = gx, \dot{y} = hy$ for some real numbers $g, h,$ which clearly can not have periodic orbits either.

4.4 Importance of Dulac Criterion: [1,3]

It is well known that gradient systems cannot have periodic orbits. In this work we find a general dynamical system on the plane without periodic orbits. We use Dulac's criterion that gives sufficient conditions for the non–existence of periodic orbits of dynamical systems in simply connected regions of the plane. Using a Dulac function we can rule out periodic orbits.

Chapter Five: HIV Vaccine Model

Here I will present the HIV vaccine model [7] with differential infectivity and staged progression (DISP).

5.1 Model formulation and basic properties: [7]

The total population, N, is subdivided into mutually-exclusive compartments namely susceptible $(S(t))$, vaccinated susceptible $(V(t))$, infected individuals in the differential infectivity group i stage j $(Yi,j(t))$, for $(i,j = 1; 2)$, vaccinated infected individuals in the differential infectivity group i stage j $(Wi;j(t))$, for $(i; j = 1; 2)$, HIV infected individuals at the AIDS stage of infection $(A(t))$, so that

$$N = S + V + \sum_{i=1}^{2}\sum_{j=1}^{2}(Y_{i,j} + W_{i,j})$$

The susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population at a rate A. These individuals acquire infection, following contact with infected individuals in the $Y_{i;j}, W_{i;j}$ $(i; j = 1; 2)$ classes, at a rate λ where

$$\lambda = \sum_{i=1}^{2}\sum_{j=1}^{2}(\beta_{i,j}\frac{Y_{i,j}}{N}S_{i,j}\beta_{i,j}\frac{W_{i,j}}{N})$$

It is assumed, for mathematical convenience, that AIDS individuals do not partake in further HIV transmission. The parameter $\beta_{i,j}$ is the effective contact rate of infected individuals in subgroups $(Y_{i,j}\ and\ W_{i,j})$, while $s_{i,j}$ is the relative risk of infectiousness of vaccinated individuals. A fraction, ρ_1 ; of the newly-infected unvaccinated susceptible individuals move to the differential infectivity group 1 stage 1 $(Y_{1;1})$; while the remaining fraction, $\rho_2 = 1 - \rho_1$ move to the differential infectivity group 2 stage 1 $(Y_{2,1})$. Infected individuals in theunvaccinated differential infectivity group 1 stage 1 $(Y_{1,1})$ progress to unvaccinated differential infectivity group 1 stage 2 $(Y_{1,2})$; at a rate $\sigma_{1,1}$; while infected individuals in the unvaccinated differential infectivity group 2 stage 1 $(Y_{2,1})$ progress to the unvaccinated differential infectivity group 2 stage 2 $(Y_{2,2})$; at a rate $\sigma_{2,1}$. Infected individuals in differential infectivity groups 1 and 2 and stage 2 of infection progress to the AID stage at a rate $\sigma_{1,2}$ and $\sigma_{2,2}$ with $\sigma_{1,2} < \sigma_{2,2}$ respectively. It is assumed that a fraction, p; of susceptible individuals are vaccinated. It is further assumed that the vaccine induced protection acquired by vaccinated individuals wanes, at a rate γ (so that these vaccinated individuals move to the susceptible class at the rate γ). Since vaccinated individuals are not fully-protected against infection (owing to the vaccine imperfection), it is assumed that vaccinated individuals acquire infection at a rate that is q times lower than that of unvaccinated susceptible individuals. A fraction, π_1; of the newly-infected vaccinated individuals move to the vaccinated differential in-fectivity group 1 stage 1 $(W_{1,1})$; while the remaining fraction, $\pi_2 = 1 - \pi_1$, move to the vaccinated differential

infectivity group 2 stage 1 ($W_{2,1}$). Infected individuals in the vaccinated differential infectivity group 1 stage 1 ($W_{1;1}$) progress to vaccinated differential infectivity group 1 stage 2 ($W_{1,2}$) at a rate $\theta_{1,1}\sigma_{1,1}$, while infected individuals in the vaccinated differential infectivity group 2 stage 1 ($W_{2,1}$) progress to the vaccinated differential infectivity group 2 stage 2 ($W_{2,1}$) at a rate $\theta_{2,1}\sigma_{2,1}$. Infected individuals in both final stages progress to the AIDS stage at a rate $\theta_{1,2}\sigma_{1,2}$ and $\theta_{2,2}\sigma_{2,2}$ respectively (where $\theta_{i,j} < 1$ (i, j = 1, 2)*;* account for the reduced vaccine-induced progression to AIDS). Further, natural mortality occurs in all classes, at a rate μ*;* and AIDS individuals suffer a disease-induced death, at a rate α. In summary, the differential infectivity and staged-progression (DISP) HIV vaccine model is given by

$$\frac{dS}{dt} = (1-p) \wedge -\mu S - \lambda S + \gamma V,$$

$$\frac{dV}{dt} = p \wedge -\mu V - q\lambda V + \gamma V,$$

$$\frac{dY_{1,1}}{dt} = \rho_1 \lambda S - \left(\mu + \sigma_{1,1}\right) Y_{1,1},$$

$$\frac{dY_{1,2}}{dt} = \sigma_{1,1} Y_{1,1} - \left(\mu + \sigma_{1,2}\right) Y_{1,2},$$

$$\frac{dY_{2,1}}{dt} = \rho_2 \lambda S - \left(\mu + \sigma_{2,1}\right) Y_{2,1},$$

$$\frac{dY_{2,2}}{dt} = \sigma_{2,1} Y_{2,1} - \left(\mu + \sigma_{2,2}\right) Y_{2,2},$$

$$\frac{dW_{1,1}}{dt} = \pi_1 q\lambda V - \left(\mu + \theta_{1,1}\sigma_{1,1}\right) W_{1,1},$$

$$\frac{dW_{1,2}}{dt} = \sigma_{1,1}\theta_{1,1} W_{1,1} - \left(\mu + \theta_{1,2}\sigma_{1,2}\right) W_{1,2},$$

$$\frac{dW_{2,1}}{dt} = \pi_2 q\lambda V - \left(\mu + \theta_{2,1}\sigma_{2,1}\right) W_{2,1},$$

$$\frac{dW_{2,2}}{dt} = \sigma_{2,1}\theta_{2,1} W_{2,1} - \left(\mu + \theta_{2,2}\sigma_{2,2}\right) W_{2,2},$$

$$\frac{dA}{dt} = \sigma_{1,2}Y_{1,2} + \sigma_{2,2}Y_{2,2} + \sigma_{1,2}\theta_{1,2}W_{1,2} + \sigma_{2,2}\theta_{2,2}W_{2,2} - (\alpha + \mu)A \ \ldots.(1)$$

Yi,j : unvaccinated infected individuals in differential infectivity group i stage j, Wi,j : vaccinated infected individuals in differential infectivity group i stage j. All the parameters of the model are assumed to be non-negative. We can show that the following region is positively-invariant and attracting

$$D = \{(S, V, Y_{1,1}, Y_{1,2}, Y_{2,1}, Y_{2,2}, W_{1,1}, W_{1,2}, W_{2,1}, W_{2,2}) \epsilon \mathbb{R}_+^{10}: (S + V + Y_{1,1} + Y_{1,2} + Y_{2,1} + Y_{2,2} + W_{1,1} + W_{1,2} + W_{2,1} + W_{2,2}) \leq \wedge/\mu\}$$

5.2 Vaccination-free model: [7]

5.2.1 Local and global stability of DFE::

We consider, first of all, the model in the absence of vaccination. In this case, $p = \gamma = V = W_{1,1} = W_{1,2} = W_{2,1} = W_{2,2} = 0$; so that the model reduces to

$$\frac{dX}{dt} = \wedge - \mu S - \lambda S,$$

$$\frac{dY_{1,1}}{dt} = \rho_1 \lambda S - (\mu + \sigma_{1,1})Y_{1,1},$$

$$\frac{dY_{1,2}}{dt} = \sigma_{1,1}Y_{1,1} - (\mu + \sigma_{1,2})Y_{1,2},$$

$$\frac{dY_{2,1}}{dt} = \rho_2 \lambda S - (\mu + \sigma_{2,1})Y_{2,1},$$

$$\frac{dY_{2,2}}{dt} = \sigma_{2,1}Y_{2,1} - (\mu + \sigma_{2,2})Y_{2,2},$$

$$\frac{dA}{dt} = \sigma_{1,2}Y_{1,2} + \sigma_{2,2}Y_{2,2} - (\alpha + \mu)A \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(2)$$

with,

$$\lambda = \sum_{i=1}^{2}\sum_{j=1}^{2}\frac{\beta_{i,j}Y_{i,j}}{N} \;\&\; N = S + Y_{1,1} + Y_{1,2} + Y_{2,1} + Y_{2,2} + A \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

The model has a DFE given by,

$$\varepsilon_0 = \left(S^*, Y_{1,1}^*, Y_{1,2}^*, Y_{2,1}^*, Y_{2,2}^*, A^*\right) = (\wedge/\mu\,, 0,0,0,0,0).$$

Here, the next generation matrices are given by,

$$F = \begin{bmatrix} \frac{\rho_1\beta_{1,1}S^*}{N^*} & \frac{\rho_1\beta_{1,2}S^*}{N^*} & \frac{\rho_1\beta_{2,1}S^*}{N^*} & \frac{\rho_1\beta_{2,2}S^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\rho_2\beta_{1,1}S^*}{N^*} & \frac{\rho_2\beta_{1,1}S^*}{N^*} & \frac{\rho_2\beta_{1,1}S^*}{N^*} & \frac{\rho_2\beta_{1,1}S^*}{N^*} \\ 0 & 0 & 0 & 0 \end{bmatrix},\; V = \begin{bmatrix} K_{32} & 0 & 0 & 0 \\ -\sigma_{1,1} & K_{33} & 0 & 0 \\ 0 & 0 & K_{34} & 0 \\ 0 & 0 & -\sigma_{2,1} & K_{35} \end{bmatrix},$$

Where,

$$K_{32} = \mu + \sigma_{1,1}, \quad K_{33} = \mu + \sigma_{1,2}, \quad K_{34} = \mu + \sigma_{2,1}, \quad K_{35} = \mu + \sigma_{2,2}$$

The basic reproduction number, R_0 is given by

$$R_0 = \rho(FV^{-1})$$
$$= \frac{\rho_1 K_{34}K_{35}\left(\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}\right) + \rho_2 K_{32}K_{33}\left(\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1}\right)}{K_{32}K_{33}K_{34}K_{35}} \ldots (4)$$

Thus, the following result is established.

Lemma 5.1. The DFE of the vaccination-free model (2), given by ε_0, is LAS if

$R_0 < 1$ and unstable if $R_0 > 1$.

Further, we claim the following result.

Theorem 5.1. The DFE of the vaccination-free model (2), given by ε_0, is GAS if $R_0 < 1$.

Proof. Consider the Lyapunov function given by,

$$F = \frac{\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}}{K_{32}K_{33}}Y_{1,1} + \frac{\beta_{1,2}}{K_{33}}Y_{1,2} + \frac{\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1}}{K_{34}K_{35}}Y_{2,1} + \frac{\beta_{2,2}}{K_{35}}Y_{2,2}$$

with Lyapunov derivative given by,

$$\dot{F} = \frac{\beta_{1,1}K_{33} + \beta_{1,2}\sigma_{1,1}}{K_{32}K_{33}}\dot{Y_{1,1}} + \frac{\beta_{1,2}}{K_{33}}\dot{Y_{1,2}} + \frac{\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1}}{K_{34}K_{35}}\dot{Y_{2,1}} + \frac{\beta_{2,2}}{K_{35}}\dot{Y_{2,2}}$$

$$= \frac{\beta_{1,1}K_{33}+\beta_{1,2}\sigma_{1,1}}{K_{32}K_{33}}\left(\rho_1 S\lambda - K_{32}Y_{1,1}\right) + \frac{\beta_{1,2}}{K_{33}}\left(\sigma_{1,1}Y_{1,1} - K_{33}Y_{1,2}\right) +$$

$$\frac{\beta_{2,1}K_{35} + \beta_{2,2}\sigma_{2,1}}{K_{34}K_{35}}(\rho_2 S\lambda - K_{34}Y_{2,1}) + \frac{\beta_{2,2}}{K_{35}}(\sigma_{2,1}Y_{2,1} - K_{35}Y_{2,2})$$

$$= N\lambda\left[\frac{S\rho_1 K_{34}K_{35}(\beta_{1,1}K_{33}+\beta_{1,2}\sigma_{1,1})+\rho_2 K_{32}K_{33}(\beta_{2,1}K_{35}+\beta_{2,2}\sigma_{2,1})}{NK_{32}K_{33}K_{34}K_{35}}\right],$$

$$\leq \lambda_1\left[\frac{\rho_1 K_{34}K_{35}(\beta_{1,1}K_{33}+\beta_{1,2}\sigma_{1,1})+\rho_2 K_{32}K_{33}(\beta_{2,1}K_{35}+\beta_{2,2}\sigma_{2,1})}{K_{32}K_{33}K_{34}K_{35}}\right],$$

$$= \lambda_1(R_0 - 1) < 0 \text{ for } S \leq N \;\&\; R_0 < 1.$$

Where,

$$\lambda_1 = \sum_{i=1}^{2}\sum_{j=1}^{2}\beta_{i,j}Y_{i,j}$$

The proof is completed.

5.3 DISP model with wholly-vaccinated population: [7]

Consider the model (1) in which every member of the population is vaccinated (obtained by setting $Y_{1,1} = Y_{1,2} = Y_{2,1} = Y_{2,2} = p = 0$ in (1)), given by

$$\frac{dV}{dt} = \wedge - \mu V - q\lambda V,$$

$$\frac{dW_{1,1}}{dt} = \pi_1 q\lambda V - \left(\mu + \theta_{1,1}\sigma_{1,1}\right)W_{1,1},$$

$$\frac{dW_{1,2}}{dt} = \sigma_{1,1}\theta_{1,1}W_{1,1} - \left(\mu + \theta_{1,2}\sigma_{1,2}\right)W_{1,2},$$

$$\frac{dW_{2,1}}{dt} = \pi_2 q\lambda V - \left(\mu + \theta_{2,1}\sigma_{2,1}\right)W_{2,1},$$

$$\frac{dW_{2,2}}{dt} = \sigma_{2,1}\theta_{2,1}W_{2,1} - \left(\mu + \theta_{2,2}\sigma_{2,2}\right)W_{2,2},$$

$$\frac{dA}{dt} = \sigma_{1,2}\theta_{1,2}W_{1,2} + \sigma_{2,2}\theta_{2,2}W_{2,2} - (\alpha + \mu)A, \quad \ldots\ldots\ldots\ldots\ldots(5)$$

With,

$$N = V + \sum_{i=1}^{2}\sum_{j=1}^{2} W_{i,j} \;\; and \;\; \lambda = \sum_{i=1}^{2}\sum_{j=1}^{2} s_{i,j}\beta_{i,j}\frac{W_{i,j}}{N}$$

5.3.1 Local and global stability of DFE::

The model (5) has a DFE given by

$$\varepsilon_{0v} = \left(V^*, W_{1,1}^*, W_{1,2}^*, W_{2,1}^*, W_{2,2}^*\right) = (\wedge/\mu\,, 0,0,0,0), \quad \ldots\ldots\ldots\ldots(6)$$

with the associated next generation matrices,

$$F = \begin{bmatrix} \frac{\pi_1 q s_{1,1}\beta_{1,1}V^*}{N^*} & \frac{\pi_1 q s_{1,2}\beta_{1,2}V^*}{N^*} & \frac{\pi_1 q s_{2,1}\beta_{2,1}V^*}{N^*} & \frac{\pi_1 q s_{2,2}\beta_{2,2}V^*}{N^*} \\ 0 & 0 & 0 & 0 \\ \frac{\pi_2 q s_{1,1}\beta_{1,1}V^*}{N^*} & \frac{\pi_2 q s_{1,2}\beta_{1,2}V^*}{N^*} & \frac{\pi_2 q s_{2,1}\beta_{2,1}V^*}{N^*} & \frac{\pi_2 q s_{2,2}\beta_{2,2}V^*}{N^*} \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} K_{36} & 0 & 0 & 0 \\ -\sigma_{1,1}\theta_{1,1} & K_{37} & 0 & 0 \\ 0 & 0 & K_{38} & 0 \\ 0 & 0 & -\sigma_{2,1}\theta_{2,1} & K_{39} \end{bmatrix},$$

Where,

$$K_{36} = \mu + \theta_{1,1}\sigma_{1,1},\ \ K_{37} = \mu + \theta_{1,2}\sigma_{1,2},\ \ K_{38} = \mu + \theta_{2,1}\sigma_{2,1},\ \ K_{39} = \mu + \theta_{2,2}\sigma_{2,2}$$

Thus, the basic vaccination reproduction number, denoted by $R_{ov} = \rho(FV^{-1})$, is

$$R_{ov} = \frac{q[\pi_1 K_{38}K_{39}\left(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}\right) + \pi_2 K_{36}K_{37}\left(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}\right)]}{K_{36}K_{37}K_{38}K_{39}}$$

……..(7)

The following result is established.

Lemma 5.2. The DFE of the model (5), given by ε_{0v}, is LAS if $R_{ov} < 1$ and unstable if $R_{ov} > 1$.

Further, we claim the following:

Theorem 5.2. The DFE of the model (5), given by E_{0v}, is *GAS if* $R_{ov} < 1$.

Proof. Consider the Lyapunov function given by,

$$F = \frac{\left(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}\right)}{K_{36}K_{37}}W_{1,1} + \frac{s_{1,2}\beta_{1,2}}{K_{37}}W_{1,2} +$$

$$\frac{\left(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}\right)}{K_{38}K_{39}}W_{2,1} + \frac{s_{2,2}\beta_{2,2}}{K_{37}}W_{2,2},$$

with Lyapunov derivative given by,

$$\dot{F} = \frac{\left(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}\right)}{K_{36}K_{37}}\dot{W}_{1,1} + \frac{s_{1,2}\beta_{1,2}}{K_{37}}\dot{W}_{1,2} +$$

$$\frac{\left(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}\right)}{K_{38}K_{39}}\dot{W}_{2,1} + \frac{s_{2,2}\beta_{2,2}}{K_{37}}\dot{W}_{2,2}$$

$$= \frac{\left(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}\right)}{K_{36}K_{37}}\left(\pi_1 q\lambda V - K_{36}W_{1,1}\right) + \frac{s_{1,2}\beta_{1,2}}{K_{37}}\left(\sigma_{1,1}\theta_{1,1}W_{1,1} - K_{37}W_{1,2}\right) +$$

$$\frac{\left(s_{2,1}\beta_{2,1}K_{39}+s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}\right)}{K_{38}K_{39}}\left(\pi_2 q\lambda V - K_{38}W_{2,1}\right) + \frac{s_{2,2}\beta_{2,2}}{K_{37}}\left(\sigma_{2,1}\theta_{2,1}W_{2,1} - K_{39}W_{2,2}\right)$$

$$= N\lambda\left[\frac{Vq\left[\pi_1 K_{38}K_{39}\left(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}\right) + \pi_2 K_{36}K_{37}\left(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}\right)\right]}{NK_{36}K_{37}K_{38}K_{39}} - 1\right]$$

$$< \lambda_2\left[\frac{q\left[\pi_1 K_{38}K_{39}\left(s_{1,1}\beta_{1,1}K_{37} + s_{1,2}\beta_{1,2}\sigma_{1,1}\theta_{1,1}\right) + \pi_2 K_{36}K_{37}\left(s_{2,1}\beta_{2,1}K_{39} + s_{2,2}\beta_{2,2}\sigma_{2,1}\theta_{2,1}\right)\right]}{K_{36}K_{37}K_{38}K_{39}} - 1\right]$$

$$= \lambda_{\,2}(R_{ov} - 1) \leq 0, \text{for } V \leq N \text{ and } R_{ov} - 1,$$

Where,

$$\lambda_2 = \sum_{i=1}^{2}\sum_{j=1}^{2} s_{i,j}\beta_{i,j}W_{i,j}$$

The proof is completed.

Table 5.1: Description of variables and parameters for the vaccination model (1)

Variables/ parameters	Description
$S(t)$	unvaccinated susceptible individuals
$V(t)$	vaccinated susceptible individuals
$Y_{1,1}(t)$	unvaccinated infected individuals with high viral load, stage 1
$Y_{1,2}(t)$	unvaccinated infected individuals with high viral load, stage 2
$Y_{2,1}(t)$	unvaccinated infected individuals with low viral load, stage 1
$Y_{2,2}(t)$	unvaccinated infected individuals with low viral load, stage 2
$W_{1,1}(t)$	vaccinated infected individuals with high viral load, stage 1
$W_{1,2}(t)$	vaccinated infected individuals with high viral load, stage 2
$W_{2,1}(t)$	vaccinated infected individuals with low viral load, stage 1
$W_{2,2}(t)$	vaccinated infected individuals with low viral load, stage 2
$A(t)$	individuals in AIDS stage of infection
$\wedge$	rate of recruitment into the population
$\beta_{1,1}, \beta_{1,2}, \beta_{2,1}, \beta_{2,2}$	transmission coefficients (contact rates)
p	fraction of individuals vaccinated
$1-q$	vaccine efficacy
$s_{1,1}, s_{1,2}, s_{2,1}, s_{2,2}$	rate of infectiousness
$\theta_{1,1}, \theta_{1,2}, \theta_{2,1}, \theta_{2,2}$	modification parameters
μ	natural death rate
γ	waning rate of vaccine
$\sigma_{1,1}, \sigma_{1,2}, \sigma_{2,1}, \sigma_{2,2}$	progression rates
α	disease-induced mortality rate
$\rho_1, \rho_2, \pi_1, \pi_2$	probabilities

Conclusion

Epidemiology plays a very important role in public health program. In epidemiology, mathematical modeling and dynamical systems are very important. In this project we have discussed some dynamical system tools such as Lyapunov Function, Dulac Criterion which are very powerful method to find the local and global stability of epidemic models.

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