6-2014

On the Evolution of Virulence

Thi Nguyen
California State University - San Bernardino

On the Evolution of Virulence

A Thesis

Presented to the

Faculty of

California State University,

San Bernardino

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

in

Mathematics

---

by

Thi Nguyen

June 2014

On the Evolution of Virulence

A Thesis

Presented to the

Faculty of

California State University,

San Bernardino

---

by

Thi Nguyen

June 2014

Approved by:

Dr. Chetan Prakash, Committee Chair	Date
Dr. Min-Lin Lo, Committee Member	
Dr. Shawnee McMurran, Committee Member	
Dr. Peter Williams, Chair, Department of Mathematics	Dr. Charles Stanton Graduate Coordinator, Department of Mathematics

Abstract

The goal of this thesis is to study the dynamics behind the evolution of virulence. We examine first the underlying mechanics of linear systems of ordinary differential equations by investigating the classification of fixed points in these systems, then applying these techniques to nonlinear systems. We then seek to establish the validity of a system that models the population dynamics of uninfected and infected hosts—first with one parasite strain, then n strains. We define the basic reproductive ratio of a parasite, and study its relationship to the evolution of virulence. Lastly, we investigate the mathematics behind superinfection.

Acknowledgements

I extend my deepest gratitude to Dr. Chetan Prakash for his guidance in working on this project—it obviously wouldn't be done without his help. I would also like to thank my committee members, Dr. Shawnee McMurran and Dr. Min-Lin Lo, for their support and wisdom through the years. Thanks to Joshua Lee Hidalgo, for sharing his office; Laura Perez, for helping me stay relatively sane; and Liliana Amber Casas, for her time and effort on the first chapter. Of course, endless thanks to my family, to whom I owe everything.

Table of Contents

List of Figures

Chapter 1

A Brief Exposition on Viruses

To show a connection within the sciences, and to show just how awesome and supreme mathematics is, I thought it would be best to include a chapter about viruses. The material presented in this chapter has been adapted from *Virology: Principles and Applications*, authored by John Carter and Venetia Saunders [CS07], and *Viruses*, by K. M. Smith. [Smi62]

1.1 The Stars of Our Show

We begin with a definition.

Definition 1.1.1. A **parasite** is an organism that lives on or within another organism.

This broad category includes a number of things, such as the bacteria in your digestive tract, helping convert all of that food you ate earlier into usable components for the body; the appendix in the abdomen, that sits comfortably all day, never really contributing anything to one's development, but capable of unleashing a terrible evil upon the body—just for fun; or the virus that eats away at the immune system, making it possible for weaker infectious agents and other malignant sources to affect an otherwise healthy individual. It is the last example that is the focus of this chapter, so it would be a good idea to define them.

Definition 1.1.2. A **virus** is a very small, non-cellular parasite of cells. While not within a host cell, virus particles are called **virions**. Viruses that infect bacteria are called **bacteriophages**, or **phages** for short.

Due to their size, viruses are able to infect all levels of cellular life, and are thus the most abundant biological object in the world; they are not catergorized as "organisms" because it is debatable as to whether or not a virus is "living" to begin with.

1.2 A Brief History on Their Discovery

Once upon a time, Louis Pasteur, famous for his work on pasteurization—a method of reducing the number of infectious agents in a solution by heating it—and Robert Koch had both shown that some diseases were caused by small organisms, in the form of bacteria. Under this impression, they believed that all diseases were caused by such organisms, and turned their focus in that direction; this ended in failure when Pasteur was unable to isolate a bacterial specimen after passing a solution containing the rabies virus through a porcelain (also called Chamberland) filter.

The first successful evidence of a submicroscopic cause came with the study of the tobacco mosaic virus, which infects (you guessed it) tobacco plants and other vegetation.[1] Adolf Mayer was first in showing that the sap of infected plants was the medium in which this mysterious infectious agent travelled about, and, by injecting it into healthy plants, they, too, would become infected. He was convinced that the cause was bacterial, and pursued research in that direction; this ended in failure.

Next was Dmitri Ivanovski, who repeated Mayer's experiments and confirmed his result: the sap of the diseased was the culprit. Where he differed from Mayer was his decision to pass the sap through filters to remove all bacterial agents, and showed that the sap was still infectious, though he, too, felt the reason was because the organisms were submicroscopic.

Then along came Martinus Beijerinck. He confirmed Ivanovski's results about the filter-bypassing abilities of the agent, but—and this is important—he did not believe like the last two that the cause was a bacteria too small to see. Though he could not isolate the virus himself, he decided to call it *contagium vivum fluidum* (or "contagious

[1] "The plant virologist has two great advantages over his colleague working with animal viruses: much greater quantities of virus are available and they are easier to extract." [Smi62]

living fluid"), noting that "the virus must really be regarded as liquid or soluble and not as [minute organisms or cells]." [Smi62]

It would be Wendell Stanley who showed that the viruses are not fluid in nature, but particulate.

1.3 Structure

All viruses contain genetic material called the **genome**. For viruses, there are four types: single- and double-stranded DNA, and single- and double-stranded RNA. Surrounding the genome is the **capsid**, which serves to protect the genome. These take a few forms, most commonly helices, icosahedrons (20-sided figures with triangular faces), rods, or cones. Together, the genome and capsid make up the **nucleocapsid**.

Some virions have a lipid outer layer (called also an envelope) that provides further protection for the genome, as well as containing proteins that aid in the virions' access into host cells. Viruses that lack this envelope are said to be naked. Figure 1.1 shows an example of an icosahedron, one with an envelope, a helix, and one with an envelope.

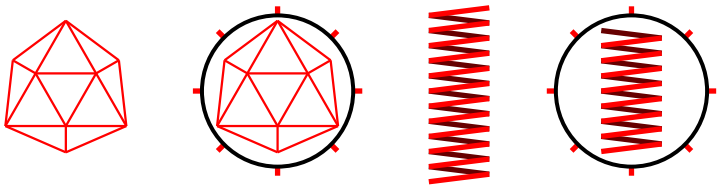

Figure 1.1: Examples of virion structures

The majority of phages are composed of an icosahedronal head that houses the genetic core, which is attached to a tail. The tail has a connector and tail fibers that aid in the attachment to host cell membranes. By using this connector, they are able to penetrate the cell membrane, and inject their genome directly into the host.

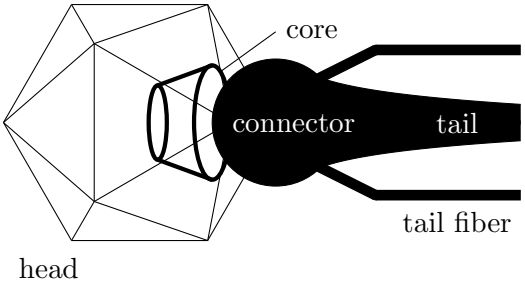

Figure 1.2: A bacteriophage

1.4 How They Reproduce

Viruses do not grow then separate, like other organisms. Alone, they do not have the means to replicate themselves, and require a living host cell to provide them with the necessary machinery with which to do so.[2] With the proteins present on the surface of the virion, the particles bind to specific receptors located on the surface of host cells; some viruses require co-receptors in order to successfully infect a cell. One of a few things happens at this point:

1. For naked viruses, once they are bound to the membrane of their host cell, the membrane wraps around the virion, drawing it within itself; this small body, called the **endosome**, undergoes **endocytosis**, the process by which the cell breaks down whatever it brings into itself. By doing this, it frees the genome of the virion.

2. For enveloped viruses, either

    a. the virion undergoes endocytosis, but fuses to the membrane of the endosome, and releases itself into the host, or

    b. the virion fuses at the surface of the cell membrane and passes through,

    where both cases lead to the release of the virus genome into the host.

Once within the host, the virus proceeds to take control of the cell and its machinery, effectively turning them into little factories that produce the necessary materials to build and package additional virions to be sent to other susceptible hosts.

[2] "Luria puts it like this—'virus multiplication belongs on the level of the replication of subcellular elements', or according to Pirie 'it is the exploitation and diversion of the pre-existing synthetic capacities of the host cell.'" [Smi62]

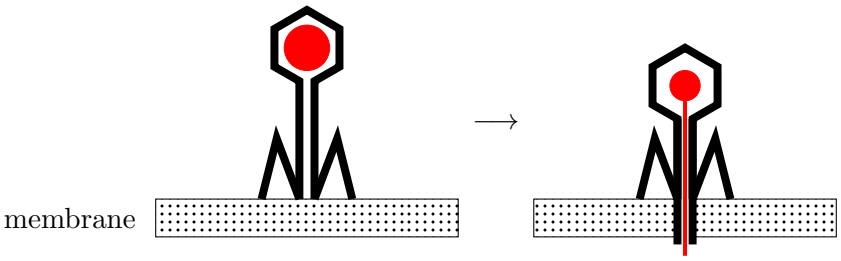

Figure 1.3: A phage injecting its genome

Chapter 2

Foundational Materials

We now discuss the mechanics of systems. To that end, we utilize the definitions, theorems, and notations of Steven Strogatz's text, *Nonlinear Dynamics and Chaos.* [Str94]

2.1 Linear One-Dimensional Systems

We begin by defining a **general system of ordinary differential equations** as

$$\begin{aligned} \dot{x}_1 &= f_1(x_1, \ldots, x_n) \\ &\vdots \\ \dot{x}_n &= f_n(x_1, \ldots, x_n) \end{aligned} \tag{2.1}$$

where $x_1, \ldots, x_n$ are variables, $\dot{x}_i = \frac{dx_i}{dt}$ represents the rate of change of that variable over time, and where f_i is the function of the set of the variables. As there are n variables, (2.1) is also called an ***n*-dimensional system** or an ***n*th order system**.

Example 2.1.1.

$$\begin{aligned} \dot{x}_1 &= x_1 + x_2 \\ \dot{x}_2 &= x_1 - x_2 \end{aligned} \tag{2.2}$$

is an example of a 2-dimensional system. Moreover, it is also a **linear system** because all variables are of the first order (in that each term has at most one variable appearing to the first power). Otherwise, the system would be described as **nonlinear**. We will refer back to (2.2) later in this chapter.

2.2 The Space, Fixed Points, and Flow

Nonlinear systems are difficult to solve analytically, so it is often best to study the systems with an intuitive, geometric approach. The space $\mathbb{R}^n$ of the variables, the one in which we analyze the dynamics of differential equations, is called the **phase space**. The **vector field** $(f_1, f_2, \ldots, f_n)$ dictates the velocity of the vector $\dot{\boldsymbol{x}}$ at each $\boldsymbol{x}$. Given an initial point x_0, called a **phase point**, it will move along through the phase space, tangential to the vector field, making a path; this path is called its **trajectory**.

The points in the system where $\dot{x} = 0$ are called **fixed points**, denoted as x^*, and are places where the flow, or the motion, of points through the space is at zero speed. In one dimension, the flow is to the **right** if $\dot{x} > 0$, and it is to the **left** if $\dot{x} < 0$. Fixed points where the all of the flow is towards them are called **stable fixed points** (also called sinks or attractors), whereas points that have the flow moving away are called **unstable fixed points** (likewise called sources or repellers). Points where the flow is in the same direction on either side are called **half-stable fixed points**. Fixed points represent **equilibria** to the system.

For n-dimensional systems with $n > 1$, the concept of flow is generalized to the **vector flow**, which consists of trajectories moving along in the phase space. A picture that includes all of the qualitative information about the system—the fixed points and trajectories—is called a **phase portrait**.

Example 2.2.1. Given $\dot{x} = 1 - x^2$, its fixed points are

$$f(x^*) = 0 = 1 - (x^*)^2$$
$$x^* = \pm 1.$$

We see that $\dot{x} > 0$ when $x \in (-1, 1)$, and that $\dot{x} < 0$ when $x \in (-\infty, -1) \cup (1, \infty)$. Thus, according to the direction of the flow, $x^* = -1$ is an unstable node, while $x = 1$ is stable, as we can see in the phase portrait below.

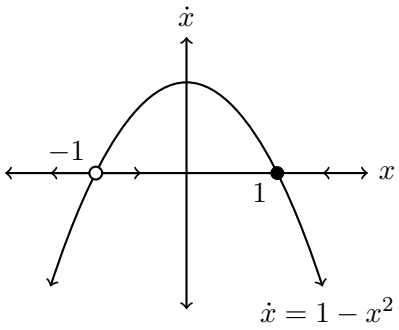

Figure 2.1: Phase portrait for $\dot{x} = 1 - x^2$

■

Analyzing things using flows makes it easier to see what is happening in more complicated situations, where an analytic approach is prohibitively difficult. For another example,

Example 2.2.2. Consider $\dot{x} = \sin(x)$ on the interval $\left(-\frac{\pi}{2}, \frac{5\pi}{2}\right)$. Then $f(x^*) = 0$ when $x^* = 0, \pi$, and 2π. We have then that $\dot{x} > 0$ when $x \in \left(0, \pi\right) \cup \left(2\pi, \frac{5\pi}{2}\right)$, and that $\dot{x} < 0$ when $x \in \left(-\frac{\pi}{2}, 0\right) \cup (\pi, 2\pi)$. Thus, $x^* = \pi$ is a stable node, while $x^* = 0$ and $x^* = 2\pi$ are unstable nodes.

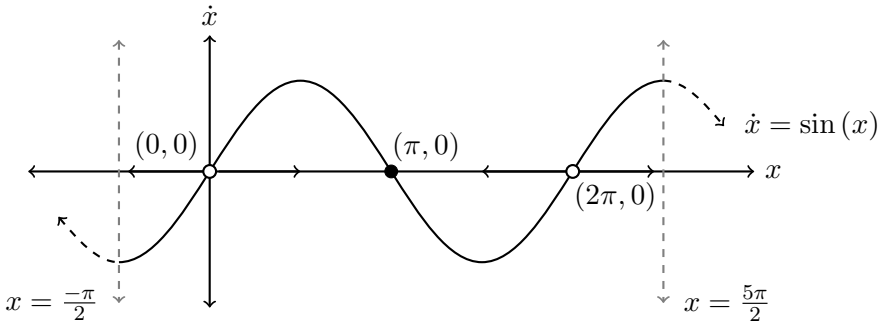

Figure 2.2: Phase portrait for $\dot{x} = \sin(x)$

■

2.3 Two-Dimensional Systems

As we have seen before, though now with a bit of notational adjustments, a **two-dimensional linear system** is of the form

$$\begin{aligned} \dot{x} &= ax + by \\ \dot{y} &= cx + dy \end{aligned} \tag{2.3}$$

where a, b, c, d are the parameters of the system. This system can be rewritten as

$$\dot{\boldsymbol{x}} = A\boldsymbol{x}, \tag{2.4}$$

where

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \quad \text{and} \quad \boldsymbol{x} = \begin{pmatrix} x \\ y \end{pmatrix}.$$

As before, fixed points in this system are where $\boldsymbol{x}^* = 0$. In more than one dimension, we have more interesting possibilities when classifying fixed points, as opposed to the stable, unstable, and half-stable points (for an example of a half-stable point, consider $\dot{x} = (x-1)^2$ at $x = 1$).

2.4 Classification of Fixed Points

In order to classify the fixed points of the 2-dimensional linear system (2.3), we consider its matrix form, and seek to find its **eigenvector**—a nonzero vector v such that, when the matrix A is multipled by v, a scalar multiple of v is obtained. This scalar multiple of v, denoted as λ, is called the **eigenvalue** of A corresponding to the vector v.

The eigenvalues of a matrix are determined by the fact that $A - \lambda I = 0$ has nontrivial solutions, and therefore $\det(A - \lambda I) = 0$, where I is the identity matrix $\left(\begin{smallmatrix} 1 & 0 \\ 0 & 1 \end{smallmatrix}\right)$. So, for A as in (2.4), the **characteristic equation** is

$$\begin{aligned} \det(A - \lambda I) &= \det \begin{pmatrix} a - \lambda & b \\ c & d - \lambda \end{pmatrix} = (a - \lambda)(d - \lambda) - bc \\ &= \lambda^2 - (a + d)\lambda + (ad - bc) \\ &= \lambda^2 - \tau\lambda + \Delta, \end{aligned} \tag{2.5}$$

where $\tau = a + d$ is the **trace** and $\Delta = ad - bc$ is the **determinant** of A. Then, using the characteristic equation, we find that the eigenvalues are

$$\lambda_1 = \frac{\tau + \sqrt{\tau^2 - 4\Delta}}{2}, \quad \text{and} \quad \lambda_2 = \frac{\tau - \sqrt{\tau^2 - 4\Delta}}{2}. \tag{2.6}$$

So we can see finding the eigenvalues depends on only the trace and determinant of A, which are both simple to compute. Finally, if the corresponding eigenvalues are $\vec{v}_1$ and $\vec{v}_2$, with $\vec{v}_1 \neq \vec{v}_2$, the general solution is

$$\vec{x}(t) = c_1 \cdot e^{\lambda_1 t} \cdot \vec{v}_1 + c_2 \cdot e^{\lambda_2 t} \cdot \vec{v}_2. \tag{2.7}$$

In the event that the eignvalues are complex (so that $\tau^2 - 4\Delta < 0$), then we may rewrite (2.6) as $\tau^2 = \alpha \pm i\omega$, where $\alpha = \tau/2$ and $\omega = \frac{1}{2}\sqrt{4\Delta - \tau^2} \neq 0$. Since the eigenvalues are distinct, then the solution is

$$\vec{x}(t) = c_1 \cdot e^{(\alpha + i\omega)t} \cdot \vec{v_1} + c_2 \cdot e^{(\alpha - i\omega)t} \cdot \vec{v_2}, \tag{2.8}$$

where $e^{i(\omega t)} = \cos(\omega t) + i \sin(\omega t)$ by Euler's formula. If $\alpha < 0$, then the solution represents an **exponentially decaying oscillation**, corresponding to a **stable spiral**. If $\alpha > 0$, then it is an **exponentially growing oscillation**, corresponding to an **unstable spiral**. If $\alpha = 0$, then the eigenvalues are purely imaginary. These correspond to fixed points that are **centers with concentric stable ellipses** around them.

Thus, we have

Theorem 2.4.1.

1. *If $\Delta < 0$, then both of the eigenvalues are real, but with opposite signs, so the fixed point is a **saddle point**.*
2. *If $\Delta > 0$, and*
   a. *if $\tau^2 - 4\Delta > 0$, then the eigenvalues are real, with the same sign, and are **nodes**; or*
   b. *if $\tau^2 - 4\Delta < 0$, then the eigenvalues are complex conjugates, and are **centers** or **spirals**.*

3. *If $\Delta = 0$, then at least one of the eignvalues is zero. This means that the origin is not an isolated fixed point, so there is either a line of fixed points, or (in the trivial case) a plane of fixed points.*

The stability diagram that summarizes all of this is given in Figure 2.3.

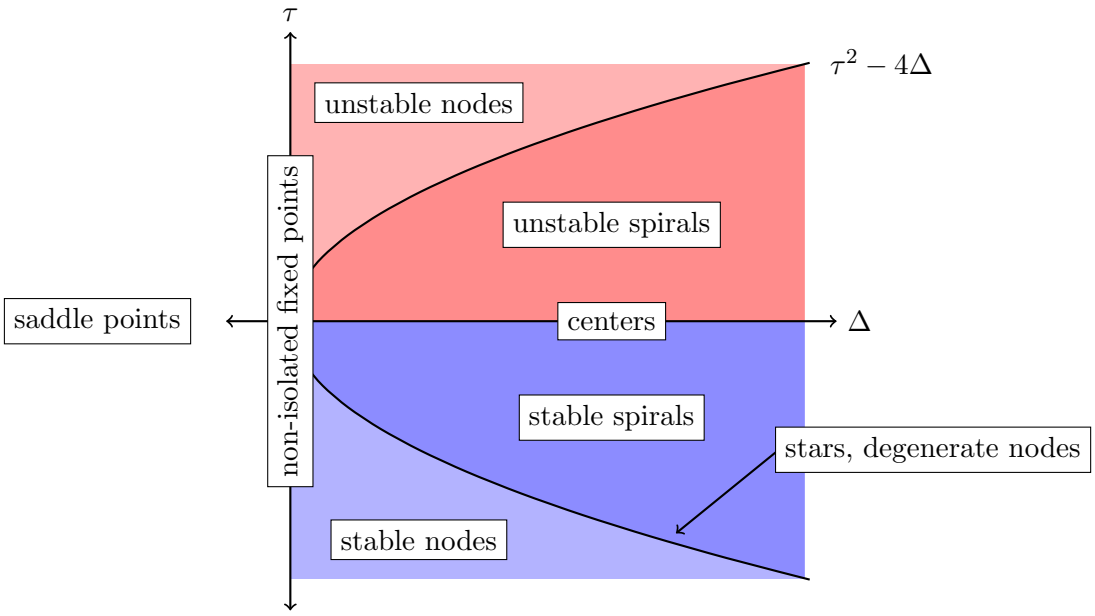

Figure 2.3: Stability diagram for fixed points

Example 2.4.2. We return to (2.2) to analyze the stability of its fixed points. We have first that the fixed point is given by $(x_1^*, x_2^*) = (0, 0)$. Since

$$A = \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix},$$

then $\tau = 0$, and $\Delta = -1$. From the stability analysis, since $\Delta < 0$, and the origin is a saddle point. The general solution is given by

$$\vec{x}(t) = ce^{t}\begin{pmatrix} 1 \\ 0 \end{pmatrix} + de^{-t}\begin{pmatrix} 0 \\ 1 \end{pmatrix},$$

where c and d are constants. The phase portrait along with trajectories for initial conditions $\left(-\frac{1}{2}, \frac{3}{2}\right)$ in blue, and $\left(\frac{1}{2}, -\frac{3}{2}\right)$ in red, is given in the figure below.

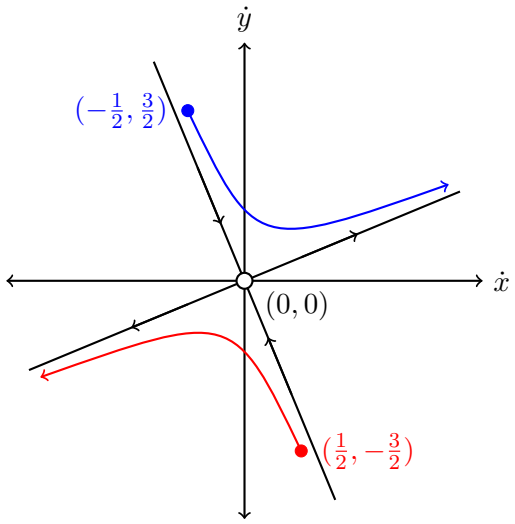

Figure 2.4: A phase portrait with trajectories

■

Example 2.4.3.

1. Given

$$\dot{x} = x - 7y$$
$$\dot{y} = 9x + y,$$

the only fixed point of the system is the origin $(0, 0)$. The matrix associated with the system is

$$A = \begin{pmatrix} 1 & -7 \\ 9 & 1 \end{pmatrix}.$$

Then $\tau = 2 > 0$, and $\Delta = 64 > 0$, so the origin is either a spiral, center, or just a node. To be sure, we have that $\tau^2 - 4\Delta = -252 < 0$, so we the origin is either a center or spiral. Since $\alpha = \tau/2 = 1 > 0$, then the origin is an unstable spiral. The trajectory for a solution with initial point $(1, 0)$ is given in Figure 2.5.

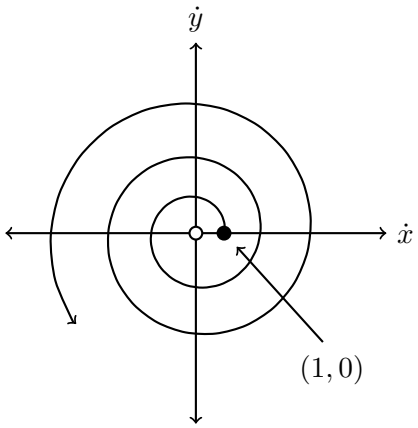

Figure 2.5: An example of an unstable spiral

2. To contrast, consider

$$\dot{x} = -x - 5y,$$

$$\dot{y} = 8x - y.$$

Similar to the previous example, the origin is again the only fixed point. We have that

$$\tau = -2, \qquad \Delta = 41, \qquad \text{and} \qquad \tau^2 - 4\Delta = -160,$$

so the origin is a stable spiral. The trajectory for the solution with initial condition $(-4, 4)$ is given in Figure 2.6.

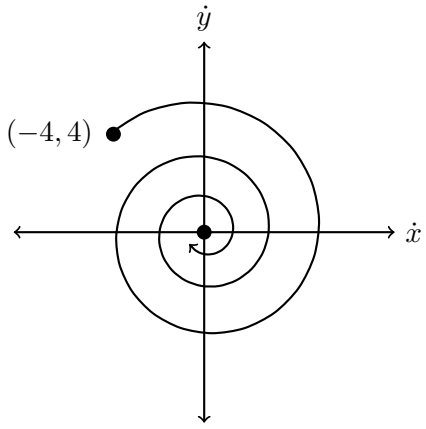

Figure 2.6: An example of a stable spiral

■

2.5 Nonlinearity, and an Analysis

A **nonlinear system** has the form

$$\begin{aligned} \dot{x}_1 &= f_1(x_1, x_2) \\ \dot{x}_2 &= f_2(x_1, x_2), \end{aligned} \tag{2.9}$$

where one of the functions f_1 or f_2 are nonlinear (or that each term has at least one variable appearing to a power greater than one). Finding solutions to trajectories analytically is usually extremely difficult, if not impossible, so we will continue with our geometric approach.

We rewrite (2.9) for smooth functions f_1 and f_2 with variables $x = x_1$ and $y = x_2$, so that

$$\begin{aligned} \dot{x} &= f_1(x, y) \\ \dot{y} &= f_2(x, y), \end{aligned}$$

with a fixed point (x^*, y^*). Let $u = x - x^*$, and $v = y - y^*$. So, by Taylor's theorem on power series,

$$\begin{aligned} \dot{u} &= f_1(x^* + u, y^* + v) \\ &= f_1(x^*, y^*) + u \cdot \frac{\partial f_1}{\partial x} + v \cdot \frac{\partial f_1}{\partial y} + O(u^2, v^2, uv, \ldots) \\ &= u \cdot \frac{\partial f_1}{\partial x} + v \cdot \frac{\partial f_1}{\partial y} + O(u^2, v^2, uv, \ldots), \end{aligned} \tag{2.10}$$

where $\dfrac{\partial f_1}{\partial x}$ and $\dfrac{\partial f_1}{\partial y}$ are the partial derivatives of f_1 with respect to u and v, evaluated at the fixed point (x^*, y^*), and $O(u^2, v^2, uv, \ldots)$ denotes terms of quadratic or higher order with respect to u and v. Similarly,

$$\dot{v} = u \cdot \frac{\partial f_2}{\partial x} + v \cdot \frac{\partial f_2}{\partial y} + O(u^2, v^2, uv, \ldots). \tag{2.11}$$

Thus,

$$\begin{pmatrix} \dot{u} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix} + O(u^2, v^2, uv, \ldots). \tag{2.12}$$

We define the **Jacobian at (x^*, y^*)** to be

$$A = \left. \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{pmatrix} \right|_{(x^*, y^*)}.$$

If we choose to ignore the comparatively small terms of quadratic (or higher) order, then we have the **linearized system**, given by

$$\begin{pmatrix} \dot{u} \\ \dot{v} \end{pmatrix} = \left. \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{pmatrix} \right|_{(x^*,y^*)} \begin{pmatrix} u \\ v \end{pmatrix}. \tag{2.13}$$

As long as the fixed points used in the analysis are not non-isolated fixed points, stars, or degenerate nodes (cases when $\Delta = 0$ or $\tau^2 - 4\Delta = 0$; these types of fixed points are also called the **borderline cases**), then the terms of quadratic (or higher) order can be ignored, as they do not influence the results of the linearization enough to matter. The purpose of linearizing the system is to employ the analytic methodology proposed by Theorem 2.4.1.

2.6 Lotka-Volterra Equations

Lotka-Volterra equations, also called predator-prey equations, are a pair of first-order, nonlinear differential equations used to describe the dynamics of biological systems of species (with one being the prey, and the other predator). They are written as

$$\begin{aligned} \dot{x} &= x(a - by) \\ \dot{y} &= -y(c - dx), \end{aligned} \tag{2.14}$$

where x and y are the number of prey and predators, respectively, so that $\dot{x}$ and $\dot{y}$ represent their respective changes over time. The parameters $a, b, c, d > 0$ represent the dynamics of and between the two populations.

Example 2.6.1. Suppose we have a population of sheep and wolves, whose rates of change are given, respectively, as

$$\begin{aligned} \dot{s} &= 3s(t) - 2s(t)w(t), \\ \dot{w} &= -w(t) + 1.1s(t)w(t). \end{aligned} \tag{2.15}$$

Here, the sheep population, $s(t)$, has a rate of increase, per sheep, equal to three times their population, and are killed off at a rate, per wolf, of twice their poulation due to the predation of the wolves. The wolf population, $w(t)$, on the other hand, suffers from the loss of one wolf per unit time, but has a rate of increase equal to 1.1 times their

population, per sheep.

We find that the equilibria of the system are given by

$$\begin{aligned} E_1: &\qquad s^* = 0, \quad w^* = 0, \qquad \text{or} \\ E_2: &\qquad s^* = \tfrac{10}{11}, \quad w^* = \tfrac{3}{2}. \end{aligned} \tag{2.16}$$

Using the linearization method described earlier, we have that

$$A = \begin{pmatrix} 3 - 2w & -2s \\ 1.1w & -1 + 1.1s \end{pmatrix}. \tag{2.17}$$

Evaluating this matrix at E_1, we have

$$A|_{\substack{s^* = 0, \\ w^* = 0}} = \begin{pmatrix} 3 - 2(0) & -2(0) \\ 1.1(0) & -1 + 1.1(0) \end{pmatrix} = \begin{pmatrix} 3 & 0 \\ 0 & -1 \end{pmatrix}. \tag{2.18}$$

Thus, $\Delta = 3(-1) - 0 = -3 < 0$, so that the fixed point $(0, 0)$ is a saddle point. Evaluating the matrix at E_2, we have

$$A|_{\substack{s^* = {}^{10}/_{11}, \\ w^* = {}^{3}/_{2}}} = \begin{pmatrix} 3 - 2\left(\frac{3}{2}\right) & -2\left(\frac{10}{11}\right) \\ 1.1\left(\frac{3}{2}\right) & -1 + 1.1\left(\frac{10}{11}\right) \end{pmatrix} = \begin{pmatrix} 0 & -1.81 \\ 1.65 & 0 \end{pmatrix}. \tag{2.19}$$

We have that

1. $\tau = 0$, so the fixed point is neutrally stable.
2. $\Delta = 0 - 1.65(-1.81) = 0.29865 > 0$, so the fixed point is either a node, spiral, or center. To determine this, we need
3. $\tau^2 - 4\Delta = 0 - 4(0.29865) = -11.946 < 0$, so the fixed point is either a spiral or center (because the eigenvalues are complex). Since the fixed point is neutrally stable, then $\left(\frac{10}{11}, \frac{3}{2}\right)$ is a center surrounded by a family of closed orbits.

Here, we include the phase portrait for this system. The trajectory for $(s(0), w(0)) = (6, 3)$ is given in black, while the trajectories for any given set of initial conditions flow along the green vectors in the vector field.

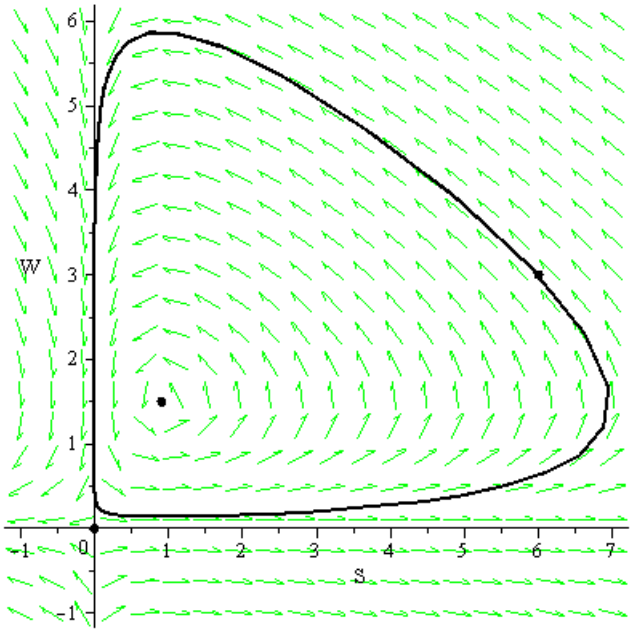

Figure 2.7: The dance of sheep and wolves

We can see that near $(0, 0)$, the vector field nearby points towards it along the w-axis, and away from it along the s-axis. Hence, the equilibrium at the origin is unstable in the s-direction, and stable in the w-direction. The other fixed point, $\left(\frac{10}{11}, \frac{3}{2}\right)$, sits inside of the closed orbits, and is clearly seen to be a center. On the other hand, if there are no wolves, the sheep population increases (exponentially, since $\dot{s} = 3 \cdot s(t)$, and $s(t) = s(0) \cdot e^{3t} = 6e^{3t}$). Thus, if there are no sheep, the wolves will die out. ■

Chapter 3

The Evolution of Virulence

As mentioned in the first chapter, parasites are usually detrimental to the host. To study the dynamics between parasites and their hosts, we begin our analysis with a single parasite strain and an uninfected host cell population. We will, at first, assume that a host cell infected by a parasite cannot be infected by another parasite (in other words, there is no "superinfection"). For the next three chapters, we adapt the material from Martin Nowak's *Evolutionary Dynamics: Exploring the Equations of Life*. [Now06]

3.1 One Parasite

To begin our study, we consider first the case with one parasite strain, which motivates

Definition 3.1.1. The **basic model of infection by a single parasite** is defined by the following system of ordinary differential equations in the variables x and y, where x is the number of uninfected hosts and y is the number of infected hosts:

$$\begin{aligned} \dot{x} &= k - ux - \beta xy, \\ \dot{y} &= y(\beta x - u - v). \end{aligned} \tag{3.1}$$

Here, k is the constant rate of immigration of uninfected hosts; u is the natural death rate per host, so that ux is the rate of uninfected hosts dying naturally per unit time. β is the rate of infection of the parasite, and xy is the number of encounters between infected and uninfected hosts. Thus, since encounters between uninfected and infected hosts are proportional to *both* their numbers, βxy is the rate of uninfected hosts

becoming infected. Thus, the rate of change of uninfected hosts is the number of new ones coming in minus the ones who die naturally minus the ones who are getting infected. Hence, the first equation in (3.1).

βxy is the rate in which uninfected hosts are becoming infected per unit time, and v is the disease-induced rate of death for infected hosts (this is also called its **virulence**), so that uy is the rate of infected hosts dying naturally per unit time, and vy is the rate of infected hosts dying due to the parasite per unit time. Thus, the rate of change of infected hosts is the number of uninfected hosts who are getting infected minus the already-infected hosts who die naturally minus the already-infected hosts that are dying due to the parasite. Hence, the second equation in (3.1).

Theorem 3.1.2. *The two equilibria of (3.1) are*

1. *in the absence of infected hosts:*

$$E_1 : \quad x^* = \frac{k}{u} \quad , \quad y^* = 0 \tag{3.2}$$

2. *in the presence of infected hosts:*

$$E_2 : \quad x* = \frac{u+v}{\beta} \quad , \quad y^* = \frac{\beta k - u(u+v)}{\beta(u+v)} \tag{3.3}$$

Proof. The fixed points of (3.1) are defined by $\dot{x} = \dot{y} = 0$. So, $\dot{y} = y(\beta x - u - v) = 0$ implies that either $y = 0$ or $\beta x - u - v = 0$.

1. If $y = 0$, then the first equation, with $\dot{x} = 0$, yields

$$\begin{aligned} 0 &= k - ux \\ x &= \frac{k}{u} \end{aligned}$$

Since $y = 0$, then there is an absence of infected hosts. Thus, the equilibrium is given by $(x^*, y^*) = \left(\frac{k}{u}, 0\right)$.

2. If $\beta x - u - v = 0$, then $x = \dfrac{u+v}{\beta}$. Since $\dot{x} = 0$, then this says

$$\begin{aligned} 0 &= k - u\left(\frac{u+v}{\beta}\right) - \beta\left(\frac{u+v}{\beta}\right)\cdot y \\ (u+v)\cdot y &= k - u\left(\frac{u+v}{\beta}\right) \\ y &= \frac{k}{u+v} - \frac{u(u+v)}{\beta(u+v)} \\ &= \frac{\beta k}{\beta(u+v)} - \frac{u(u+v)}{\beta(u+v)} \\ &= \frac{\beta k - u(u+v)}{\beta(u+v)} \end{aligned}$$

Thus, the equilibrium, in the presence of infected hosts, is given by $(x^*, y^*) = \left(\frac{u+v}{\beta}, \frac{\beta k - u(u+v)}{\beta(u+v)}\right)$. □

Definition 3.1.3. The **basic reproductive ratio** R_0 **of a parasite** is the expected number of infections that a single infected host can cause to uninfected hosts in its lifetime.

If there are x uninfected hosts to begin with, then the first infected host will generate βx new infected hosts per unit time. At equilibrium, $x = \frac{k}{u}$, and the one infected host will infect $\beta \cdot \frac{k}{u}$ more infected hosts per unit time. Since $u + v$ is the death rate of an infected host, $\frac{1}{u+v}$ is its average lifespan. Thus, we have that the number of secondary infections caused by a single infected host is, over its lifetime,

$$R_0 = \frac{\beta}{u+v} \cdot \frac{k}{u}, \tag{3.4}$$

With this in hand, we can talk about the two types of chain reactions that follow infections: either there is an **epidemic** (i.e., an explosive increase in the number of infected hosts), or there is not. Also, if $R_0 > 1$, then $\beta k > u(u+v)$ so that $y^* = \dfrac{\beta k - u(u+v)}{\beta(u+v)} > 0$. So the second equilibrium is physiologically realizable when $R_0 > 1$.

Theorem 3.1.4. *If $R_0 < 1$, then an epidemic cannot occur. If $R_0 > 1$, then an epidemic will occur. In terms of chain reactions, $R_0 < 1$ gives a subcritical process, while $R_0 > 1$ gives a supercritical process.*

Proof. We have that

$$R_0 = \frac{\beta}{u+v} \cdot \frac{k}{u}.$$

If $R_0 > 1$, then

$$\frac{\beta}{u+v} \cdot \frac{k}{u} > 1$$

so that

$$\frac{\beta k}{u} - (u+v) > 0.$$

Because the difference in $\frac{\beta k}{u}$—the rate of uninfected hosts becoming infected—and $(u+v)$—the total rate in which the uninfected and infected hosts are dying—is positive, the number of infected hosts being created exceeds the number of them dying. Thus, an epidemic will occur.

Similarly, if $R_0 < 1$, then

$$\frac{\beta k}{u} - (u+v) \quad < \quad 0$$

Because the difference in $\frac{\beta k}{u}$ and $(u+v)$ is negative, then the number of infected hosts being created is less than the number of them dying. Thus, an epidemic cannot occur. □

Theorem 3.1.5. *If $R_0 > 1$, in the presence of an infected host, the infection will (for large enough x, though not necessarily at first) increase to a maximum and then settle in a damped oscillation to a stable equilibrium given by* (3.3)*. If $R_0 < 1$, there are damped oscillations to the $y = 0$ equilibirium given by* (3.2)*, and the infection dies out.*

Proof. To check the stability of the equilibria given in (3.3) and (3.2), respectively, we linearize the system of differential equations given by (3.1), as per the method outlined in Section 2.4, resulting in

$$A = \begin{pmatrix} \frac{\partial \dot{x}}{\partial x} & \frac{\partial \dot{x}}{\partial y} \\ \frac{\partial \dot{y}}{\partial x} & \frac{\partial \dot{y}}{\partial y} \end{pmatrix} = \begin{pmatrix} -u - \beta y & -\beta x \\ \beta y & \beta x - u - v \end{pmatrix}.$$

We evaluate this matrix at each of the two equilibria given by Theorem 3.1.2.

1. If $R_0 > 1$, then

$$\begin{aligned} A|_{\substack{x^* = \frac{u+v}{\beta}, \\ y^* = \frac{\beta k - u(u+v)}{\beta(u+v)}}} &= \begin{pmatrix} -u - \beta\left(\dfrac{\beta k - u(u+v)}{\beta(u+v)}\right) & -\beta\left(\dfrac{u+v}{\beta}\right) \\ \beta\left(\dfrac{\beta k - u(u+v)}{\beta(u+v)}\right) & \beta\left(\dfrac{u+v}{\beta}\right) - u - v \end{pmatrix} \\ &= \begin{pmatrix} -u - \dfrac{\beta k - u(u+v)}{u+v} & -(u+v) \\ \dfrac{\beta k - u(u+v)}{u+v} & 0 \end{pmatrix} \\ &= \begin{pmatrix} -uR_0 & -(u+v) \\ u(R_0 - 1) & 0 \end{pmatrix}. \end{aligned}$$

Because

a. $\tau = \operatorname{trace}(A) = -uR_0 < 0$,

b. $\Delta = \det(A) = u(u+v)(R_0 - 1) > 0$

the fixed point is stable. To know what kind, we have that

c.

$$\begin{aligned} \tau^2 - 4\Delta &= (-uR_0)^2 - 4u(u+v)(R_0 - 1) \\ &= u^2 {R_0}^2 - 4u(u+v)(R_0 - 1) \\ &= u^2\left(R_0 - \frac{2(u+v)}{u}\right)^2 - 4v(u+v) \end{aligned}$$

This expression, as a function of R_0, is a parabola with roots

$$R_- = \frac{2}{u}\left(u + v - \sqrt{v(u+v)}\right), \qquad R_+ = \frac{2}{u}\left(u + v + \sqrt{v(u+v)}\right)$$

both of which are positive. The vertex of this parabola is at the point

$$\left(\frac{2(u+v)}{u}, -4v(u+v)\right),$$

whose height is negative, and is below the R_0-axis. We make a few notes about $R_\pm$:

1. If we suppose that $R_- < 1$, then

$$\begin{aligned} \frac{2}{u}\left(u + v - \sqrt{v(u+v)}\right) &< 1 \\ 2\left(u + v - \sqrt{v(u+v)}\right) &< u \\ u^2 &< 0, \end{aligned}$$

which is impossible. Thus, $1 < R_-$.

2. We have that

$$\begin{aligned} R_- &= \frac{2}{u}\left(u+v-\sqrt{v(u+v)}\right) \\ &= \frac{2\sqrt{u+v}}{u}\left(\sqrt{u+v}-\sqrt{v}\right) \\ &= \frac{2\sqrt{u+v}}{u}\left(\frac{(u+v)-v}{\sqrt{u+v}+\sqrt{v}}\right) \\ &= \frac{2\sqrt{u+v}}{\sqrt{u+v}+\sqrt{v}} \\ &< \frac{2\sqrt{u+v}}{\sqrt{u+v}} \\ &= 2. \end{aligned}$$

Thus, $R_- < 2$.

3. Similarly,

$$\begin{aligned} R_+ &= \frac{2}{u}\left(u+v+\sqrt{v(u+v)}\right) \\ &= \frac{2\sqrt{u+v}}{\sqrt{u+v}-\sqrt{v}} \\ &\geq \frac{2\sqrt{u+v}}{\sqrt{u+v}} \\ &= 2. \end{aligned}$$

Thus, $2 \leq R_+$.

So we may conclude that $1 < R_- < 2 \leq R_+$.

The graph of this parabola is given in Figure 3.1.

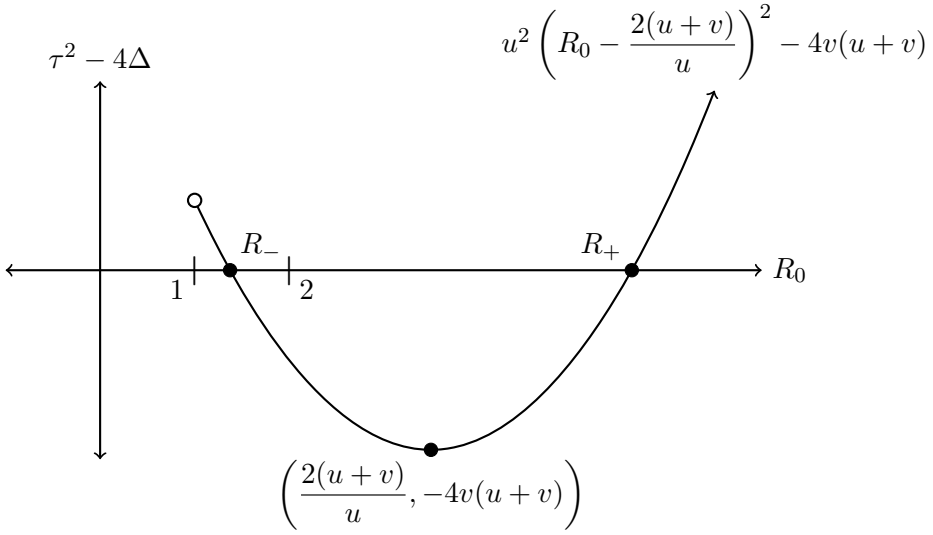

Figure 3.1: The graph of $\tau^2 - 4\Delta$ as a function of $R_0 > 1$

i. If $R_0 \in (1, R_-) \cup (R_+, \infty)$, then $\tau^2 - 4\Delta > 0$—the fixed point is a stable node.

ii. If $R_0 \in (R_-, R_+)$, then $\tau^2 - 4\Delta < 0$—the fixed point is the center of a stably decaying spiral.

iii. If $R_0 = R_\pm$, then $\tau^2 - 4\Delta = 0$, resulting in degenerate nodes, with trajectories that have failed to become (stable) spirals.

2. If $R_0 < 1$, then

$$A|_{\substack{x^*=\frac{k}{u},\\ y^*=0}} = \begin{pmatrix} -u & \frac{-\beta k}{u} \\ 0 & \frac{-\beta k}{u}\left(\frac{1}{R_0} - 1\right) \end{pmatrix}.$$

We have then that

a.
$$\tau = -u - \frac{\beta k}{u}\left(\frac{1}{R_0} - 1\right).$$
Since $R_0 < 1$, then $\beta k - u(u+v) < 0$, so that $\tau < 0$. This implies that the equilibrium is characterized by decay to equilibrium.

b. $\Delta = -\beta k\left(1 - \frac{1}{R_0}\right)$. Since $R_0 < 1$, $1 - \frac{1}{R_0} < 0$. So $\Delta > 0$.

c. Since $\Delta > 0$, then

$$\begin{aligned}\tau^2 - 4\Delta &= \left[-u + \frac{\beta k}{u}\left(1 - \frac{1}{R_0}\right)\right]^2 - 4\left[-\beta k\left(1 - \frac{1}{R_0}\right)\right] \\ &= \left[u + \frac{\beta k}{u}\left(1 - \frac{1}{R_0}\right)\right]^2 \\ &> 0.\end{aligned}$$

Since $\tau^2 - 4\Delta > 0$, the fixed point is a node. Since $\tau < 0$, it is stable. Therefore, the uninfected population settles into $x = \frac{k}{u}$, while the infected approach $y = 0$, thus dying out. □

3.2 Two Parasites

Now we start the study of how virulence evolves in the presence of multiple parasites. We will first assume that a host can be infected by one or another of two different strains of parasite, but not both. Under this assumption, Definition 3.1.1 is replaced by

Definition 3.2.1. The **basic model of infection for two parasites** is defined by the following system of ordinary differential equations, where the number of uninfected hosts is given by x, and the number of hosts infected by parasite strains 1 and 2 is given by y_1 and y_2, respectively:

$$\begin{aligned}\dot{x} &= k - ux - x(\beta_1 y_1 + \beta_2 y_2), \\ \dot{y_1} &= y_1(\beta_1 x - u - v_1), \\ \dot{y_2} &= y_2(\beta_2 x - u - v_2),\end{aligned} \tag{3.5}$$

Here, k is again the constant rate of immigration of uninfected hosts; u is the natural death rate of all hosts, so that ux is the number of uninfected hosts dying naturally per unit time. β_1 and β_2 are the rates of infection of strains 1 and 2, respectively, so that $\beta_1 x y_1$ and $\beta_2 x y_2$ are the number of uninfected hosts becoming infected by strains 1 and 2, respectively, per unit time. Thus, the rate of change of uninfected hosts is the number of new ones coming in minus the ones who die naturally minus the ones who are getting infected. Thus, we have the first equation in (3.5).

Similarly, $\beta_1 x y_1$ is the number of uninfected hosts who are becoming infected

by strain 1 per unit time; v_1 is the disease-induced rate of death for infected hosts, so that uy_1 is the number of infected hosts of strain 1 dying naturally per unit time, and v_1y_1 is the number of infected hosts of strain 1 dying due to the parasite. Thus, the rate of change of infected hosts of strain 1 is the number of uninfected hosts who are getting infected by strain 1 minus the already-infected hosts who die naturally minus the already-infected hosts that are dying due to the parasite. Thus, we have the second equation in (3.5).

And by identical reasoning for strain 2, we have the third equation. We will also extend Definition 3.1.3 and equation (3.4) into the following:

Definition 3.2.2. The **basic reproductive ratios of parasite strains 1 and 2**, respectively, are given by

$$R_1 = \frac{\beta_1}{u+v_1} \cdot \frac{k}{u} \qquad \text{and} \qquad R_2 = \frac{\beta_2}{u+v_2} \cdot \frac{k}{u}. \tag{3.6}$$

Theorem 3.2.3. *The equilibria in the presence of a double infection are characterized as follows:*

1. *If $R_1 < 1$ and $R_2 < 1$, then the only stable equilibrium is given by*

$$E_1 : \qquad x^* = \frac{k}{u} \qquad y_1^* = 0 \qquad y_2^* = 0 \tag{3.7}$$

2. *If $R_1 > 1 > R_2$, then strain 2 becomes extinct and the only stable equilibrium is*

$$E_2 : \qquad x^* = \frac{u+v_1}{\beta_1} \qquad y_1^* = \frac{\beta_1 - u(u+v_1)}{\beta_1(u+v_1)} \qquad y_2^* = 0 \tag{3.8}$$

3. *If $R_1 < 1 < R_2$, then strain 1 becomes extinct and the only stable equilibrium is*

$$E_3 : \qquad x^* = \frac{u+v_2}{\beta_2} \qquad y_1^* = 0 \qquad y_2^* = \frac{\beta_2 - u(u+v_2)}{\beta_2(u+v_2)} \tag{3.9}$$

4. *If both $R_1 > 1$ and $R_2 > 1$, then the strain with the higher basic reproductive ratio will dominate, leading to cases* (3.8) *or* (3.9).

One can show this using similar methods to the proof of Theorem 3.1.5. The implication of this theorem is that evolution, when nothing else particularly matters, will maximize the basic reproductive ratios of the parasite strains. In order for this maximizing to go on, R_0 must increase, which would mean that, observing Definition 3.2.2, the infectivity β sees an increase, or the virulence v sees a decrease, or both.

3.3 Superinfection

We now remove the limitation previously set, that an infected host cannot be infected by another parasite.

Definition 3.3.1. Superinfection takes place when an already-infected host is infected by a new parasite strain.

To have a better understanding of superinfection, we now consider a (heterogeneous) population of parasite strains, equipped with varying virulences, along with the assumption that more virulent parasite strains will outcompete/outlast less virulent ones.

Definition 3.3.2. The **basic model of infection for multiple parasites** is defined, analogous to our previous work, by the following system of ordinary differential equations:

$$\begin{aligned} \dot{x} &= k - ux - x\sum_{i=1}^{n} \beta_i y_i \\ \dot{y}_i &= y_i \left(\beta_i x - u - v_i + s\beta_i \sum_{j=1}^{i-1} y_j - s \sum_{j=i+1}^{n} \beta_j y_j \right), \quad i = 1, \ldots, n, \end{aligned} \tag{3.10}$$

where v_i is the virulence of parasite strain i, and each strain is ordered from least to greatest virulence—namely, without loss of generality, that $v_1 < v_2 < \ldots < v_n$; and s, the **superinfection parameter**, is the rate at which superinfection occurs relative to infection of already infected hosts.

It is empirically reasonable to assume that infectivity grows linearly with virulence when the latter is small, but the infectivity saturates at some maximum as virulence increases. One way to model this is by the formula

$$\beta_i = \frac{av_i}{c + v_i}, \tag{3.11}$$

where β_i and v_i are the virulence and parasite-induced mortality rate of strain i, respectively, and some $a, c > 0$.

Definition 3.3.3. The **basic reproductive ratio of parasite strain** i is given by

$$R_{0,i} = \frac{akv_i}{u(c + v_i)(u + v_i)}. \tag{3.12}$$

for some $a, c > 0$.

Theorem 3.3.4. *Assuming constant a, c, k, and u, the optimal virulence is given by*

$$v_{opt} = \sqrt{cu}. \tag{3.13}$$

Proof. Differentiating (3.12), we have

$$\begin{aligned}(R_{0,i})' &= \frac{d}{dv_i}R_{0,i} = \frac{aku(cu + cv_i + uv_i + v_i^2) - akuv_i(c + u + 2v_i)}{u^2(c + v_i)^2(u + v_i)^2} \\ &= \frac{ak(cu + cv_i + uv_i + v_i^2 - cv_i - uv_i - 2v_i)}{u(c + v_i)^2(u + v_i)^2} \\ &= \frac{ak(cu - v_i^2)}{u(c + v_i)^2(u + v_i)^2}.\end{aligned}$$

Setting $(R_{0,i})' = 0$, we have, after some algebra, that $v_i = \pm\sqrt{cu}$. Since the virulence v_i cannot be negative, we have that $v_i = \sqrt{cu}$.

Differentiating with respect to v_i again, we have

$$\begin{aligned}(R_{0,i})'' &= \frac{-2akv_i[u(c + v_i)^2(u + v_i)^2] - ak(cu - v_i^2)[2u(c + v_i)(u + v_i)(c + u + v_i)]}{u^2(c + v_i)^4(u + v_i)^4} \\ &= \frac{-2ak[(c + v_i)(u + v_i) + (cu - v_i^2)(c + u + 2v_i)]}{u(c + v_i)^3(u + v_i)^3}\end{aligned}$$

so that

$$(R_{0,i})''\big|_{v_i=\sqrt{cu}} = \frac{-2ak(c + \sqrt{cu})(u + \sqrt{cu})}{u(c + \sqrt{cu})^3(u + \sqrt{cu})^3} < 0.$$

Since $(R_{0,i})'|_{v_i=\sqrt{cu}} = 0$ and $(R_{0,i})''|_{v_i=\sqrt{cu}} < 0$, then, by the Second Derivative Test, $v_i = \sqrt{cu}$ is a maximum. □

Chapter 4

An Analytical Model of Superinfection

We will assume now that the total number of hosts stays constant. This requires that the rate of replenishment of uninfected hosts, k, take the following form:

Definition 4.0.5. The **immigration rate of uninfected hosts** is given by

$$k = ux + uy + \sum_{i=1}^{n} v_i y_i. \tag{4.1}$$

Note that this rate of immigration is not necessarily constant. Instead, the number of uninfected hosts repopulating the system is equal to the sum of the uninfected and infected hosts that have died naturally (ux and uy, respectively), and the infected hosts that have died due to their respective parasite's virulence, or $v_i y_i$.

If we let the total number of infected hosts be $y = \sum_{i=1}^{n} y_i$, then $x + y =$ a constant, so, by a scaling, we can choose $x + y = 1$. With these changes, equation (3.10) becomes

$$\dot{y}_i = y_i \left[\beta_i(1-y) - u - v_i + s \left(\beta_i \sum_{j=1}^{i-1} y_j - \sum_{j=i+1}^{n} \beta_j y_j \right) \right], \quad i = 1, 2, \ldots, n \tag{4.2}$$

where now each y_i lies in $[0, 1]$.

Equation (4.2) is a Lotka-Volterra equation, and can be rewritten as

$$\dot{y}_i = y_i \left(R_i + \sum_{j=1}^{n} A_{ij} y_j \right), \quad i = 1, 2, \ldots, n \tag{4.3}$$

where $R_i = \beta_i - v_i - u$, and

$$A = - \begin{pmatrix} \beta_1 & \beta_1 + s\beta_2 & \beta_1 + s\beta_3 & \ldots & \beta_1 + s\beta_n \\ \beta_2(1-s) & \beta_2 & \beta_2 + s\beta_3 & \ldots & \beta_2 + s\beta_n \\ \beta_3(1-s) & \beta_3(1-s) & \beta_3 & \ldots & \beta_3 + s\beta_n \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \beta_n(1-s) & \beta_n(1-s) & \beta_n(1-s) & \ldots & \beta_n \end{pmatrix}. \tag{4.4}$$

As a special case, suppose all infectivity rates are the same, so that $\beta_i = \beta$ (this happens when $c = 0$ in (3.11)). Then (4.2) becomes

$$\dot{y}_i = y_i \beta \left[1 - y - \frac{v_i + u}{\beta} + s \left(\sum_{j=1}^{i-1} y_j - \sum_{j=i+1}^{n} y_j \right) \right], \quad i = 1, 2, \ldots, n, \tag{4.5}$$

and the matrix (4.4) becomes

$$A = -\beta \begin{pmatrix} 1 & 1+s & 1+s & \ldots & 1+s \\ 1-s & 1 & 1+s & \ldots & 1+s \\ 1-s & 1-s & 1 & \ldots & 1+s \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1-s & 1-s & 1-s & \ldots & 1 \end{pmatrix} \tag{4.6}$$

Josef Hofbauer and Karl Sigmund have shown that, for this equation, there exists a globally stable equilibrium, and it is the only one, attracting all orbits. [HS03]

This equilibrium can be found as follows: set

$$f_i = 1 - \frac{v_i + u}{\beta} - (1-s)y - 2s \sum_{j=i+1}^{n} y_j. \tag{4.7}$$

Then

$$\begin{aligned} f_i - sy_i &= 1 - \frac{v_i + u}{\beta} - y + sy - sy_i - 2s \sum_{j=i+1}^{n} y_j \\ &= 1 - \frac{v_i + u}{\beta} - y + s \sum_{j=1}^{i-1} y_j + s \sum_{j=i+1}^{n} y_j - 2s \sum_{j=i+1}^{n} y_j \\ &= 1 - \frac{v_i + u}{\beta} - y + s \left(\sum_{j=1}^{i-1} y_j - \sum_{j=i+1}^{n} y_j \right). \end{aligned}$$

Thus, we can rewrite (4.5) as

$$\dot{y}_i = y_i \beta (f_i - sy_i). \tag{4.8}$$

The equilibria of (4.5) and (4.8) can now be seen to require that

$$\begin{aligned} &\text{either} \quad y_1 = 0 \quad \text{or} \quad y_1 = f_1/s, \quad \text{and} \\ &\text{either} \quad y_2 = 0 \quad \text{or} \quad y_2 = f_2/s, \quad \text{and} \\ &\qquad\qquad \vdots \\ &\text{either} \quad y_n = 0 \quad \text{or} \quad y_n = f_n/s, \end{aligned} \tag{4.9}$$

where each f_i depends only on the total sum y and all the y_j with virulence greater than v_i. Suppose we know y. Then $f_n = 1 - \dfrac{v + u}{\beta} - (1 - s)y + 0$, so we know f_n. Thus, we can set $y_n = \max\{0, f_n/s\}$ as one coordinate of an equilibrium point with (possibly) nonzero infection of the n^{th} kind. Now we know y_n, so we know f_{n-1}, and we can set $y_{n-1} = \max\{0, f_{n-1}/s\}$ to get an equilibrium point with (possibly) nonzero infection of the n^{th} and $n-1^{\text{th}}$ kinds. Continuing in this way recursively, we see that one equilibrium point can be defined as

$$\begin{aligned} y_n &= \max\{0, f_n/s\} \\ y_{n-1} &= \max\{0, f_{n-1}/s\} \\ y_{n-2} &= \max\{0, f_{n-2}/s\} \\ &\vdots \\ y_1 &= \max\{0, f_1/s\}. \end{aligned} \tag{4.10}$$

As Hofbauer and Sigmund have shown [HS03], this is the only equilibrium. If $f_i < 0$, (4.8) says that $\dot{y}_i < 0$, so $y_i \to 0$. If $f_i > 0$, (4.8) says that

$$\left. \frac{\partial \dot{y}_i}{\partial y_i} \right|_{y_i = f_i/s} = \beta f_i - 2\beta s y_i |_{y_i = f_i/s} = \beta f_i - \frac{2\beta s f_i}{s} = \beta f_i - 2\beta f_i = -\beta f_i < 0,$$

so that $\dfrac{f_i}{s}$ is stable for y_i and $y_i \to f_i/s$.

4.1 The Case When $s = 1$

Here, $f_i = 1 - \dfrac{v_i + u}{\beta} - 2\sum_{j=i+1}^{n} y_j$. So (3.10) says that, when $s = 1$, the only stable equilibrium is given recursively by

$$\begin{aligned} y_n &= \max\{0, 1 - \frac{v_n + u}{\beta}\} \\ y_{n-1} &= \max\{0, 1 - \frac{v_{n-1} + u}{\beta} - 2y_n\} \\ y_{n-2} &= \max\{0, 1 - \frac{v_{n-2} + u}{\beta} - 2(y_n + y_{n-1})\} \\ &\vdots \\ y_1 &= \max\{0, 1 - \frac{v_1 + u}{\beta} - 2(y_n + y_{n-1} + \ldots + y_2)\} \end{aligned} \tag{4.11}$$

For each strain y_i with equilibrium $y_i^* = 0$, we have $\partial \dot{y}_i / \partial y_i < 0$ regardless of parameters.

4.2 The Case When $s > 0$

Now we include only those strains that are present at equilibrium, i.e., $y_i > 0$ for $1 \le i \le n$. In equation (4.5), replace $\displaystyle\sum_{j=1}^{i-1} y_j$ by $y - y_i - \sum_{j=i+1}^{n} y_j$, to get

$$\begin{aligned} \dot{y}_i &= y_i\beta\left[1 - y - \frac{v_i + u}{\beta} + s\left(y - y_i - \sum_{j=i+1}^{n} y_j - \sum_{j=i+1}^{n} y_j\right)\right] \\ &= y_i\beta\left(1 - y - \frac{v_i + u}{\beta} + sy - sy_i - 2s\sum_{i+1}^{n} y_j\right) \\ &= y_i\beta\left(1 - \frac{v_i + u}{\beta} - (1 - s)y - sy_i - 2s\sum_{i+1}^{n} y_j\right). \end{aligned}$$

At equilibrium, $\dot{y}_i = 0$, and $y_i > 0$ for all $1 \le i \le n$, so

$$0 = 1 - \frac{v_i + u}{\beta} - (1 - s)y - sy_i - \sum_{j=i+1}^{n} y_j.$$

Solving for y_i, we get

$$y_i = B_i - 2\sum_{j=i+1}^{n} y_j, \tag{4.12}$$

where $B_i = [1 - \frac{v_i+u}{\beta} - (1-s)y]/s$. From this, we obtain

$$\begin{aligned} y_n &= B_n \\ y_{n-1} &= -2B_n + B_{n-1} \\ y_{n-2} &= 2B_n - 2B_{n-1} + B_{n-2} \end{aligned} \tag{4.13}$$

For even n, we obtain

$$\begin{aligned} y &= B_1 - B_2 + B_3 + \ldots + B_n \\ &= \frac{(v_n - v_{n-1} + \ldots - v_1)}{\beta s}. \end{aligned} \tag{4.14}$$

For odd n, we obtain

$$\begin{aligned} y &= B_1 - B_2 + B_3 - \ldots + B_n \\ &= \frac{(\beta - u - v_n + v_{n-1} - \ldots - v_1)}{\beta}. \end{aligned} \tag{4.15}$$

To calculate $v_{\max}$, the maximum level of virulence present in an equilbrium distribution for a given s, we assume equal spacing (on average)—that is, $v_k = kv_1$—which leads to $y = \frac{v_n}{2\beta s}$ for n even and to $y = 1 - \frac{u}{\beta} - \frac{v_n}{2\beta}$ for n odd.

1. for n even, we have

$$\begin{aligned} y &= \frac{1}{\beta s}(v_n - v_{n-1} + \ldots - v_1) \\ &= \frac{1}{\beta s}\left(\sum_{k=1}^{n}(-1)^k \frac{kv_n}{n}\right) \\ &= \frac{1}{\beta s} \cdot \frac{v_n}{2} \quad = \quad \frac{v_n}{2\beta s}, \end{aligned}$$

2. and for n odd, we have approximated $n-1$ by n, so we have similarly that

$$\begin{aligned} y &= 1 - \frac{u}{\beta} - \frac{1}{\beta}(v_n - v_{n-1} + \ldots + v_1) \\ &\approx 1 - \frac{u}{\beta} - \frac{1}{\beta}\left(\sum_{k=1}^{n}(-1)^k \frac{kv_n}{n}\right) \\ &= 1 - \frac{u}{\beta} - \frac{v_n}{2\beta}. \end{aligned}$$

From $y_n \geq 0$, we get, in both cases, that

$$v_{\max} = \frac{2s(\beta - u)}{1+s}. \tag{4.16}$$

This is the maximum level of virulence that can be maintained in an equilibrium distribution. For $s = 0$, this is simply $v_{\max} = 0$, that is, the strain with the lowest virulence, which for our choice of parameters is also the strain with the highest basic reproductive ratio. For $s > 1$, strains can be maintained with virulences above $\beta - u$. These are strains that are by themselves unable to invade an uninfected host population, because their basic reproductive ratio is smaller than one.

We resolve the differences between odd and even n by exchanging $v_{\max}$ for v_n into the two (different) expressions for y, and we get (with a tiny bit of algebra) in both cases

$$y = \frac{\beta - u}{\beta(1 + s)}. \tag{4.17}$$

This is the equilibrium frequency of infected hosts. The more superinfection, the fewer infected hosts (because as $s \to \infty$, then $y \to 0$).

Chapter 5

Further Study

Recall that

$$\dot{y_i} = y_i \left[\beta_i(1-y) - u - v_i + s \left(\beta_i \sum_{j=1}^{i-1} y_j - \sum_{n}^{j=i+1} \beta_j y_j \right) \right], \tag{4.2}$$

where the infectivities of each strain y_i were assumed to be the same. A more realistic scenario is that each β_i differs. Then the solutions of (4.2) would not necessarily converge to stable equilibria, which potentially leads to more complicated dynamics.

When $n = 2$, there's the possibility for coexistence—a stable equilibrium—between the two strains, or a **bistable** situation—one in which the strains are nearly equal, but the victor is determined by the initial conditions of a solution, delicately balanced between the two (stable) equilibria for each strain.

Consider the case when $s > 1$, where strain 1 has an extremely high virulence such that it cannot normally sustain itself and so $R_1 < 1$, while strain 2 has a lower virulence but has a greater infectivity, so that $R_2 > 1$. Because $s > 1$, superinfection is more likely to occur, thus leading to situations where strain 1 benefits from strain 2's ability to infect hosts and infect them in turn. Thus, superinfection can allow multiple strains to survive—even ones with high virulence.

Since I can't do any better, it is easiest to quote the source:

> For three or more strains of parasite, we may observe oscillations with increasing amplitude and period, tending toward a heteroclinic cycle. Imagine three parasite strains, each of which by itself is capable of establishing equilibrium between uninfected and infected hosts (that is, all have $R_0 > 1$). The system in which these three strains occur simultaneously has three boundary

equilibria, where two strains always have frequency 0 and the population consists of uninfected hosts and hosts infected by the third strain only. There is also one unstable interior equilbrium with all three strains present. The system converges toward the boundary equilibria and cycles from the first one to the second to the third and back to the first. The period of such cycles gets larger and larger There will be long times where the infection is just dominated by one parasite strain (and hence only one level of virulence), and then suddenly another strain takes over. Such a dynamic can, for example, explain sudden upheavals of pathogens with dramatically altered levels of virulence. If we wait long enough, one of the parasite strains may become extinct by some fluctuation when its frequency is low. Then one of the two remaining strains will outcompete the other.

For small values of s all elements of matrix (4.4) will be negative. Such a Lotka-Volterra system is called "competitive," and all trajectories will converge to an $n-1$-dimensional subspace, which reduces the dynamical complexities. This implies that for $n = 2$ there are damped oscillations, and for $n = 3$ one can exclude chaos. [Now06]

Bibliography

[CS07] John Carter and Venetia Saunders. *Virology: Principles and Applications*. Wiley Publishing, Hoboken, New Jersey, 2007.

[HS03] Josef Hofbauer and Karl Sigmund. Evolutionary game dynamics. *Bulletin (New Series) of the Americal Mathematical Society*, 40(4):479–519, 2003.

[Now06] Martin A. Nowak. *Evolutionary Dynamics: Exploring the Equations of Life*. Belknap Press, Cambridge, Massachusetts, 2006.

[Smi62] K. M. Smith. *Viruses*. Cambridge University Press, Cambridge, England, 1962.

[Str94] Steven H. Strogatz. *Nonlinear Dynamics and Chaos*. Perseus Books, Reading, Massachusetts, 1994.