Cities in Ecology: Settlement Patterns and Diseases

by

D. Murillo

A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Approved June 2012 by the
Graduate Supervisory Committee:

J.M. Anderies, Co-chair
C. Cástillo-Chavez, Co-chair
C. Boone

ARIZONA STATE UNIVERSITY

August 2012

ABSTRACT

A sequence of models is developed to describe urban population growth in the context of the embedded physical, social and economic environments and an urban disease are developed. This set of models is focused on urban growth and the relationship between the desire to move and the utility derived from city life. This utility is measured in terms of the economic opportunities in the city, the level of human constructed amenity, and the level of amenity caused by the natural environment. The set of urban disease models is focused on examining prospects of eliminating a disease for which a vaccine does not exist. It is inspired by an outbreak of the vector-borne disease dengue fever in Peru, during 2000-2001.

DEDICATION

This work is dedicated to the memory of a loving Grandmother, Victoria Murillo, and a beloved cousin, Carlos Marquez. The hard work and sacrifices of our grandparents, parents, aunts, uncles, immediate and extended family can never be repaid but will always be remembered and cherished. The love of our families continues to, and will always, drive us.

ACKNOWLEDGEMENTS

I would like to thank God who has given me the strength, family and friends who have given me the support, and my advisors, mentors, and committee members who have given me the encouragement, advice, and insight necessary to succeed. I would like to give a special thanks to the many funding agencies that have made this journey possible and the many organizations that have made this journey fruitful including: NSF, the Sloan Foundation, IGERT, WAESO, MGE@MSA, LSAMP, and MTBI/SUMS. I thank all the staff that have made this possible, they are true enablers, dedicated people and friends. Lastly, I wanted to reiterate my thanks to Dr. Carlos Castillo-Chávez, who I met as an undergraduate. In the past 10 years he has provided countless hours inside and outside the office that have been instrumental to my growth as a scholar and a person. Thank you.

This material is based upon work supported by the National Science Foundation under Grant No. DGE 05040248, Integrative Graduate Education Research Training (IGERT) in Urban Ecology. Any opinions, findings and conclusions or recommendation expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation (NSF).

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1

Introduction

Men come together in cities in order to live, but they remain together in order to live the good life. -Aristotle

In this dissertation I outline a systematic approach to develop a sequence of models aimed at exploring the relationship between 1) amenity and migration and 2) vertical transmission and disease invasion. This approach builds on the well established applied mathematics framework (specifically the dynamical systems and stochastic processes approach to mathematical ecology and biology) and represents a novel approach to modeling urban growth mechanistically. It also offers several extensions on the current literature of dengue fever modeling.

The impetus of this dissertation is the observation of extraordinary regularity in the pattern of human settlements across temporal and spatial scales (Zipf's Law) in the face of an extremely heterogenous social-ecological landscape. Central to the arguments presented here is the notion of feedbacks between various aspects of the complex landscape and settlement patterns, especially in terms of the drivers and markers of the true state of the system. In this formulation, migration is the force of change for settlement patterns and it is modulated by a sense of the economic, environmental and social landscape. While it may be difficult for the individual to ascertain the "true" state of a city due to imperfect information (uncertainty, information lag, etc.) there are several important indirect indicators of the happiness one might expect living in a certain area.

Crime, poverty, diseases, among others, may be better indicators of the the healthiness and cleanliness of an area than arbitrary measures of land values and easements. While I will not expound on the well known ideas of Jane Jacobs [Jacobs, 1992] or the more recent notions of ecohealth, I will mention that diseases may serve as markers of environmental degradation. If an area has an unusu-

ally high prevalence of disease, it may indicate that there are some environmental determinants such as toxic release sites or naturally contaminated soil, water, etc. If the disease is an infectious one, it may also indicate that the environmental degradation may have roots in failed public infrastructure. This is especially true for disease like dengue fever where the distribution of breeding sites for the mosquito that transmits the disease is strongly influenced by the socio-political context; how private actions are influenced by the provision/absence of public services and infrastructure [Gubler, D., 2005]. Then those with the resources to identify and avoid these areas will do so. Thus, diseases are not necessarily a driver of migration (except for rare cases such as in areas endemic with HIV/AIDS) but may serve as an indicator of expected happiness that influences migration in the sense of Tiebot sorting.

This approach to studying urban growth is novel in the implementation of a mechanistic approach based on the methodology of compartmental models. The migration rate between cities is assumed to be a function of the population sizes and the social, environmental and economic environments of the cities. A precise model of each of these factors is beyond the scope of this dissertation and we restrict ourselves to a consideration of the *effect* of those factors on the migration rate. This work is motivated by a series of overarching questions (to be elaborated later): in a mechanistic model of urban migration, does the interplay between the natural environment, economic and social institutions alter the long term distribution of city populations? Do institutions that impact the amenity people derive from living in a particular city impact the long term sustainability of that city? Does diversity in individual preferences increase the robustness of urban populations? Does the ability to move between neighboring cities increase the stability of urban populations? What is the role of uncertainty (information lag and/or stochasticity) in the long-term distribution of city populations?

The urban environment provides unique opportunities for disease emergence and reemergence. Some facilitating factors include a high concentration of individuals, immigration that may bring in more susceptible or infectious individuals, and emigration that may export diseases to other urban areas. One particular disease that has thrived in the urban environment is dengue fever, a vector-borne disease. The primary vectors of dengue have also thrived in urban environments, displaying an increased resilience to adverse weather conditions and a generally aggressive and invasive predisposition. The models of dengue formulated here have been inspired by the 2000-2001 outbreak in Peru that saw the introduction of a novel strain to the area and one of the worse epidemics in Peruvian history. This work is also motivated by a set of overarching questions: is it possible to contain/eradicate a reemerging infectious urban disease without vaccination? What is the role of vertical transmission in the persistence and invasion potential of dengue fever? What is the role of diapause and egg reservoirs in the persistence of dengue? Is site reduction and/or insecticide spraying sufficient to control/prevent dengue outbreaks?

Every model is a simplification of reality, and thus incomplete. The goal of this dissertation is to establish a set of models that open up a new avenue for a discussion of sustainability and robustness of cities (via population growth and disease control). These models are a tool, a mechanism for the realization of certain hypothesis to be used in conjunction (either in series or parallel) with existing models and frameworks. Every model has advantages and disadvantages and it is hoped that by offering a different perspective, that can be used in conjunction with existing and future models, I can contribute to a more comprehensive and robust evaluation of sustainability [Page, 2011].

Chapter 2

Mathematical Modeling

One of the pleasures of looking at the world through mathematical eyes is that you can see certain patterns that would otherwise be hidden. - Steven Strogatz

To model, mathematically or otherwise, is to simplify reality. It is to articulate a perceived understanding of the core boundaries, agents, processes and interactions of a system based on observations. Thus every model is wrong, however some can be useful. Two such examples are Malthusian growth model and Newton's Second Law. The Malthusian model is perhaps one of the most fundamental relationships and will be discussed later. The other, more tangible, example of a useful model, Newton's Second law, is most commonly written as

$$F = ma,$$

where F is the sum of all the forces on an object, m is the mass of that object, and a is its acceleration. This model is useful because of two important features: 1) it is a robust description of how objects move at the correct scales, and 2) it opened up a whole new area of mathematical investigation. It is the confluence of the applied and the theoretical that has given this model the value it has to this day.

Modeling follows the scientific method in many ways. Observations are necessary to formulate assumptions, conjectures and hypothesis concerning the construction of the model. Analysis and simulation of the model provides predictions that can be tested against further data. Refinement and calibration, often called verification and validation in certain applications, is as critical in modeling as it is in the scientific method. This iteration continues until the model becomes useful on some level.

Much like science, modeling is an art with numerous combinations of media, bases, tools and techniques. The form chosen here leverages compartmental models and the dynamical systems approach because 1) I have some familiarity with that medium and 2) I feel it is similar, but distinctively different, than other approaches that have been taken in the study of settlement patterns. Every model has advantages and disadvantages and mine allows us to express the city as a unique yet mimetic construct.

Before I unveil the model, I will briefly review how others have expressed the city in models that are conceptually similar. There are generally two modeling extremes, the highly complex, large-scale urban simulation pioneered by Forrester [Forrester, 1969] such as Urbansim at UC Berkeley, LEAM at UI Urbana-Champaing, and Geosimulation at ASU, and the highly simplified, stylized models of the new urban economics [Dendrinos and Mullally, 1985]. In many ways this parallels the application of mathematical modeling in ecology and biology [Dendrinos and Mullally, 1981], and these models have had a tremendous impact on the field both in terms of the mathematics and the ecology/biology (for examples see[Brauer and Castillo-Chavez, 2001, Allen, L.J.S., 2003] and the references therein). I apply some of the methods employed in mathbiology while keeping in mind that social systems are generally more complicated than biological ones; the units of social systems are often biological systems which express some agency and thus some inclination to not follow the rules.

Predator-Prey Models

The Kolmogorov or Lotka-Volterra type predator-prey models have been extensively studied (with over 130,000 google scholar hits) and several authors have modeled the population density and per capita income level of a city using this framework [Dendrinos and Mullally, 1985, Samuelson, 1971]. The essential premise of these nonlinear urban population dynamic models is that there exists a com-

petitive environment that relates the city population to the per capita income of the form

$$\begin{aligned} \dot{N} &= N * f(N,K) \\ \dot{K} &= K * g(N,K) \end{aligned}$$

where N is the population size and K is the per capita income. Then $f(N,K)$ and $g(N,K)$ are generally linear functions. This framework is general enough to exhibit a wide range of dynamical behavior including nodes, foci, saddles, centers and limit cycles. These types of models can also be coupled to include several connected cities. Despite this generality, they have not had good agreement with data[Dendrinos and Mullally, 1985].

Scaling Laws

The economics literature has taken advantage of these types of mathematical formulations and have used them to, among many other things, describe the growth of cities (see [Córdoba, 2008] for a review of some recent success and limitations). One pattern that has proven to be ubiquitous among cities in different regions is Zipf's Law or the Rank Size Rule. The rule essentially states that there is a correlation between the population size of a city and its rank (determined by ordering all the cities in a region according to its population size). What is surprising is that this relationship is very robust and similar relationships hold for not just the rank, but also the creativity, wealth, crime and number of gas stations in cities [Bettencourt et al., 2007] (as well as applications in other fields such as linguistics [Zipf, 1972]).

Agglomeration and Central Place Theory

Geographers are also interested in the distribution of resources and firms within a city. One of the most significant concepts in this area is central place theory es-

tablished by Christaller in the 1930s and Losch in the 1950s (see [Mulligan, 1984, Richardson, H. W., 1973] and the references therein for a review). Christaller established the idea that the centrality of a city (or firm) had a direct relationship to its size or potential size. Additionally, cities (or firms) of different sizes had different functions in terms of the services they received or provided to the surrounding areas. Losch extended Christaller's ideas by adding several considerations including the welfare of the individual in addition to distance. Central place theory is a framework to understand economic agglomeration and is still in use today, particular when considering the location of firms and the theory tends to give rise to hierarchical spatial patterns

GIS and Multi-Agent Models

One critique of these models is that they tend to be too simplistic in their descriptions and restrictive in their assumptions. To address this critique, experimental economists tend to look at large data sets with many variables to describe the problem of interest, in much the same way urban geographers may study urban growth [Knox and McCarthy, 1994]. The rise of GIS has revolutionized these fields by allowing the incorporation of spatial data. Among other things, this has helped reveal the importance of place and uncover spatial correlations. However, these models have limitations as well since correlations do not imply causation and confounding factors can lead to misleading results.

Geographical information system (GIS), cellular automata (CA), and agent based models (ABM) have gained much popularity due to their ability to visualize and explicitly model space [Clapp et al., 1997, Batty, 2005, Shiode and Torrens, 2008, White and Engelen, 2000, Clarke and Gaydos, 1998]. However, they have also drawn criticism due to their complexity, high data requirements and computational intensity [Lee, 1973]. They have also been used to study organizations and institutions within a city [Prietula et al., 1998]. CA and ABM are also the basis

of complex adaptive systems and this has generated a lot of research in urban and other models. As a tool for visualization, they are great for communication and coupling with other modeling types.

Catastrophe

Catastrophe theory was introduced into urban geography by Amson in 1975 and popularized in a book by Wilson in 1981, [Amson, J.C., 1975, Wilson, 1981]. This branch of bifurcation theory and non-linear dynamics focuses on the change of state of a system as some parameters are varied. The focus is on urban form and the supply side problem of urbanization.

Synergetics

Synergetics is concerned with self-organization and macro-scale structures from mulit-component systems. It has contributed much to the field of complexity science and has its roots in much of the early work by Haken in 1983 and later by Weidlich in 1991 who also expanded on these concepts in his Sociodynamics in 2000 [Weidlich, 2000]. It makes heavy use of methods from statistical physics and economic concepts such as dynamic utility functions, "At the core of my model-building philosophy is the insight that the transition rates...will themselves be general functions of the socio- and trend configurations," that is, they use concepts from social sciences (utility functions) to derive the master equations or equation of motion that is the basis of statistical mechanics [Weidlich, 2000].

World Systems Theory

World Systems Theory attempts to look at the macro-scale level and rejects many of the base assumptions of classical analysis. Municipal borders are de-emphasized and the city or state is no longer the basic unit of analysis [Hopkins et al., 1982, Goldfrank et al., 1999]. These are replaced by a group of core-states that dominate key global industries. While world systems theory generally focus on the

global scale of these interactions, a similar approach has been undertaken at a smaller scale.

Amenity in Models

There has been a lot of effort in the economics and geography literature to include natural and urban amenity (the quality of the physical environment). Aristotle noticed the importance of the quality of life circa 350 BC, then Bath and Brighton remarked on the positive effect of “fashionable watering-places" in 1811 [Mulligan, 2009]. However, Mulligan remarks that amenity as a concept for urban growth did not gain traction until the work of Ullman in 1954. The question of how to value these amenities became pressing and several different methods have been developed [De Groot et al., 2002]. I will highlight just one of the more quantitative methods here: hedonic modeling. Lancaster introduced this concept in 1971 and the methodology was formalized later by Rosen in 1974, [Lancaster, 1971, Rosen, 1974]. Hedonic modeling tries to disentangle the different components, and how people value those components, of something that has a suite of benefits. When one choses to buy a house or move into a city, it is generally a decision made on many factors such as the proximity of parks, open spaces, schools, grocery stores etc. Hedonic modeling aims to put a price on each of these factors and many others that go into making a decision. What complicates this analysis is the fact that different factors may have multiple benefits and externalities. One example is municipal parks; they can be both a source of amenity due to recreational values, [Larson et al., 2010], and a disamenity due to increased crime prevalence, [Troy and Grove, 2008]. Hedonic analyses are statistical in nature and generally temporally static as opposed to my mechanistic and dynamic approach. Although I take a different approach, my efforts can be informed by the results of these other modeling efforts. I want to indicate how my approach is different from the existing literature and its contributions to the field, but I em-

phasize that my efforts are meant to be taken in the broader context, as a piece of the puzzle and to be connected from and connect to the other pieces (modeling efforts).

My approach is in the vein of population ecology and mathematical biology and has its roots in the works of Reverend Thomas Robert Malthus who at the turn of the 19th century gave rise to the eponymous Malthusian Growth Model [Malthus and edited by Appleman, 2004]. While not the first, his work was definitely the most influential in theory and practice. His exponential growth law has spawned several other eponymous models including those of Verhulst and Gompertz. In his own words, “Population, when unchecked, increases in a geometrical ratio," mathematically, this is equivalent to the relationship

$$P(t) = P(0)e^{rt},$$

where $P(t)$ is the population at some time t, e is the exponential function, and r is the growth/decay rate. Evaluating this model at standard increments of time, reveal a geometrical ratio. Armed with this simple model and a handful of simple postulates, Malthus engaged in a philosophical, political and economic discussion about populations and the distribution of resources that resonate to this day. Fundamentally he was concerned about the welfare of society and this mirrors the motivation of this work. Although my methodology will differ, I ascribe to the same philosophy linking great modelers such as Malthus, Einstein and Newton: We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances.

Chapter 3

Cities in Ecology: Settlement Patterns

Traditional Approaches

The model derived in this paper describes how the economic, social and natural environments of an urban area influence the rate of migration into and out of that area. In this stylized model, population and built capital are the dynamic variables which will allow us to derive the, multiple, stable characteristics of an urban area. The overall goal of this paper is to examine the robustness of these stable states and to explore how the interactions of the economic, social and natural environment impact the resilience of the urban are. This pursuit necessitates that our model be simple yet capable of depicting a broad range of city types; hence we use an abstract, qualitative, model described in further detail below.

In this context, robustness refers to the number and nature of the stable configurations of an urban area. The methodology employed is similar to the catastrophe theory of Amson and Wilson [Amson, J.C., 1975, Wilson, 1981], which is an application of bifurcation theory [Dendrinos and Mullally, 1985, Kuznetsov et al., 1998, Strogatz, 1994]. However, our approach is similar to theoretical ecology and social-ecological-systems (SES) [Anderies et al., 2002, Brauer and Castillo-Chavez, 2001, Clark, 1985, Edelstein-Keshet, L., 1988]. Here, analyzing the robustness translates to essentially determining how the landscape changes in response to the slow variables, or parameters, of our system.

Complementary to this analysis is a consideration of the resilience of an urban area, a topic that has received much attention in SES [Anderies et al., 2006, Berkes et al., 2000, Carpenter et al., 2001, Holling, 1973]. In this context, resilience refers to the ability of a system to endure disturbances without a qualitative change in its state. In the parlance of dynamical systems, this amounts to an analysis of

the basins of attraction in our landscape. Here, disturbances can either impact our fast variables, state variables, or our slow variables, parameters. It should be noted that our model is dynamic and the population and built environment change over time; hence resilience is not just a function of how large a disturbance is, but also when it occurs. In this sense, path dependence may have a large impact in the qualitative dynamics of our model. In the next section we develop the model and show the qualitative dynamics. Then we show how the effect of different institutional arrangements can impact the landscape of the model, followed by some numerical results. Finally, we conclude with an interpretation of the model results in the context of SES.

3.1 Mathematical Model

In our stylized model, a city is described using just two factors, population size (N) and infrastructure (K). Many neoclassical economic models assume the population size and infrastructure are at equilibrium [Greenwood, 1985] and only move in response to changes in wages. Other theories propose labor markets are in disequilibrium and migration moves these markets towards equilibrium. Although we do not model wages specifically, we can model the *effect* of changing wages and labor market as the change in population and infrastructure due to migration:

$$\dot{N} = f(N,K) \tag{3.1}$$

$$\dot{K} = g(N,K), \tag{3.2}$$

Thus $f(N,K)$ describes the net migration process and $g(N,K)$ describes how infrastructure changes over time in response to changing population and infrastructure. In order to have migration, there must be somewhere individuals migrate to/from. In our first model, we assume individuals are migrating to our city and migrating from a collection of possible sources that we simply call the hinter-

land. We assume the hinterland is much bigger than the city and thus in-migration does not significantly reduce the size of the hinterland. Instead, we will simply assume there is some constant rate of flow, γ. However, not everyone that may want to migrate into or out of the city does so since there are several costs associated with moving including transaction opportunity and psychic costs[Massey, 1990]. Let $I(N,K,U)$ be the per capita immigration rate into the city and $E(N,K,U)$ is the per capita emigration rate out of the city. Note that these rates are functions of N and K, and thus change over time. The utility, U, also changes over time and will be described below. Then $\gamma \cdot I$ represents the total rate of actual immigration into the city. Similarly, the total rate of emigration is $N \cdot E$. Thus $f(N,K)$ is net migration[1]:

$$\dot{N} = \gamma \cdot I(N,K,U) - N \cdot E(N,K,U). \tag{3.3}$$

Next we assume infrastructure (K) to be a proxy for the built environment contained within a city. Most creatures shape their local environment and this is especially true in social species. The arduous task of creating and maintaining an infrastructure requires energy. Thus infrastructure is under the influence of a natural decay such as our deteriorating roads and bridges that decay with use, collapse with overuse such as the Mississippi River bridge in Minneapolis, or ruin through disuse such as Troy in the Old World or Teotihuacán in the New World. We will call this natural decay rate of infrastructure δ. The rate of resources devoted to growing and maintaing the infrastructure is proportional to the base productivity of the city, $Y(N,K)$, i.e. the capital investment rate (s). According to classical economic theory, the productivity of the city should, at minimum, be a function of the labor supply and infrastructure. We choose the traditional Cobb-Douglas formulation of the production function where the exponents sum to one

[1] In our simplified model, we will ignore the contribution to population change from intrinsic growth.

to imply there is constant returns to yield that scales uniformly for different city sizes. Then $g(N,K)$ is the differences between investment and decay and we can explicitly state the rate of change of infrastructure:

$$Y(N,K) = N^{\alpha_1}K^{\beta_1} \tag{3.4}$$

$$\text{where } \alpha_1+\beta_1=1 \tag{3.5}$$

$$\dot{K} = s\cdot Y(N,K)-\delta K, \tag{3.6}$$

where α_1 is the relative contribution of the labor pool to productivity and β_1 is the relative contribution of infrastructure to productivity.

Now we will delve into the individual motivations of migration. The most dominant factors to move or stay includes what the layman would refer to as economic, job and business driven, opportunities. However, many other factors are also vital [Center, 2008] including some that are uniquely supplied by the city itself. We can broadly define two types of good: traded and non-traded or location based goods [Graves and Linneman, 1979]. Traded goods can be purchased, thus the utility gained from traded goods increases with income. However, the utility derived from non-traded goods may not directly increase with income. While not all residents in a particular location may benefit equally, the change in the quality of that good, and hence the utility derived from it, may be more strongly influenced by factors other than income. For example, safety, congestion and infrastructure can greatly influence the value placed on environmental amenities [Troy and Grove, 2008]. For simplicity, we split non-traded goods into two broad categories: human and natural amenities. Human amenity, $A_h(N,K)$, are the facets of the city, built by people, that add to the enjoyability of that city. For example, walkable streets, a vibrant night life or medical facilities. Natural amenity, $A_n(N,K)$, are natural features that add to the enjoyability of a city, "topological, climatological, and environmental amenities–such as mountains, seashore, tem-

perate climate, sunshine and pollution" [Greenwood, 1985]. It has been clearly demonstrated from empirical studies that not only are these amenities different in various cities, but they are valued and factor into the migration decision of individuals [Center, 2009].

Both of human and natural amenity should be functions of both population size and infrastructure. However, the direction of this relationship is not clear. Consider a lake. Increased infrastructure can represent a dock and services that increase the ability of people to enjoy the lake. It can also represent investment by businesses that may pollute the lake and reduce its amenity value. As the population increases, more people may visit the like, thus increasing the popularity and prestige of the lake. However, if the increased popularity leads to increased littering or congestion, then this can detract from the amenity value of the lake. Human amenity operates in an analogous manner. The modeling process is inherently iterative and as a first approximation, we assume a simple linear relationship between amenity and population and infrastructure.

But first we must introduce the utility function ($U(N,K)$), or the measure of relative happiness. We assume people expect some average level of utility outside the city ($\bar{U}$). Then people in the hinterland may choose to move into the city, $I(N,K,U)$, or residents of the city may choose to move out of the city, $E(N,K,U)$ depending on whether they expect to be happier inside the city or out[2]. For people in the city, we characterize their utility as being functions of human amenity, natural amenity, and production $Y(N,K)$ (which serves as a proxy for the level of income they might expect to have in the city). We also assume this to have a Cobb-Douglas formulation, but with decreasing returns to scale (all the exponents sum to less than one) since handling time may diminish a person's ability to enjoy a larger provision of goods and services. This formulation is in accordance with neoclassical micro-economic theory. However, the

[2]The costs of migrating may be assumed constant and factored into $\bar{U}$

"new economics of migration" theory holds that decision makers are not just individuals but also households that seek to both maximize income and minimize risk [Massey et al., 1993]. This perspective is compatible with our formulation with the following interpretations: instead of N being the number of individuals in a city, it may consist of the decision making actors in a city with an appropriate scaling, and the utility functions include the *effects* of both maximizing income and reducing risk (thus we may interpret human amenity to include a level of income insurance). In addition to these micro scale consideration, there are several macro scale or structural factors that may influence migration including migrant networks, institutional theory and cumulative causation [Massey et al., 1993, Massey, 1990]. Although the decision to move is formulated here as an individual one, it is based on aggregate information. The nonlinearity in the aggregation functions chosen replicates the effect of these large scale phenomenon, most notably the inertia and saturation effects [Greenwood, 1985]. While we do not describe the preconditions to migration, the model can explain how further migration will persist once it has been initiated.

Then

$$A_h(N,k) = a_{hk}K + a_{hn}N + a_{h0} \tag{3.7}$$

$$A_n(N,K) = a_{nk}K + a_{nn}N + a_{n0} \tag{3.8}$$

$$I(N,K,U) = I_0\left(\frac{\pi}{2} + \arctan a_m(U(N,K) - \bar{U})\right) \tag{3.9}$$

$$E(N,K,U) = E_0\left(\frac{\pi}{2} + \arctan a_m(\bar{U} - U(N,K))\right) \tag{3.10}$$

$$U(N,K) = A_h(N,K)^{\alpha_h} A_n(N,K)^{\alpha_n} Y(N,K)^{\alpha_y} \tag{3.11}$$

$$\text{where } \alpha_h + \alpha_n + \alpha_y < 1 \tag{3.12}$$

where a_{hk} determines how infrastructure changes human amenity, a_{hn} determines how the population size changes human amenity and a_{h0} is the basic level of

human amenity. Similarly, a_{nk} determines how infrastructure changes natural amenity, a_{nn} determines how the population size changes natural amenity and a_{n0} is the basic level of natural amenity. Then I_0 is the maximum per capita immigration rate, and E_0 is the maximum per capita emigration rate. Also, α_h is the relative strength of human amenity to utility, α_n is the relative strength of natural amenity to utility, α_y and is the relative strength of productivity to utility. The arctan function is sigmoidal and has been shifted so that it returns only positive values. Thus even at low expected utility in the city, there is some inflow of migrants. Then a_m controls the steepness or drop-off of the sigmoidal response. Then we can write our complete set of equation to describe urban growth

$$\begin{aligned}
\dot{N} &= \gamma I(N,K,U) - N \cdot E(N,K,U) && (3.13)\\
\dot{K} &= s \cdot N^{\alpha_1} K^{\beta_1} - \delta K && (3.14)\\
I(N,K,U) &= I_0 \left(\frac{\pi}{2} + \arctan a_m (U(N,K) - \bar{U}) \right)\\
E(N,K,U) &= E_0 \left(\frac{\pi}{2} + \arctan a_m (\bar{U} - U(N,K)) \right)\\
U(N,K) &= A_h(N,K)^{\alpha_h} A_n(N,K)^{\alpha_n} Y(N,K)^{\alpha_y}.
\end{aligned}$$

Next we will describe the analytical results of our model.

Trivial Equilibrium

Our system of equations are 3.13 and 3.14. Clearly $K = 0$ is an equilibrium solution and we can solve for the equilibrium value of population, N^0, when $K = 0$:

$$N^0 = \frac{\gamma I_0 (\pi - 2 \arctan a_m(\bar{U}))}{E_0 (\pi + 2 \arctan a_m(\bar{U}))} \qquad (3.15)$$

this represents a city with no significant infrastructural development. Even though this means that there is no utility gained by residents in the city, there is still an equilibrium population in the city (N^0). This may seem counterintuitive until we

consider the transaction costs associated with moving. Even if you are not happy in the city, there is a cost to move out. Thus N^0 represents a transient population. Although each individual may not stay in the city for very long, the population level remains constant since there are equal numbers of people moving in and moving out. Note, a linear stability analysis is not possible because it would lead to division by zero. We refer to this as our "trivial" equlibrium[3]. Next we look for non-trivial equilibria.

Non-Trivial Equilibria

In general we cannot solve equations 3.13 and 3.14 explicitly and we employ phase-plane analysis to describe the number and stability of the equilibria. Let us first examine 3.14 and note $\alpha_1 + \beta_1 = 1$:

$$\dot{K} = sN^{\alpha_1}K^{1-\alpha_1} - \delta K, \tag{3.16}$$

which we can now set to zero and solve for the equilibrium population size (N^*)

$$\begin{aligned}
0 &= sN^{\alpha_1}K^{1-\alpha_1} - \delta K && (3.17)\\
\delta K &= sN^{\alpha_1}K^{1-\alpha_1} && (3.18)\\
N^{\alpha_1} &= \frac{\delta K}{sK^{1-\alpha_1}} && (3.19)\\
N^{\alpha_1} &= \frac{\delta}{s}\frac{K}{K^{1-\alpha_1}} && (3.20)\\
\frac{\delta}{s}K^{\alpha_1} &= N^{\alpha_1} && (3.21)\\
N &= \left(\frac{\delta}{s}\right)^{(1/\alpha_1)} K, && (3.22)
\end{aligned}$$

From equations 3.18 and 3.22 we see that if we have an equilibrium, then $\dot{K} = 0$ implies either $K = 0$ or $N = \left(\frac{\delta}{s}\right)^{(1/\alpha_1)} K$. These two curves are called nullclines of

[3]Trivial in the mathematical sense as one of the state variables, capital, is equal to zero.

our system. The term $\left(\frac{\delta}{s}\right)$ is the net decay ratio. If he decay rate is larger than the capital investment rate, then the net decay ratio will be larger than one. Then we can re-write equation 3.22 as $N\left(\frac{\delta}{s}\right)^{\alpha_1} = K$, that is the equilibrium level of capital is directly proportional to the equilibrium population size scaled by the net decay ratio and the share of labor to productivity. The larger the decay rate, the more capital you need to support a given population size. The larger the share of labor to productivity, the more accentuated the impact of the net decay ratio will be.

Then we can solve equation 3.13 for N.

$$N = \gamma \frac{I(N,K,U)}{E(N,K,U)} \tag{3.23}$$

and equation 3.23 is another nullcline. Nullclines divide the state space of our system into distinct regions with different growth patterns for the city. Each point in the state space is a different realization of a city. A city may have a large population and a large level of infrastructure, or low population and low level of infrastructure, or any other combination of infrastructure and capital. Each city would be represented as a point in the state space. This information is observable and measurable. It can even be recorded over time and analyzed for trends, and of course this has been done by historians, demographers, anyone interested in cities. However, what has been lacking in the literature is an understanding of the underlying dynamics of urban growth that gives rise to the patterns in city growth in the context presented in this dissertation: the unobservables that produces the cities as we know them.

Nullclines are one such unobservable. They are a mathematical abstraction that are a direct consequence of the simplifying assumptions made in our formulation of the city. Generally speaking, the dynamics of the city can only change if it crosses a nullcline. Thus, if a city is in a growth phase, it will stay in a growth phase if it does not cross a nullcline, *ceteris paribus*, although the rate of

the growth is free to increase or decrease. Also, equilibria at the intersection of nullclines, that is when both $\dot{N}$ and $\dot{K}$ equal zero simultaneously. Understanding the nullclines and equilibria would provide tremendous insight into the how we would expect the city to evolve over time.

Ideally, we would simply solve for nullcline 3.23 with either nullcline 3.18 or 3.22. Unfortunately nullcline 3.23 is a transcendental equation that cannot be solved explicitly, even in our highly stylized and simplified model. However, for a fixed set of parameters we can solve for the nullclines numerically. Using parameter values from Table 3.1, we constructed the phase-portrait, Figure 3.1, that indicates the flow of solutions over time. Solid blue circles indicate stable equilibria (attractors) while open circles indicate unstable equilibria (repellers). In this particular system, all trajectories (solutions from any set of initial conditions) will tend towards one of the (attracting) equilibria. Notice the equilibria occur at the intersection of the nullcline for $\dot{N}$, solid blue line, with either nullcline for the $\dot{K}$, the dashed red lines. Additionally we have drawn the separatrix or unstable manifold, dotted green line, of the saddle point, which is the interior unstable equilibrium in this case.

The separatrix is another unobservable driving force in the evolution of a city. Like the nullcline, the separatrix divides the state space of our system into regions of different growth patterns of the city. However the nullcline has a much more of a “local" impact in that the growth pattern of the city will only reverse when it crosses a nullcline as it evolves over time. A city cannot cross the separatrix during its evolution over time. The separatrix has more of a “global" impact in that it determines the eventual long term evolution of the city. The separatrix divides our phase-space into two basins of attraction. Solutions that start above the green line will tend towards the upper stable equilibrium, and solutions that start below will tend towards the lower stable equilibrium. The only way the city can cross the separatrix is via some external force not captured in the model. Figure

3.2 takes a closer look at the unstable point and the separatrix, while Figure 3.3 displays the two equilibria near the origin, note the trivial equilibrium is unstable.

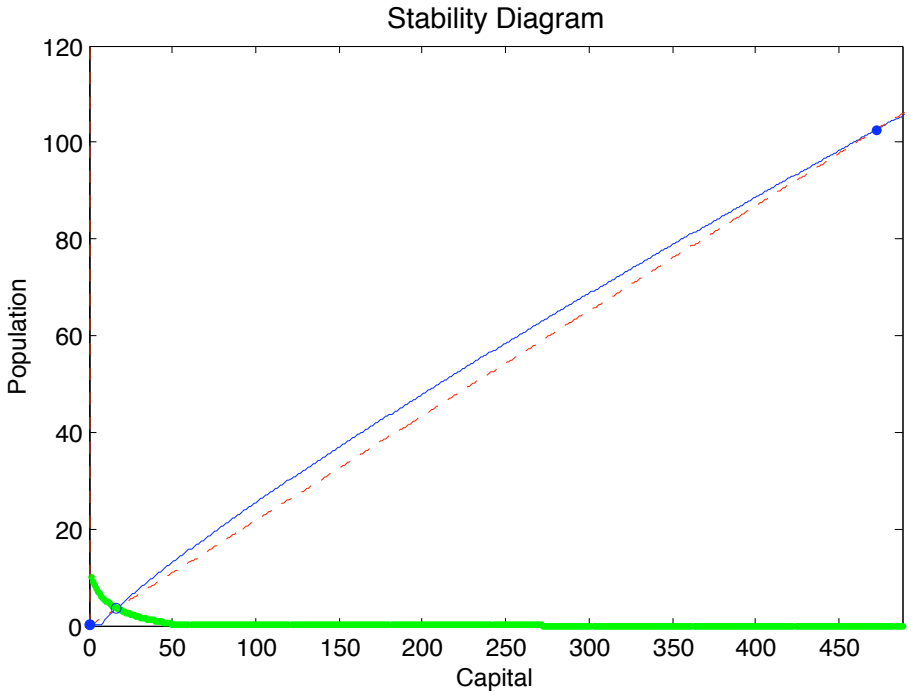


Figure 3.1: There are four fixed points, two stable (blue dots) and two unstable (blue circles), that correspond to the intersection of the nullclines for $\dot{K}$, blue line, and $\dot{N}$, dashed red line. The basins of attraction for the two stable points are separated by the unstable manifold, separatrix of the saddle point (dotted green line).

Table 3.1: Default parameter values for numerical simulations

Parameter	value		Parameter	value
I_0	0.6		a_{nk}	0.5
E_0	0.5		a_{nn}	0.5
δ	0.1		a_{n0}	1
α_h	0.3		a_{hn}	1.5
α_n	0.3		a_{hk}	1.5
α_y	0.3		a_{h0}	1
α_1	0.6		a_s	0.25
β_1	0.4		$\bar{U}$	3
γ	.1381		a_m	1

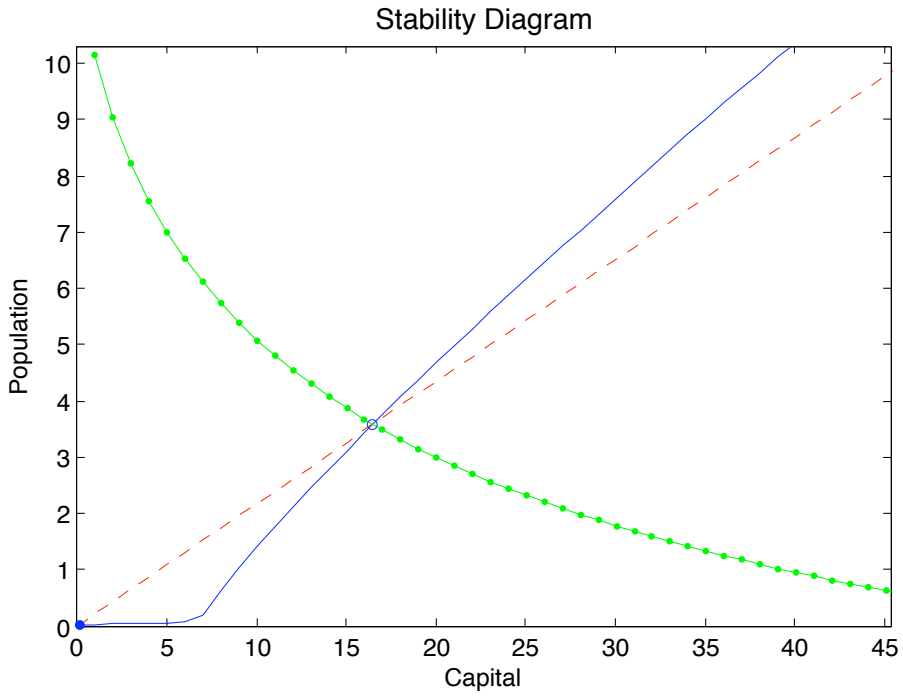


Figure 3.2: Here the separatrix clearly divides the phase space into two separate basins of attraction between the smaller stable fixed point and the larger stable fixed point (not shown).

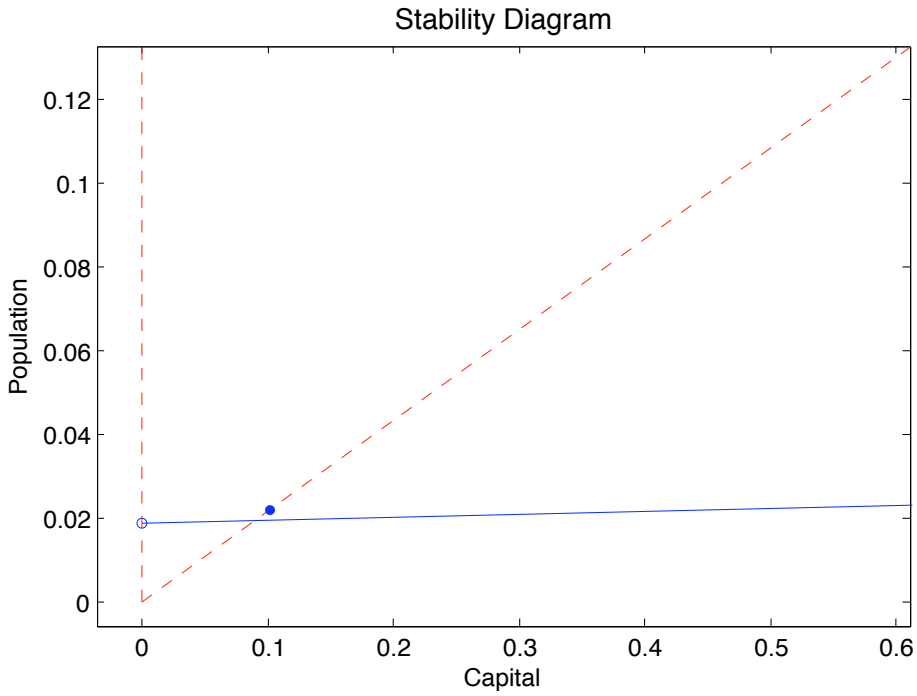


Figure 3.3: Near the origin, there is an unstable trivial equilibrium and a stable interior equilibrium. The scale makes this equilibrium hard to distinguish from the unstable equilibrium unless a comprehensive phase-plane analysis is undertaken.

With certain parameters we have shown that there are two positive stable states and by changing the initial conditions, we can enter different basins of attraction. The existence of two different basins of attraction are significant because it makes it possible to move from one basin to another. The initial conditions determine which basin of attraction the city is in: with low initial conditions, the city will eventually[4] evolve towards the lower attractor in this system, see figure 3.4; with high initial conditions, the city will eventually evolve towards the higher attractor in this system, see figure 3.5. The boundary between the basins is defined by the separatrix (see figure 3.2) and as a general rule, the city may never cross this boundary in its evolution over time. There are, however some exceptions to this "rule."

One is a shift in the state of the system itself from an exogenous force. This may be due to an influx in population or infrastructure (perhaps due to some policy change), or loss such as famine, war, disease, natural (or anthropogenic) disaster, etc. Then the state of the city has shifted in a manner that is outside the normal dynamics described by the model. If this shift is short lived and the time evolution of the city can continue to be described by the model, then the city can be pushed accross the separatrix and be forced into a different basin of attraction. The magnitude of the push depends on the state of the system, how close the system is to the separatrix. Because the separatrix is unobservable, small shifts can produce dramatic impacts to the long term dynamics of the city even if the local time evolution of the city does not appear to be altered significantly.

Another is a paradigm shift, a "tipping point" of the ilk described by Gladwell in 2000 in his book of the same name, but also well known in various other

[4]The evolution is not uniform towards the attractor: the rate may speed up, slow down or as in the case of the population growth with low initial conditions, the population may actually increase initially even though the long term behavior is a steady state that is below the starting population.

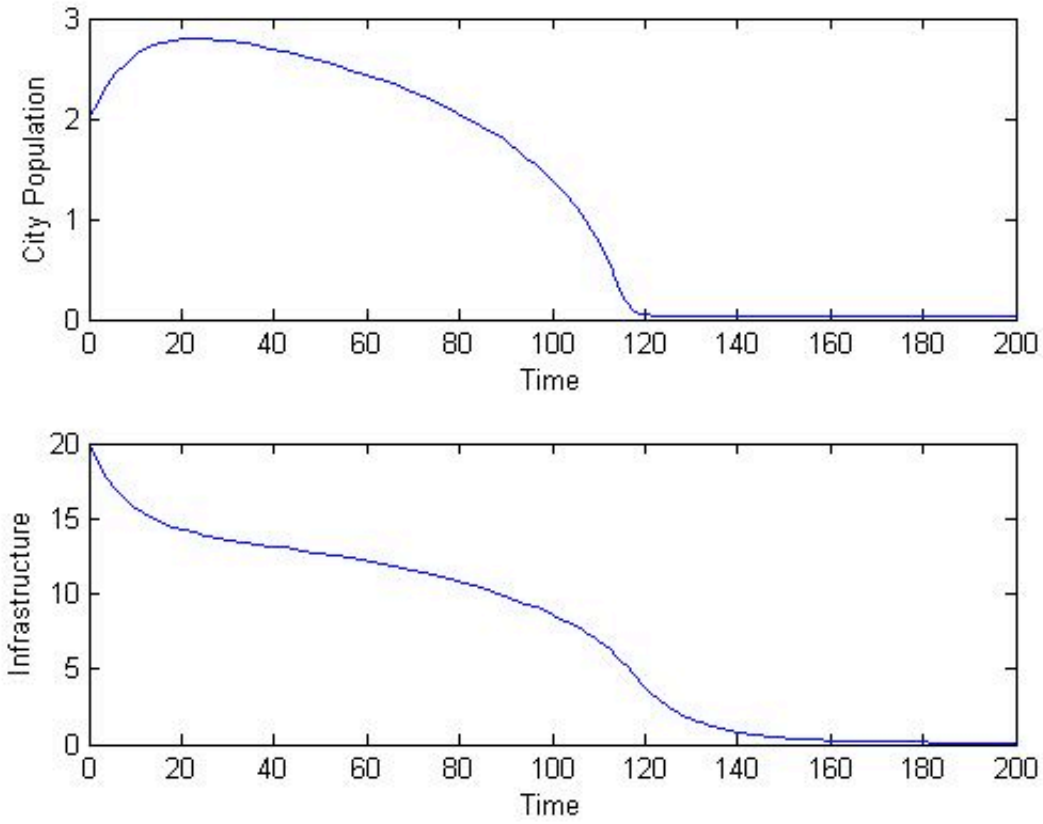


Figure 3.4: With low initial conditions, we enter a basin of attraction of a smaller, but positive non-trivial equilibrium.

scientific and mathematical contexts (the basic reproductive number, $\mathscr{R}_0$ in epidemiology and a bifurcation point in dynamical systems theory to name two examples) [Anderies, 1998, Brauer and Castillo-Chavez, 2001, Gladwell, 2000]. A tipping point refers to small changes in a parameter[5] that leads to a large change in the state of the system. The effect of this small change is a bifurcation, or fundamental alteration of the underlying dynamics of the system. The unobservable landscape has changed in such a way that the evolution of the city has been completely altered. Once attracting equilibria can transform into repelling equilibria or disappear altogether, thus altering the long term, global, dynamics of the city. In this sense, the city hasn't crossed the separatrix so much as the separatrix itself

[5]This can also be thought of as a change in a slow or exogenous variable.

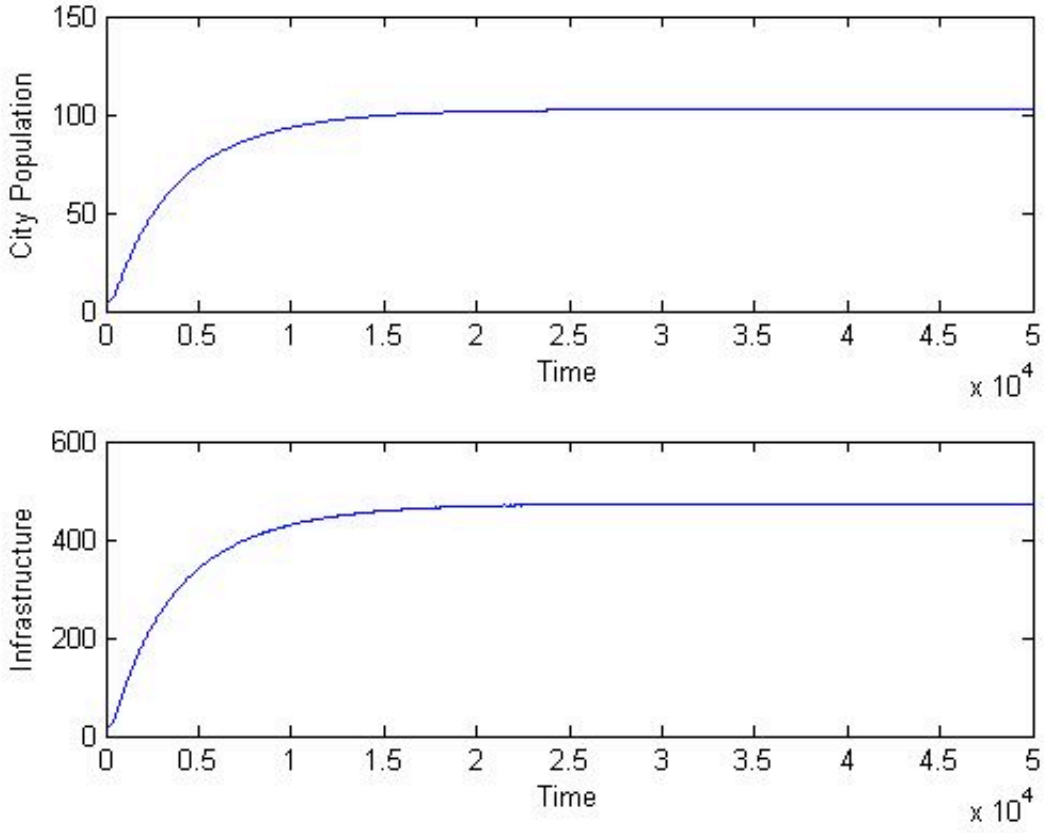


Figure 3.5: With high initial conditions, the city grows rapidly to a larger non-trivial equilibrium.

has moved. Thus the state of the city may not have changed in any perceptible manner, but the future time evolution of the city has fundamentally changed.

Thus, from what we can observe (i.e. the measurable aspects of the state of the city), the two scenarios outlined above may be indistinguishable from their genesis to their revelation. However, they are fundamentally different and an understanding of the underlying, unobservable, landscape is critical to evaluating the robustness and resilience of a system. In the former scenario, the city is close enough to the border of a basin of attraction that a shift in the state from an external force was able to move city into the a different basin of attraction. If the city remains near the border long enough, another shift can return the city into the original basin of attraction, and hence the process in this sense is reversible. In the

latter scenario, it may be practically impossible to return to the trajectory prior to the bifurcation. Some bifurcations can be considered irreversible in the sense that once a tipping point has been reached, it is impossible to reverse the long term attracting state of the city even if the parameters that drove the tipping point are reversed (for example the backward bifurcation [Brauer and Castillo-Chavez, 2001, Castillo-Chavez and Song, 2004, Kribs-Zaleta, 2002, Sanchez, F., 2007]).
Next we give a detailed illustration of the two scenarios presented.

Scenario 1: Robustness and Resilience

In this scenario, the state happens to be near the border of the basin of attraction. Note all trajectories within the basin of attraction will tend to an attractor. In figure 3.6 that attractor is the lower equilibrium and in figure 3.7 it is the larger equilibrium. However, the specific path each city takes to reach the equilibrium may be different. In figure 3.6, we first observe our city starting at the red diamond. Then the city evolves over time along a path given by the black dot-dashed line. The border of the basins of attraction is defined by the green dotted line, the unstable equilibria are the open blue circles and stable equilibrium shown is the solid blue circle. The other two lines are the nullclines, the red dashed line is the nullcline for capital, and the solid blue line is the nullcline for population.

Notice that initially our city is decreasing in population. This is what we might expect since the stable attractor here is at a much lower level of capital and population then our starting value. However, the level of capital is actually growing initially. In fact the level of capital will continue to grow until the trajectory hits the nullcline: the direction of growth cannot change until a nullcline is crossed. When the trajectory crosses the red dashed line, the nullcline for capital, the capital takes a dramatic downturn and this accelerates the reduction in both population size and infrastructure level.

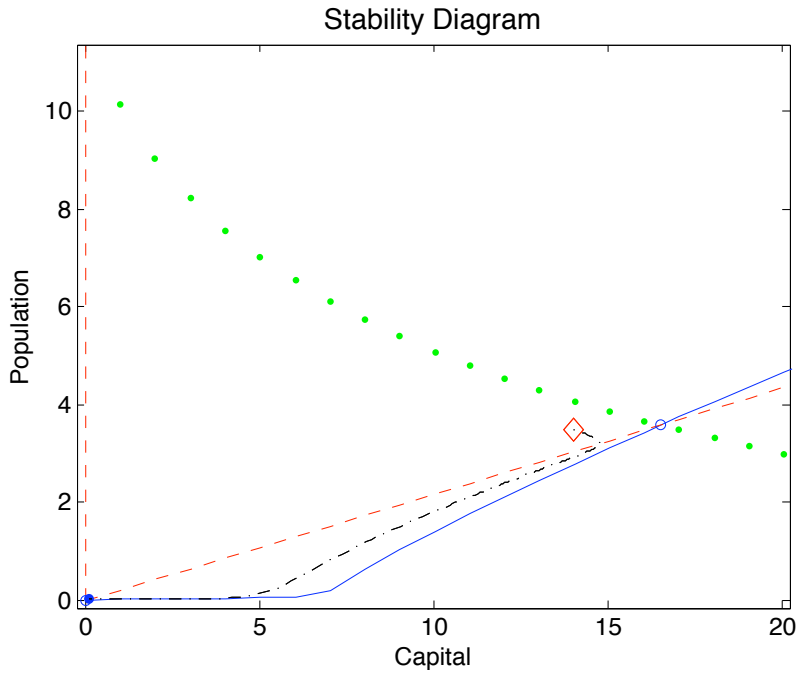


Figure 3.6: With low initial conditions we enter a basin of attraction of a smaller, but positive non-trivial equilibrium.

An outside observer looking at the state of the city could conclude that the city hit a cusp at that point, perhaps a tipping point was reached that caused the city to veer off on a different trajectory than it was previously on. However plausible that conclusion would be from the data, it is wrong. In fact, the city was always doomed to reach the lower equilibrium point since it was in the lower basin of attraction. The fact that it increased initially is a function of its starting state (the state where we first began to observe it) and the underlying, unobservable, dynamical landscape; namely the nullclines. If our initial observation point was below the blue line, then the population level would have initially increased. If our initial observation point was between the red and blue lines, then city would have decreased immediately. An observer could naturally conclude that a city in the later case was a “bad" city where any of the former two cases showed potential but fell victim to some “bad" circumstances.

If, at the initial observation period, there was in influx of population, then we would have the trajectory in figure 3.7. Notice that the initial starting point is very similar to figure 3.6, and even the initial trajectory is similar: decreasing population and increasing capital. An outside observer could conclude that both cities are on a similar trajectory and that their endpoints would naturally be similar. In fact, this would be the correct observation if the separatrix was either shifted down or up. However, the separatrix, an unobservable feature of the dynamical system landscape is between the two starting points and thus the endpoints will be drastically different. The endpoint of this city will be the high population high capital city seen in figure 3.1. There is virtually no way to distinguish these two trajectories from observing the first few data points and trends unless there is an accurate description of the dynamical systems landscape (null-clines, equlibria, basins of attraction, etc.).

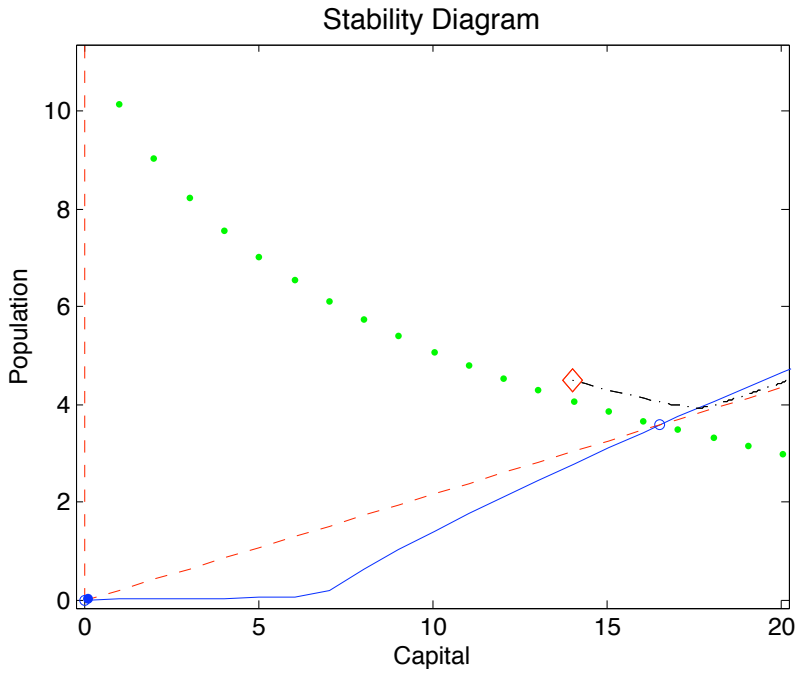


Figure 3.7: With high initial conditions the city grows rapidly to a larger non-trivial equilibrium.

Another interesting observation in this scenario is that the trajectory stays close to the separatrix initially. Thus, although an influx of people caused the trajectory of the city to jump into a different basin of attractions, a disaster that reduces the number of people or the quality of the infrastructure could likewise alter the trajectory of the city and place it back in the lower basin of attraction. This highlights the significance of path dependency or legacy effects in the time evolution of cities. Relatively small perturbations in the history of a city can have profound impacts on the evolution of cities, while other, perhaps even larger perturbations may haver marginal long term effects. The difference lies in the distance the current state is from the edge of the basin, and whether or not these perturbations alter the underlying parameters and institutions (the functional forms) that drive the dynamics of the city.

While cities are clearly sensitive to path dependence early on, because we cannot observe the separatrix, it will be unknown to the city denizens how close, or for how long, the trajectory of a city will bring it near to the border of a basin of attraction. Hence, the true vulnerability of a city from its eventual long term steady state will not be known from either its current state or its current trajectory. Even if there are no alterations to the trajectory of a city, the final state the city is trending towards cannot be predicted by the current state nor growth trends alone.

In truth, it may be difficult if not impossible to distinguish this scenario from a true tipping point. There has been tremendous research by scholars of urban areas in understanding the drivers of change including Knox, Massey, Greenwood and many others ([Greenwood, 1985, Knox, 1995, Krugman, P., 1996, Massey, 1990, Massey et al., 1994]). Several others scholars have brought to light the unforeseeable global consequences of individual or small scale actions, potential tipping points, to the general public via the profound impacts on human lives and societies such as McNeill's Plagues and Peoples and Diamond's Guns, Germs and

Steel, and the geographic landscape such as Reisner's Cadillac Desert [Diamond et al., 2005, McNeill, 1976, Reisner, 1993]. Whether these events can be explained as the consequence of an outside force, a tipping point, or a natural evolution of the trajectory the city is already on is impossible to discern without an understanding of the underlying dynamical structure of the city. True tipping points, bifurcations, will be explored below.

Scenario 2: Tipping Point

In this scenario, the parameters of the system undergo changes. Generally changes in parameters will result in quantitative but not qualitative changes in the system: growth rates may accelerate or slow down but the number and type of equilibria do not change. However, there are situations where even slight changes in the parameters can cause dramatically different, qualitative, changes in the dynamics, i.e. a bifurcation. The parameter(s) involved in this qualitative change are then called bifurcation parameter(s). For this analysis we will focus on the bifurcation parameter a_{hk} which translates how human amenity is appreciated from the built infrastructure. In our particular model, many of the parameters can be chosen as the bifurcation parameter, but the bifurcation structure is identical and it suffices to explore in detail only one such parameter.

Starting with the default value of 1.5, as we decrease a_{hk} the high stable equilibrium point and the unstable equilibrium point approach each other, see figure 3.8. At the bifurcation, which occurs at $a_{hk} = 0.941$, the two equilibria coalesce and annihilate each other in a what is termed a saddle-node bifurcation[6]. Then after the bifurcation, the separatrix dissapears and there is now only one basin of attraction for the low population-low capital equilibrium point. Thus if the infrastructure does not produce enough of a positive feedback in terms of the amenity of the city, the city will not become attractive and can persist only at

[6]The unstable equilibrium is the saddle and the stable equilibrium is the node [Brauer and Castillo-Chavez, 2001, Kuznetsov et al., 1998, Strogatz, 1994]

very marginal levels (see figure 3.9.

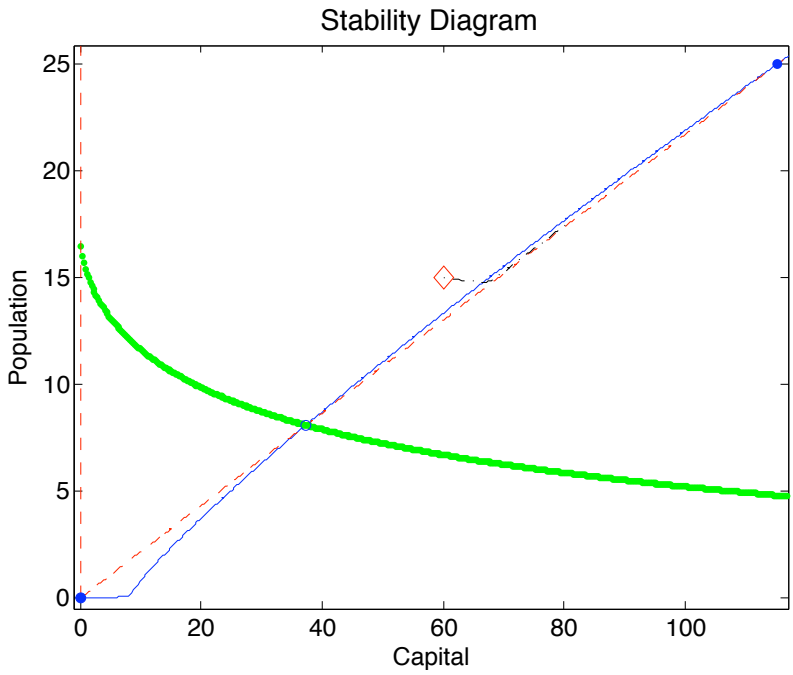


Figure 3.8: Before the bifurcation, there are two regions of attraction separated by the unstable manifold of the unstable, saddle, point. A trajectory that starts in the upper region will trend to the higher stable equilibrium point.

If we increase a_{hk} instead, then the high stable equilibrium begins to get larger and larger until another bifurcation is reached at $a_{hk} = 334.5$. At this point the unstable equilibrium point and the lower stable equilibrium point coalesce and we are left with only one basin of attraction for the higher stable point. This again occurs through a saddle-node bifurcation. Thus with a very high amplification factor for turning capital into amenity, any city that become established will eventually thrive. The bifurcation diagram for both bifurcations is given in terms of the equilibrium level of capital, figure 3.10, and population level, figure 3.11. The x-axis is the bifurcation parameter, a_{hk}, and the y-axis is the equilibrium state of the city. When there is bi-stability, there are two possible equilibria points. Before the bifurcation at $a_{hk} = 0.9375$ there is only the lower equilibrium point exists. Between 0.9375 and 334.5, there is bi-stability and the city can evolve to either the low or high equilibrium state depending on the initial conditions. After

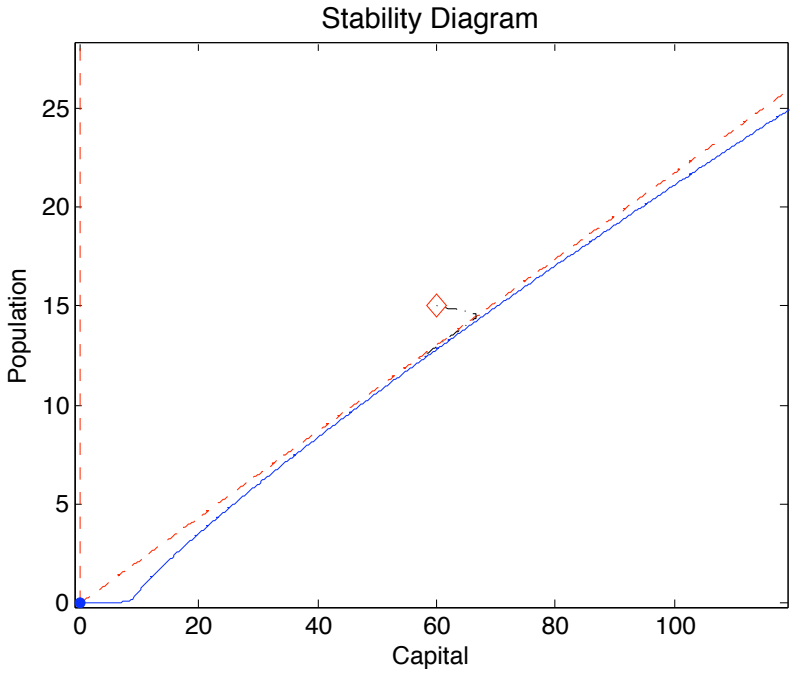


Figure 3.9: After the saddle-node bifurcation, the upper stable point and the unstable point have coalesced. There is now only one region of stability remaining for the lower equilibrium point. The same trajectory that approached the higher equilibrium before the bifurcation will now approach the lower equilibrium point over time.

334.5, only the high equilibrium point exists.

We have fully described the suite of qualitative dynamics possible in this simple, stylized, model of a single city. In the next section we classifying different types of cities by varying parameter ranges.

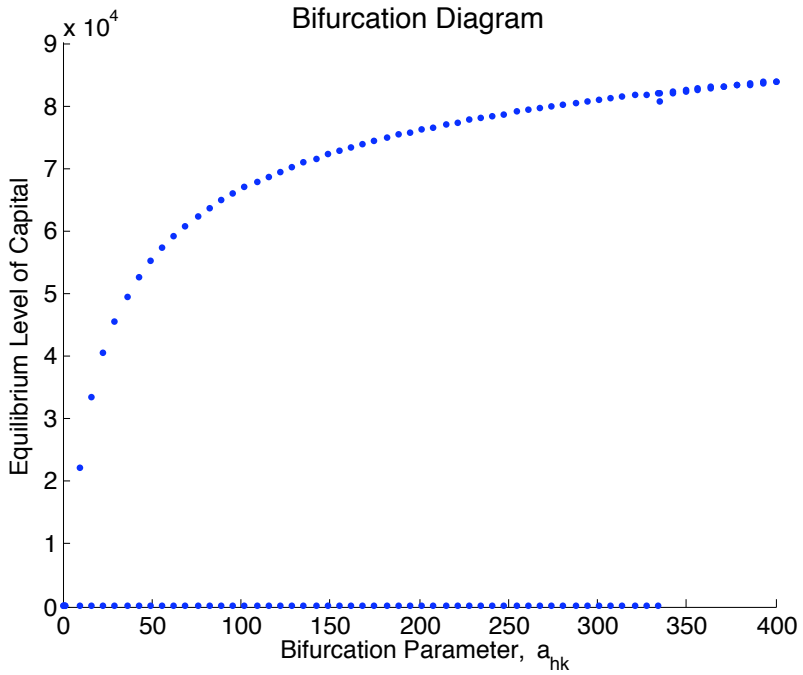


Figure 3.10: Depending on the parameter a_{hk}, there can be one or two stable equilibria for the level of capital given by the blue dots (the unstable equilibria not shown for simplicity). When $a_{hk} < 0.9375$ the only stable equilibrium is near zero. At $a_{hk} = 0.9375$ there is a saddle-node bifurcation. When a_{hk} is between 0.9375 and 334.5 there are two stable equilibria. At $a_{hk} = 334.5$ another saddle-node bifurcation occurs, and when $a_{hk} > 334.5$ the only stable equilibrium is the larger one.

3.2 City Types and Institutions

Up to this point we have considered the city as abstract construct. Although we will still formulate the city in an abstract manner, it is important to talk about what a city is, or more importantly what separates one city from another. Aristotle spent a great deal of time describing citizens and cities as they were and should be. Mumford quotes Aristotle as saying, Òmen came together in cities to live, but remained to live a good lifeÓ [Mumford, 1997]. The majority of the human population is now projected to live in cities [Wimberley et al., 2007], but will they live good lives? Cities have been described as hellish, disorderly and chaotic, but also as, Òcrucibles for innovation, tolerance, diversity, novelty surprise, and most of all economic prosperity,Ó [Batty, 2008]. Just as there is dissension on how to describe a city, there are also different ways to define a city. Visually, large build-

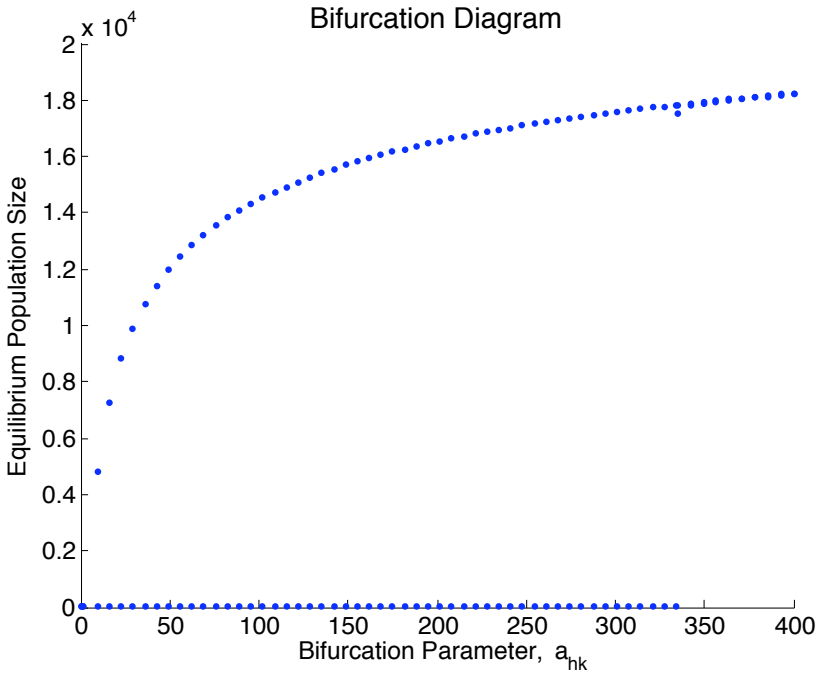


Figure 3.11: Depending on the parameter a_{hk}, there can be one or two stable equilibria for the population size given by the blue dots (the unstable equilibria not shown for simplicity). When $a_{hk} < 0.9375$ the only stable equilibrium is near zero. At $a_{hk} = 0.9375$ there is a saddle-node bifurcation. When a_{hk} is between 0.9375 and 334.5 there are two stable equilibria. At $a_{hk} = 334.5$ another saddle-node bifurcation occurs, and when $a_{hk} > 334.5$ the only stable equilibrium is the larger one..

ings, roads and other human-made structures indicate a city, but [Park, 1951] emphatically argues that a city is more than just its physical attributes. Although it may appear to have a form dominated by buildings, a city is rooted in the habits and customs of its people. Thus, a city may be *identified* by its built structures, but a city is *defined* by the people, that is, the human ecology and institutions contained within a city [Hawley, 1981].

In this section we will focus on the different components of the natural and human amenity functional response. We will describe 5 archetypal cities depending on the signs of parameters given by table 3.2. The first archetype is the Oasis or political city established by royal decree. This city is formed when there is some highly local cultural or environmental features that make the city attractive, but in general the surrounding environment is not conducive to large urban cen-

ters. The second archetype is the Ecocentric city where too much infrastructure is detrimental to the cultural lifestyle and the environment. The third archetype is the Industrial city or trading nexus where the growth of the city may improve the human amenity of the city, but at the cost of the natural environment. The fourth archetype is Mining city centered on extracting some local resource and where improving the quality of life of the citizens may not be the primary consideration as the city grows. Lastly we have the utopian city, a city with intrinsic natural and cultural values, as well as growth aimed to amplify both the quality of the city and the connection to the environment.

Table 3.2: Effect of Institutions on Amenity Function and City Type

a_{nn}	a_{nk}	a_{n0}	a_{hn}	a_{hk}	a_{h0}	Type
+	+	-	+	+	-	Oasis
+	-	+	+	-	+	Ecocentric
-	+	+	-	+	+	Industrial
-	-	+	-	-	+	Mining
+	+	+	+	+	+	Utopia

While the complete bifurcation structure has been detailed for the Utopian city, the underlying dynamics also hold for each of the other archetypes. What will be different are the parameter values at which each city archetype undergoes those bifurcations. Thus the qualitative dynamics of each city follow similar patterns. The specific value at which each bifurcation occurs is of limited value in the abstract framework presented thus far. However there is power in describing the relative values necessary for each archetype to undergo the same type of transformations. Following the previous analysis, comparisons will be made relative to the default values of the Utopian city.

The Oasis with parameters similar in magnitude to Utopia has very similar high equilibrium state, see figure 3.12. The percentage difference of the high equilibrium state is less than 5%. However, the unstable equilibrium has a percent

difference of 30%. This suggests that with enough resources both types of cities can mature into large urban centers that provide significant natural and human amenity. Although, the Oasis is more vulnerable at low population and infrastructure levels; more of an initial investment is required to establish this type of city.

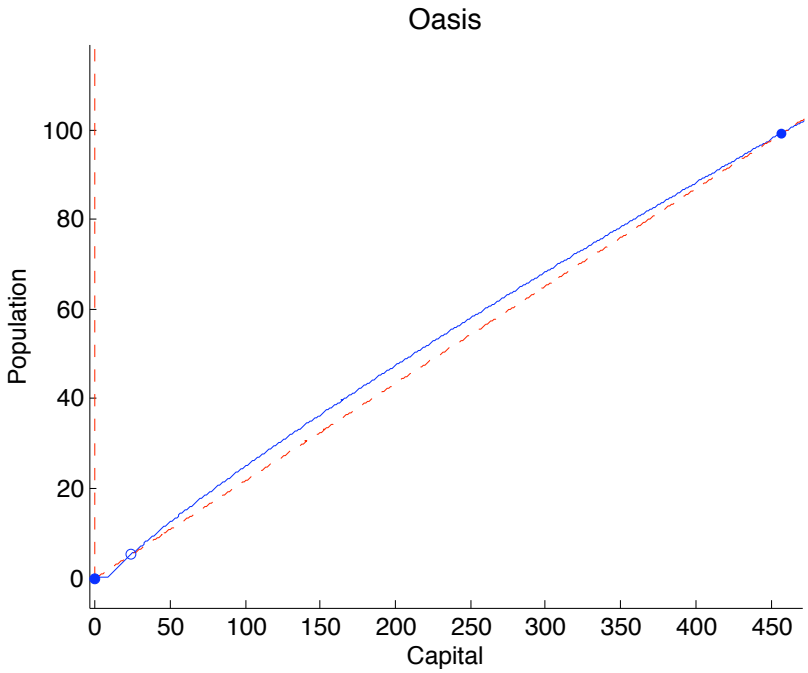


Figure 3.12: The Oasis is very similar to Utopia, however the basin of attraction of the smaller stable state is relatively larger. $a_{nn} = 0.5$, $a_{nk} = 0.5$, $a_{n0} = -1$, $a_{nn} = 1.5$, $a_{nk} = 1.5$, $a_{b0} = -1$.

The Ecocentric city can only thrive at small scales, see figure 3.13. It requires a large intrinsic natural and cultural aesthetic to facilitate any marginal population size and level of infrastructure. The added cultural value that people bring must far exceed the effects of crowding, pollution, etc that comes from urbanization. Even in these ideal conditions, the level of infrastructure it can support is less than one tenth that of the Utopian city.

The Industrial city can support a much larger population and level of infrastructure than the ecocentric city, see figure 3.14. However, it is still less than one third of the size of the Oasis or Utopian city. Although the city can grow at the

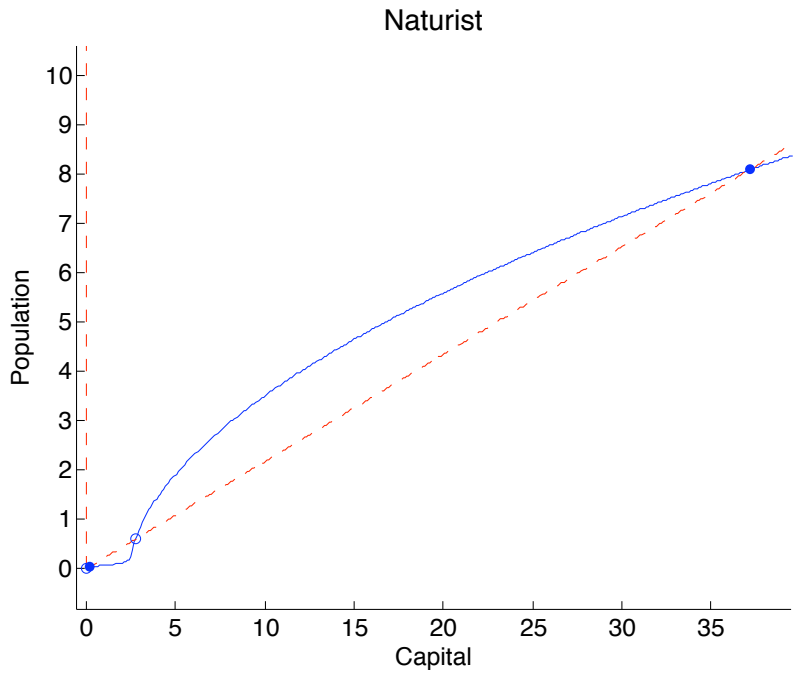


Figure 3.13: The Ecocentric city cannot support a large population or level of infrastructure. It needs to have high positive feedback of natural amenity to grow beyond the small town. $a_{nn} = 2$, $a_{nk} = -0.01$, $a_{n0} = 9$, $a_{bn} = 5$, $a_{bk} = -0.01$, $a_{b0} = 8$.

expense of the environment, the city will not thrive in this contentious relationship.

Not surprisingly, the Mining city, see figure 3.15. However, it is still less than one third of the size of the Oasis or Utopian city. Although there may be significant intrinsic natural and cultural values at the location of the city. The city itself lacks the will or the institutions to leverage those intrinsic values into an amenity for the city as it grows.

Each city essentially “looks" the same on paper because they share the same bifurcation structure, meaning the qualitative dynamics are similar. However, there are vast quantitative differences between these types of cities. To further understand the differences between different types of cities, it is important to understand the differences between the natural and human derived amenities, and these differences are explored in the next section.

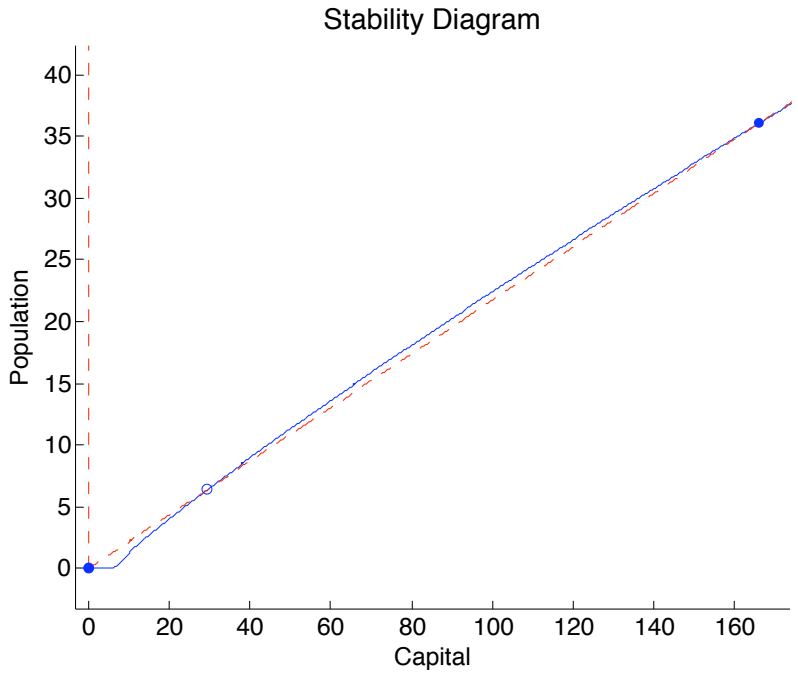


Figure 3.14: The Industrial city is much easier to establish and grow than the Ecocentric city. However, the Industrial city does not place enough emphasis on the connection to the natural environment, reducing its potential to grow relative to the Oasis or Utopian city. $a_{nn} = -0.1$, $a_{nk} = 0.9$, $a_{n0} = 1$, $a_{hn} = -0.1$, $a_{hk} = 1$, $a_{h0} = 1$.

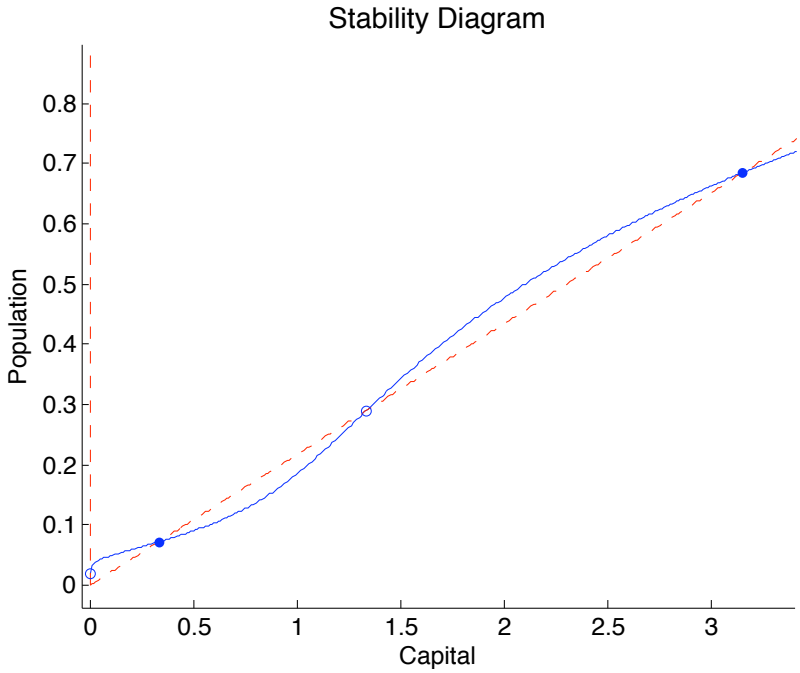


Figure 3.15: The Mining city cannot support a large population or level of infrastructure. It needs to have high positive feedback of natural amenity to grow beyond the small town. $a_{nn} = -0.2$, $a_{nk} = -0.08$, $a_{n0} = 10$, $a_{hn} = -0.1$, $a_{hk} = -0.09$, $a_{h0} = 12$.

3.3 Dual Capital

In this section we allow the natural environment to have its own dynamics in the form of a logistic equation with harvesting. This assumes there is some natural regenerative quality to natural amenity that can be "consumed" by the interaction of individuals. This type of formulation has been used extensively in bioeconomics, and resource management [Anderies, 1998, Brauer and Castillo-Chavez, 2001, Clark, 1985]. Then we can describe the new system as

$$
\begin{aligned}
A_h(N,K) &= a_{hk}K + a_{hn}N + a_{h0} \\
A_n(W,K) &= a_{nk}W + a_{nn}N + a_{n0} \\
I(N,K,U) &= I_0\left(\frac{\pi}{2} + \arctan a_m(U(N,K) - \bar{U})\right) \\
E(N,K,U) &= E_0\left(\frac{\pi}{2} + \arctan a_m(\bar{U} - U(N,K))\right) \\
U(N,K) &= A_h(N,K)^{\alpha_h} A_n(N,W)^{\alpha_n} Y(N,K)^{\alpha_y}. \\
\dot{N} &= \gamma I - N(N,K,U)\cdot E(N,K,U) \qquad (3.24) \\
\dot{K} &= s\cdot N^{\alpha_1}K^{\beta_1} - \delta K \qquad (3.25) \\
\dot{W} &= r\cdot W\left(1 - \frac{W}{a_k}\right) - h * W * N, \qquad (3.26)
\end{aligned}
$$

where r is the intrinsic growth rate of natural capital, W, a_k is the carrying capacity, and h is the harvesting constant. Also note that natural amenity now depends on natural capital and population size.

This new model allows for multiple stable states. Figure 3.16 shows a city with low initial conditions. This city essentially has never been able to establish itself and remains dominated by the natural environment which persists at its carrying capacity. Figure 3.17 shows a city with moderate initial conditions. This city is able to take full advantage of the natural environment, consuming capital at a rate that allows the environment to still be highly productive while still developing high levels of infrastructure: a resort town. Figure 3.18 shows a city with high

initial population and human capital, but low natural capital. The state of the environment started too low to ever reach its carrying capacity. Despite this, the city is able to grow initially and maintain the high levels it started with, for some period of time. Although the decline is slight at first, and can be drawn out for a long period of time, the city is doomed. The equilibrium state of the city is one with low population, low human and low natural capital: a ghost town. Eventually all the city dwellers will leave this city for another. We have seen that the future of the city is uncertain. Early growth trends can lead to sustained growth, or eventual decline. One way to understand the uncertainty inherent in natural processes is via stochastic equations, which will be discussed in the next section.

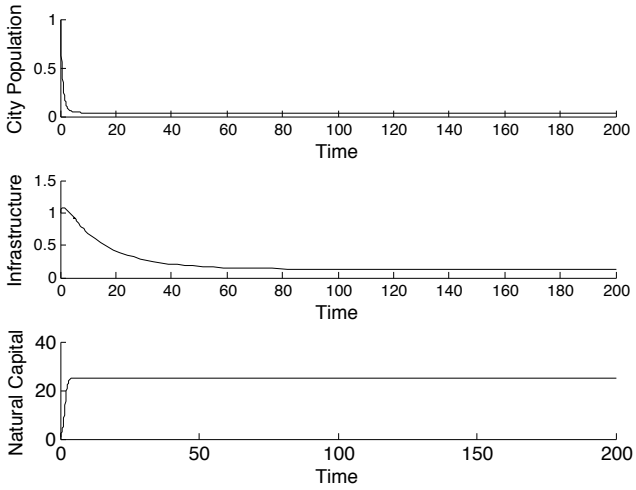


Figure 3.16: With low initial conditions we enter a basin of attraction of a city dominated by the natural environment. In this scenario, the environment grows to its carrying capacity, with little interference from the city. Initial conditions: $N(0) = 1, K(0) = 1$, and $W(0) = 1$. Parameters: $a_{nn} = 0.5, a_{nk} = 0.5, a_{n0} = 1, a_{hn} = 0.5, a_{hk} = 0.5, a_{h0} = 1$, $s = 0.25$, $r = 2$, $a_k = 25$, and $h = 0.05$.

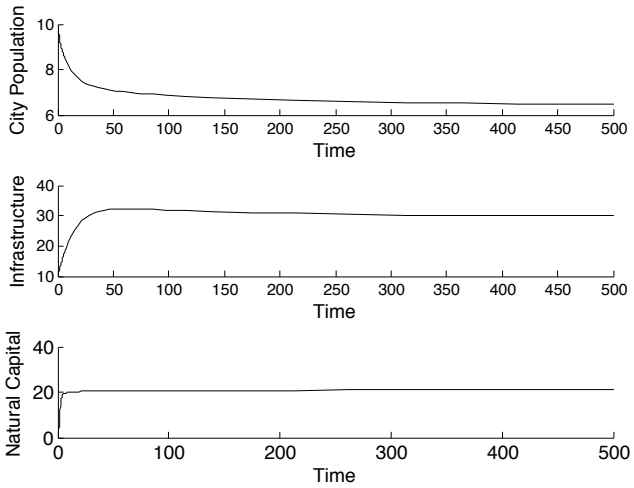


Figure 3.17: With moderate initial conditions we enter a basin of attraction of a city with high human and natural capital. Initial conditions: $N(0) = 10$, $K(0) = 10$, and $W(0) = 1$. Parameters: $a_{nn} = 0.5, a_{nk} = 0.5, a_{n0} = 1, a_{hn} = 0.5, a_{hk} = 0.5, a_{h0} = 1$, $s = 0.25$, $r = 2$, $a_k = 25$, and $h = 0.05$.

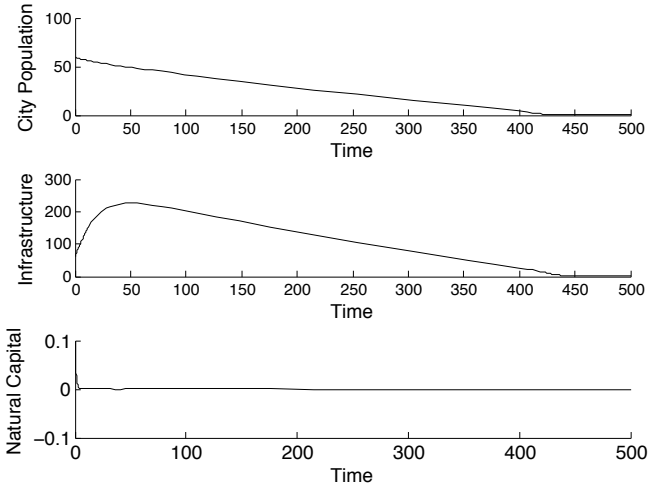


Figure 3.18: With high population and infrastructure, but low natural capital, we enter the basin of attraction of the abandoned city. Although the population and infrastructure levels may start high, and also increase initially, there is a gradual decline. This decline may be long and drawn out, but is inevitable. Initial conditions: $N(0) = 60$, $K(0) = 60$, and $W(0) = 0.1$. Parameters: $a_{nn} = 0.5, a_{nk} = 0.5, a_{n0} = 1, a_{hn} = 0.5, a_{hk} = 0.5, a_{h0} = 1$, $s = 0.25$, $r = 2$, $a_k = 25$, and $h = 0.05$.

Chapter 4

Stochastic Model

Our modeling framework has been aimed at describing the mechanistic processes in urban growth. We have used a deterministic set of equation to describe the dynamics. However, in many situations in nature thing are either random or effectively random. The methodology used in this section is similar to that used to model epidemics, molecular reactions, shot noise and population dynamics [Kuske et al., 2007, Rogers and Murillo, 2010] and centers around random events being Poisson processes [Karlin and Taylor, 1975, Kurtz, T.G., 1978, Allen, L.J.S., 2003]. Here we assume that only the migration process is random, that is, people move in/out of cities independently at some stochastic rate. Suppose we have a time interval $(t, t+\Delta t)$ where migration into or out of a city may occur. Let Δt be small enough such that it is unlikely that more than one event occurs in the time interval. Let N_t, K_t and U_t be the population, the level of capital and average utility of our city at time t, respectively. Since we only have two random events, the population changes when either someone moves into the city or moves out.

$$P(N_{t+\Delta t} = k+1 | N_t = k) = \gamma I(N_t, K_t, U_t)\Delta t + o(\Delta t) \tag{4.1}$$

$$P(N_{t+\Delta t} = k-1 | N_t = k) = N_t E(N_t, K_t, U_t)\Delta t + o(\Delta t). \tag{4.2}$$

For clarity, we state that Equation 4.1 is read, "the probability that N at time t + Δ t equals k+1, given that N at t equals k is $\gamma I(N_t, K_t, U_t)\Delta t$ plus little oh of Δt," where $o(\Delta t)$ is Landau notation [Allen, L.J.S., 2003, Karatzas and Shreve, 1991]. Informally, we include the $o(\Delta t)$ term to represent the possibility (no matter how unlikely) of other events happening in the time interval $(t, t+\Delta t)$. Note, as we allow Δt to get smaller and smaller, $\lim_{\Delta t \to 0} o(\Delta t) = 0$. Further, if we can define the increment $N_{t+\Delta t} - N_t$ to be the change in the number of susceptible individuals

in the time interval $(t, t+\Delta t)$, then Equation 4.1 can also be written as

$$P(N_{t+\Delta t} - N_t = 1) = \gamma I(N_t, K_t, U_t)\Delta t + o(\Delta t) \quad (4.3)$$

$$P(N_{t+\Delta t} - N_t = -1) = N_t E(N_t, K_t, U_t)\Delta t + o(\Delta t). \quad (4.4)$$

Now we can define $\Delta N_t = N_{t+\Delta t} - N_t$ and complete the probabilistic treatment of the population:

$$P(\Delta N_t = 1) = \gamma I(N_t, K_t, U_t)\Delta t + o(\Delta t) \quad (4.5)$$

$$P(\Delta N_t = -1) = N_t E(N_t, K_t, U_t)\Delta t + o(\Delta t) \quad (4.6)$$

$$\begin{aligned} P(\Delta N_t = 0) &= 1 - N_t E(N_t, K_t, U_t)\Delta t - \gamma I(N_t, K_t, U_t)\Delta t \\ &= +o(\Delta t) \end{aligned} \quad (4.7)$$

$$P(\Delta N_t = \text{anything else}) = o(\Delta t). \quad (4.8)$$

This formulation is important when we need to explicitly consider the movement of individual people. However, cities, by definition, have large numbers of people. Consequently large numbers of people move into/out of cities every day and this formulation would be too tedious and so we will invoke the central limit theorem to derive the stochastic differential equations (SDE's) for our model of urban growth[1].

Before we continue we observe that the increments ΔN_t are stationary (do not depend on t), independent and follows a Poisson distribution since the migration rates are Poisson processes [Shreve, 2004]. Using the definition of the expected value, we can calculate

[1]It is important to note that we are assuming our population is large, but not too large. As our population gets sufficiently large, the probabilistic model can be approximated by normally distributed random variables and lends to the construction of the SDE's [Allen, L.J.S., 2003]. In the limit the population gets very large, then the SDE's converge in distribution [Kurtz, T.G., 1978] to the system of ordinary differential equations presented in the previous section.

$$
\begin{aligned}
E[\Delta N_t] &= 1*(\gamma I(N_t,K_t,U_t)\Delta t + o(\Delta t)) - 1*(N_t E(N_t,K_t,U_t)\Delta t + o(\Delta t)) \\
&\quad +0*(1 - N_t E(N_t,K_t,U_t)\Delta t - \gamma I(N_t,K_t,U_t)\Delta t + o(\Delta t)) \\
&= (\gamma I(N_t,K_t,U_t) - N_t E(N_t,K_t,U_t))\Delta t + o(\Delta t). \qquad (4.9)
\end{aligned}
$$

Then the variances becomes

$$
Var[\Delta N_t] = (\gamma I(N_t,K_t,U_t) + N_t E(N_t,K_t,U_t))\Delta t + o(\Delta t) \qquad (4.10)
$$

note that in Equation 4.9 the terms subtract because the Poisson process is a counting process and we are counting “down" but in Equation 4.10 the terms add because variances of independent random processes add. Then we can look at how the population changes and employ the standard mathematical technique of adding zero.

$$
\begin{aligned}
\Delta N_t &= E[\Delta N_t | N_t] + \Delta Z_t \qquad (4.11) \\
\Delta Z_t &= (\Delta N_t - E[\Delta N_t | N_t]) \qquad (4.12)
\end{aligned}
$$

where ΔN_t is the conditionally centered Poisson increment. The centering shifts the mean of the Poisson increment to zero, but leaves the variance unchanged. If we let the population size get large, but not too large, then, we can apply the central limit theorem (and Itô calculus) to get the SDE for the population equation

$$
dN_t = (\gamma I(N_t,K_t,U_t) - N_t E(N_t,K_t,U_t))dt + \sigma_t dW_t \qquad (4.13)
$$

where W_t is a Weiner process (also called white noise or Brownian motion, $dB(t)$). The Weiner process has several important properties including that it is distributed as a standard normal (mean zero, variance 1) [Allen, L.J.S., 2003]. Then $\sigma_t =$

$\sqrt{\gamma I(N_t,K_t,U_t) - N_t E(N_t,K_t,U_t)dt}$. Note that $\sigma_t dW_t$ is the limiting distribution of ΔZ_t as N gets large. Now we can write the stochastic model:

$$
\begin{aligned}
dN_t &= (\gamma I(N_t,K_t,U_t) - N_t E(N_t,K_t,U_t))dt + \sigma_t dW_t && (4.14)\\
dK_t &= s \cdot N_t^{\alpha_1} K_t^{\beta_1} - \delta K_t && (4.15)\\
I(N_t,K_t,U_t) &= I_0 \left(\frac{\pi}{2} + \arctan(U_t - \bar{U}) \right)\\
E(N_t,K_t,U_t) &= E_0 \left(\frac{\pi}{2} + \arctan(\bar{U} - U_t) \right)\\
U_t &= A_h(N_t,K_t)^{\alpha_h} A_n(N_t,K_t)^{\alpha_n} Y(N_t,K_t)^{\alpha_y}.
\end{aligned}
$$

Our stochastic model, Equations 4.14 - 4.15, is a set of SDE's even though the Weiner process is only present in Equation 4.14 (K_t is now a stochastic process since it depends on N_t). Stochastic effects are the most significant when population sizes are small. In our deterministic models, there were several scenarios where city populations persisted at low levels. In a stochastic framework, these small cities have a positive probability of extinction. Even in scenarios that had high population and infrastructure levels as the equilibrium state have a chance of becoming extinct, especially in the early stages of city development.

The stochastic framework presented allows us to explore what the probability of extinction is for a city. In figure 4.1 we simulated 200,000 realizations of our stochastic model with the same parameters, but different initial conditions. The area in blue represents the simulations where the city went extinct. As we expected, with low initial conditions, the probability of extinction increases. The dark red represents the simulations where the city established a high level of built infrastructure. The simulations at the border between the upper blue region and the lower red region represent the cities that have become established, but have not reached the same level of infrastructure as the cities in red: they are at greater risk of becoming extinct in the future.

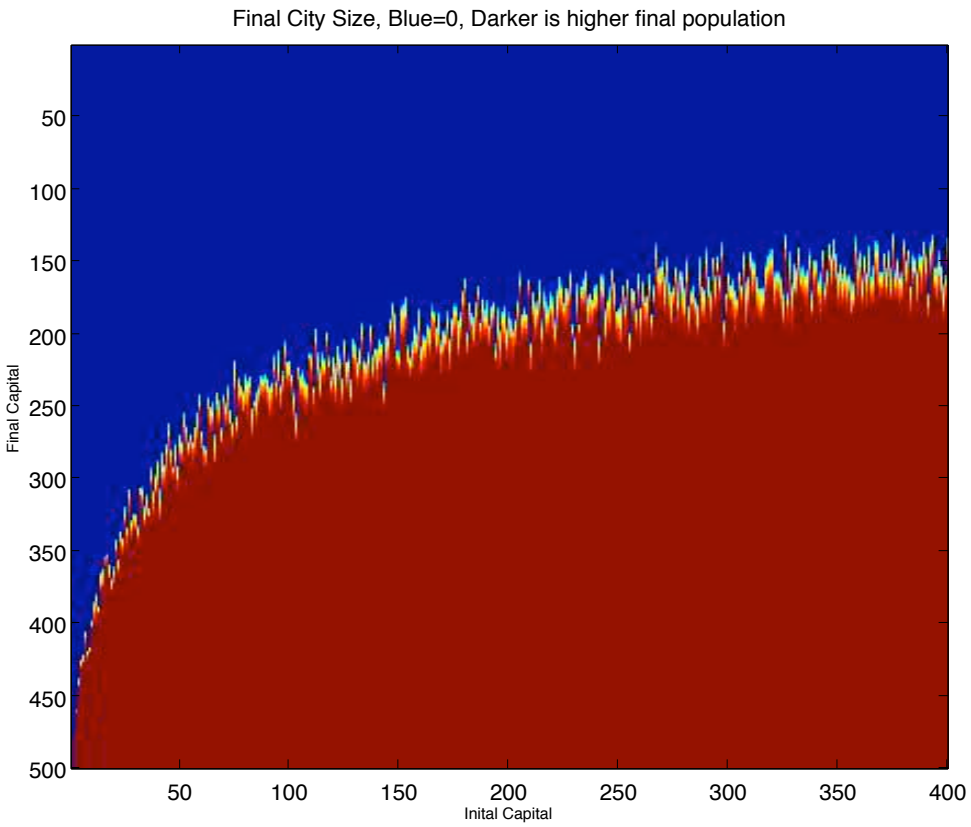


Figure 4.1: As we allow the marginal utility with respect to natural amenity vary as a random variable, the final city population size N^{∞} and capital level K^{∞} vary, but not according to a scaling law analogous to Zipf's Law.

As the initial level of capital decreases, the probability of extinction increases (the area in blue). The probability of extinction decreases rapidly as the initial capital level increases, but plateau's quickly and never reaches 100%. Because the model presented has only one absorbing state (the extinction equilibrium), eventually all simulations will become extinct. However, the time to extinction can be

so large that it effectively never happens. In the absence of major disasters, a city that has survived the early stages and is in the basin of attraction of a prosperous city will persist. However, diseases are one such disaster that have been responsible for a large number of human deaths throughout history. In the next and subsequent chapters, we will explore the dynamics of a disease that also thrives in cities.

Chapter 5

Cities in Ecology: Diseases - Why Context Matters

This history of society is intimately linked with the history of diseases. In this chapter we discuss the role of the urban ecology on dengue fever. Many attempts to control dengue have been made, and they have all failed. This chapter outlines some of the major challenges facing any control program and highlights the role mathematical modeling has played in epidemiology.

5.1 Diseases

Diseases have been with us since before recorded history and two of the deadliest diseases today are also two of the oldest: 1) there is evidence of Tuberculosis in fossile records over 500,000 years ago [Lloyd, R., 2008], 2) Malaria may be responsible for half of all deaths since the bronze age [Shah, 2010, Shah, S., 2010].

For millenia we have been at the mercy of these diseases with little recourse. There are several ancient texts which have documented diseases and their treatments including *Nei Ching* (the Chinese, “Canon of Medicine"), biblical texts, and the works of Hippocrates. However, until the advent of vaccines, the only method we had to “control" the spread of a disease has been improved hygiene and social distancing (quarantine). Although there is evidence of inoculation in China circa 1000, the vaccine as we know it today was introduced in the 1700s to combat smallpox [The College of Physicians of Philedelphia, 2012]. Since then, disease eradication, the great promise of the vaccine, has been largely unrealized. Thus far only smallpox and rinderpest (a disease that primarily infects livestock) have been eradicated despite many campaigns against polio, malaria, and many others. However, many diseases do not have vaccines including dengue fever.

5.2 Dengue

The history of dengue is fraught with ambitions, but failed attempts to eradicate the vector *mainly* responsible for the transmission of dengue fever, *Ae. ae-*

gypti [Gubler and Kuno, 1997, Gubler and Clark, 1996]. As urban centers grow, the likelihood of any successful eradication program diminishes due to the complexity of implementing any control program. There were various political, logistical and ecological issues that prevented the full eradication of *Ae. aegypti* and that have allowed its re-infestation since the mid 1960's [Arias, J.R., 2002, Soper, F.L., 1967]. In the absence of an effective vaccine, most control strategies have centered around eliminating the vector that spreads the dengue.

Vector Control Strategies

The habitat of dengue is the vector-host ecosystem (set in an urban physical and social environment). *Ae. aegypti* have several unique behavioral patterns that make them well suited to spreading dengue including: 1) they are anthropophilic, that is, they feed preferentially on humans which makes them more likely to expose humans to the dengue virus; 2) frequent ovipositions during a single egg laying cycle [Scott *et al* 2000], thus enabling a single infected vector to distribute its eggs to several breeding sites throughout the urban environment. The latter effect poses a particular problem to controlling the disease since identifying and clearing a breeding site of mosquito larvae can be challenging in urban environments.

Source Reduction

Classic source reduction is a type of control program aimed at reducing viable breeding sites. It is conducted by trained inspectors under expert supervision. It is a top-down or vertical governmental program [Reiter and Gubler, 1997] and requires careful surveillance and record keeping. Many common breeding sites are easily identified and eliminated either through removal of the container, application of insecticides, sealing or storing in a dry location [Petit *et al* 2010]. Classic source reduction is only effective with thorough, inquisitive and tenacious inspectors. Finding less common containers takes incrementally more work to elimi-

nate marginally fewer breeding sites. Despite the most well trained inspectors, it is difficult not to fall into routines and miss the more exotic or ephemeral containers [Gubler and Kuno, 1997]. Inspections can also be a stressful occupation as indoor inspections can become contentious, large cisterns or other containers are also used to store fresh water, and many containers are items of perceived utility to the household (old appliances, car parts or tires). Furthermore, all of these issues become exasperated as the programs become more successful. They are viewed as expensive and unnecessary invasions of privacy and can even become difficult positions to staff when there has not been an outbreak in the recent past [Reiter and Gubler, 1997]. Thus, they are inherently unsustainable since success induces a negative feedback - there is less willingness to endure the hardships of a strict control policy when the problem has been ameliorated (but not yet eliminated).

There has been an increasing desire to shift from paid inspectors to a community-based approach [Gubler and Clark, 1996]. In theory this shift is cost-effective as the community takes on the burden of surveillance as a civic responsibility. In practice, however, there may be poor recognition of rarer breeding sites and local knowledge and attitudes may clash with the public health agenda [Gubler and Clark, 1996]. Aside from issues of the complexity of the mosquito life cycle, there may be a fundamental disassociation between source reduction strategies, contact with vectors and the manifestation of dengue. Source reduction focuses on the removal of eggs and larvae, an aquatic animal. There may be several species of mosquitoes and biting flies or other pests that are not impacted by source reduction strategies. *Ae. aegypti* is an elusive mosquito and difficult to notice even when it is biting a host; thus the connection between dengue prevalence and the vector, among so many other flying pests, is not necessarily clear. While there has been some work to use spatial modeling to elucidate this connection, applications to dengue have been limited [Eisen and Eisen, 2008].

Often, there is no clear observable response between source reduction and the reduction of dengue prevalence. Furthermore, in poorly implemented source reduction strategies, the only observable impacts on the community are negative: increased burdens on their time, dissonance between public health “education" and traditional/empirical knowledge [Reiter and Gubler, 1997]. Any control strategy requires feedback, and the feedbacks of this strategy, as it is often implemented, precludes its success.

Insecticides

In addition to control of the egg/larval stage, it is important to control adult mosquitoes. Residual insecticides stick to surfaces, are often sprayed indoors, and kill adult mosquitoes if they land on sprayed surfaces. While effective, it is labor intensive to spray all the indoor surfaces that *Ae. aegypti* might hide on. Impregnated bed nets are sometimes used but are of limited effect because *Ae. aegypti* tends to bite during the day. Personal application of the repellant N,N-diethyl-meta-toluamide (DEET) can be very effective for visitors, but care must be taken with children and it may not be cost-effective for the local population [Reiter and Gubler, 1997].

There are also many programs that employ outdoor spraying of insecticides. Aerosols insecticides are often sprayed at low densities (ULV) that are effective at killing adult mosquitoes but insufficient to kill larvae in water. It may be delivered via airplane, ground vehicle or by hand. This is often the method of choice during an outbreak or whenever the public perceives an increased density of mosquitoes [Reiter and Gubler, 1997]. While effective in temporarily reducing the number of mosquitoes, the most important effect of these spraying programs is in easing public perception of risk and convincing them that the government is doing something [Reiter and Gubler, 1997]. Although there will be a reduction in overall mosquito density temporarily (one to several weeks), the female *Ae. aegypti* is

often found hiding indoors and thus will be protected from these programs [Amcroft *et al* 2001]. If females survive and the larvae in the breeding pools are unaffected, the total mosquito population can be replenished quickly. Furthermore, ineffective spraying programs can lead to increased levels of insecticide resistance in mosquitoes[Reiter and Gubler, 1997, Hemingway and Ranson, 2000].

The Growing Problem: Urbanization

As many cities face rapid urbanization, there is a proliferation of breeding sites: flower pots, rain gutters, fresh water containers, ditches, old tires and discarded appliances etc [Gubler and Kuno, 1997]. Densification also leads to the same breeding site being closer to a higher density of hosts. Thus urbanization can directly contribute to an increase in the suitable habitat for the vector [Reiter and Gubler, 1997] despite strong source reduction campaigns. Singapore has had one of the more successful control programs. It was called an example for other countries by PAHO [Reiter and Gubler, 1997]. Frequent inspections, large fines and slum clearance led to the reduction of the number of indigenous dengue transmissions. However, as the nation grew more affluent, they imported labor from the surrounding areas and regional travel became more common. As standards of living increased, so did the expectations of privacy and the burden of inspectors became more onerous. Thus, public support for spraying programs waned. The short term effect was to increase the pool of susceptible individuals in Singapore. Dengue outbreaks were still prevalent outside the national boundaries of Singapore and it was only a matter of time before dengue made a resurgence in Singapore [Ooi et al., 2006, Reiter and Gubler, 1997].

Control programs cannot be abandoned after they are initiated, even if they have been “successfull" for some time. Dengue fever outbreaks demonstrate strong seasonal trends [Chowell, G. and Sanchez, F., 2006, Chowell, G. *et al*]. The determinants of this temporal pattern include temperature and precipitation patterns.

Temperature impacts the rate that the vector and the virus develop. The rain inundates ephemeral breeding sites and makes them viable. However, there is some evidence that the “dry season" and droughts are also correlated with outbreaks [Sanchez et al., 2006]. At these times, local residents are more inclined to store freshwater and rain runoff which provide additional breeding sites that are distributed near dwellings.

Going to school is another human behavior that may contribute to dengue outbreaks. In Mexico, prior to the start of the school year, rainwater may have been allowed to collect in various breeding sites around the school. The high concentration of children in classrooms produces elevated levels of carbon dioxide that may attract the vectors [Hernandez-Suarez, C.M., 2009]. Also, children must wear uniforms that includes skirts for girls and shorts for boys during the warmer months. All of these factors may contribute to the seasonal outbreaks of dengue associated with the school year. A test program was initiated where local janitors and parents where presented with source reduction information and techniques. The application of these techniques was able to dramatically decrease the prevalence of dengue in the test region. However, the lack of financial support caused the program to be abandoned [Hernandez-Suarez, C.M., 2009]. The next seasonal outbreak of dengue was stronger in the test region than any of the surrounding areas.

Finding a Solution

It is important to understand the customs and practices of the people in the urban environment before a control program is initiated. This understanding will yield a more complete picture of the type and distribution of potential breeding sites [Pacheco-Coral, A.P. *et al* 2010]. No control program can be sustainable without considerable effort and support by both local communities and the government [Gomez-Dantes, H. and Willoquet, J.R., 2009, Paz-Soldan, V.A. *et al* 2009].

The history of dengue is fraught with ambitions, but failed attempts to eradicate the vector *m*ainly responsible for the transmission of dengue fever, *Ae. aegypti*. We close this chapter the same we started it, with a reiteration of the challenge to combat dengue. As urban centers grow, the likelihood of any successful eradication program diminishes. The sheer number and distribution of breeding sites makes any eradication campaign prohibitively expensive from a governmental standpoint. Perhaps the best alternative is to engage the community and have them share in the responsibility of vector control. Understanding the local ecology of the vector, and hosts, will be critical in tackling dengue at the local level [Aldstadt, J. *et al* 2011]. Although the remainder of this dissertation will be focused on the more abstract problem of the mathematical description of dengue fever, it is done so with the intention that any successful effort in controlling dengue must be a collaborative effort across the scientific, political, social and environmental landscapes. Global climate change facilitates the proliferation of *Ae. aegypti*. As the mosquito spreads, so does the hazard of dengue outbreaks. It has never been more urgent that we take steps to understand and prevent dengue outbreaks.

Chapter 6

Cities in Ecology: Diseases - A Case Study with Dengue

6.1 Introduction

Dengue is considered one of the most important emerging and re-emerging infectious diseases. According to the World Health Organization, 40% of the global population is at risk of dengue infection with an estimate of 50 to 100 million infections yearly including 500,000 cases of dengue hemorrhagic fever (DHF) and 22,000 deaths, mostly in children. Dengue has attracted some recent popular press for potential cases in the US [Kok, Y., 2010, CDC, 2010] and a large number of cases internationally [Morens and Fauci, 2008]. Dengue is considered one of the most important emerging and re-emerging infectious diseases [WHO, 2010]. Dengue virus belongs to the genus *Flavivirus*, family *Flaviviridae* [Duebel, V. *et al* 1986] and has four antigenically distinct serotypes (DENV-1, DENV-2, DENV-3 and DENV-4). The pathogenicity of the disease ranges from asymptomatic and mild dengue fever (DF) to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which primarily affects children [Nguyen, H. T., *et al* 2006, Halstead, S.B., *et al* 2002]. Dengue is a vector borne disease transmitted primarily by the mosquito *Aedes aegypti*, which has spread to a vast majority of countries in the tropics and sub-tropics [Harris, E., *et al.* 2000]. The secondary vector, *Ae. albopictus*, has a range that reaches farther north than *Ae. aegypti* and there are reports that its eggs adapt better to subfreezing temperatures which increases the risk of dengue outbreak in the US [Hawley, *et al*]. This risk could also be increased due to vertical transmission from infected females to eggs. Although previous studies suggested that vertical transmission of dengue was not possible[Siler J.F., *et al* 1926, Simmons J.S. *et al*, 1931] , recent findings have demonstrated that vertical transmission is feasible in captivity and in the wild in both *Ae. aegypti* and

Ae. albopictus species [Arunachalam, N. *et al* 2008, Cecilio A.B. *et al* 2009, Kow, C.Y. *et al* 2001, Gunther, J. *et al* 2007, Rosen L. *et al* 1983].

Differences in disease severity have been associated with particular serotypes and genotypes posing the question that some specific genotypes are more pathogenic than others [Halstead, S.B., 2006, Kyle and Harris, 2008]. Out of the four dengue serotypes, dengue outbreaks, DHF and DSS have been mostly associated with DENV-2 [Montoya Y. *et al* 2003, Rico-Hesse, R. *et al* 1997, Sittisombut, N. *et al* 1997, Zhang, C. *et al* 2006]. Infection with one serotype does not usually protect against the others, and while a secondary infection with a heterologous serotype *increases* the probability of DHF and DSS[1] [Burke, D.S. *et al* 1998, Halstead, S.B. *et al* 1970], there are also reports that indicate a primary infection can also be responsible for severe dengue cases [Barnes, W.J.S. and Rosen, L., 1974, Harris, E. *et al* 2000, Gubler, D.J. *et al* 1978, Rosen, L., *et al* 1977, Scott, R.M.N. 1976]. Because of the association of a specific genotype of DENV-2, Asian genotype, to dengue outbreaks and DHF or DSS in young children, the identification of specific DENV-2 genotypes has become one of the priorities in the study of epidemiology of the disease [Lewis, J.A. *et al* 1993, Montoya, Y. *et al* 2003, Rico-Hesse, R. *et al* 1997, Rico-Hesse, R. *et al* 1998, Sittisombut, N. *et al* 1997, Zhang, C. *et al* 2006].

Although many mathematical and statistical approaches have been conducted to study dengue [Nishiura, H., 2006], vertical transmission as a key factor has not been explored. In this paper we investigate how vertical transmission can cause one genotype of DENV-2 to outcompete or invade an area already endemic with a different genotype of DENV-2. We derive the critical proportion of vertical transmission as a function of the virulence of each genotype necessary for successful invasion. This may explain the displacement of DENV-2 American genotype by the Asian genotype as well as the speed and severity of dengue outbreaks in coun-

[1] A process sometimes called original antigenic sin or antibody-dependent enhancement.

tries like Peru where the DENV-2 Asian genotype was first introduced during the 2000-2001 epidemic [Montoya, Y. *et al* 2003]. Prior to the appearance of DENV-2 Asian genotype in the northwestern coastal city of Tumbes, only DENV-1 and DENV-2 American genotype were circulating in Peru [Kochel, T.J. *et al* 2002, Montoya, Y. *et al* 2003]. The absence of DHF and DSS in the northeastern Peruvian city of Iquitos prior to 2000 could be due to the cross-immunity conferred by DENV-1 against DENV-2 American genotype but not to the DENV-2 Asian genotype [Kochel, T.J. *et al* 2002]. This cross-immunity might also increase the pool of individuals susceptible to DENV-2 Asian genotype since they would not have had exposure to DENV-2 American genotype, and hence protection against DENV-2 Asian genotype.

Our model suggests that vertical transmission is an important mechanism that should be taken into consideration for the prediction and control of dengue outbreaks. In the absence of an effective vaccine, worldwide efforts should be focused on monitoring not only the disease but also the Aedes mosquitoes, both males[2] and females, and the DENV genotype that is being carried and transmitted.

6.2 Mathematical Model

There have been many attempts to gain insight into diseases using mathematical models and vector borne disease (like malaria and dengue) were first modeled by Ross (1910) and later Macdonald (1957). Nishiura (2006) reviews several modeling efforts specifically on dengue. We expand on the simplest model for dengue presented by [Nishiura, H., 2006]. Our model includes a progression to DHF, and for simplicity we ignore deaths due to DHF (see Figure 6.1). Another important difference is that we consider two genotypes of dengue circulating concurrently in both the host and vector populations. In general, the more severe cases of DHF and DSS are thought to be caused by a secondary infection with

[2]To estimate the contribution of vertical transmission to the prevalence of dengue in the mosquito population.

a heterologous strain, see [Sangkawibha, N. *et al* 1984, Halstead, S.B., 1988]. In this model we are only considering an outbreak of DENV-2, thus the prevalence of all other serotypes is assumed constant. We employ the mathematical epidemiology framework using an SIR model for the host and SI for the vector (see [Nishiura, H., 2006] for an introduction to this framework in the context of Dengue). Then the host system is described by S, the class of susceptible humans, D_{Am}, the class of humans infected with genotype American, D_{As}, the class of humans infected with genotype Asian, H, the class of humans that progress to DHF, and R, the class of recovered humans (see Figure 6.1). Vertical transmission is only present in the vectors infected with DENV-2 Asian (see Figure 6.2).

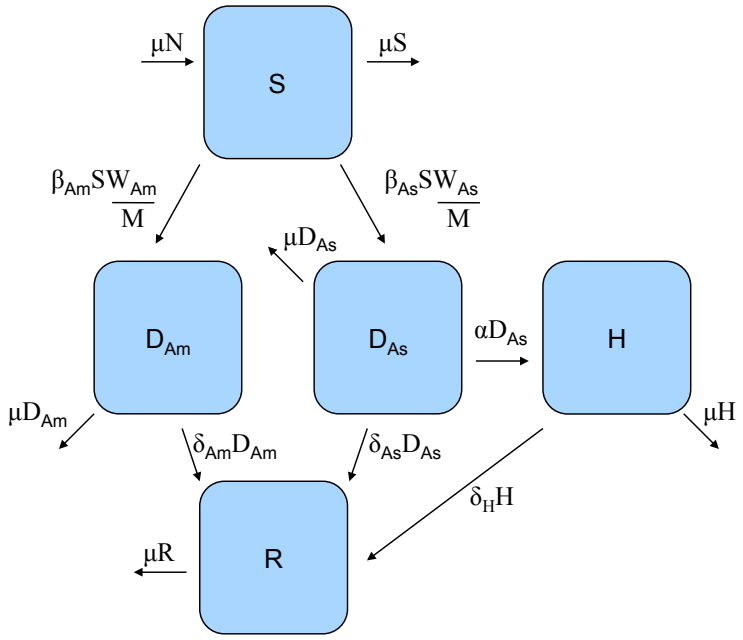


Figure 6.1: Host model. Only individuals infected with genotype Asian progress to DHF in this model.

All of the parameters are assumed to be positive constants and the natural birth/death rate of humans is μ, the rate that humans become infected with genotype American or Asian from mosquitoes is β_{Am} and β_{As}, respectively. The rate that infections develop into DHF is α, and we assume only individuals in-

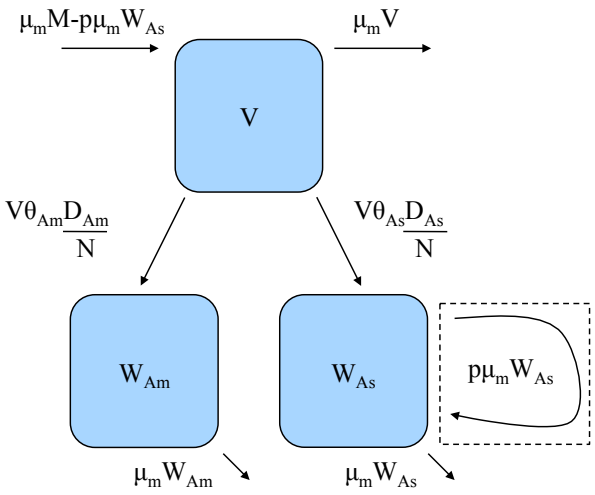


Figure 6.2: Vector model. Vertical transmission only occurs in mosquitoes infected with genotype Asian.

fected with genotype DENV2-Asian can progress to DHF after presenting DF like symptoms. The rate that humans recover from infection from either genotype American, Asian or DHF is δ_{Am} ,δ_{As}, and δ_{H}, respectively. N is the total human population size and M is the total vector population size. It is assumed that once a person has been diagnosed with DHF, that person will be hospitalized and their potential to spread dengue to vectors is negligible. The natural birth/death rate of mosquitoes is μ_m, p is the proportion of mosquitoes that are infected through vertical transmission, θ_{Am} is the rate mosquitoes get infected with genotype American and θ_{As} is the rate mosquitoes get infected with genotype Asian. These parameters are summarized in Table 6.1. The system of nonlinear differential equations is:

Table 6.1: Model parameters

Parameter	Definition
μ	human natural birth/death rate
β_{Am}	infectious rate from vectors to hosts, strain American
β_{As}	infectious rate from vectors to hosts, strain Asian
δ_{Am}	recovery rate from strain American
δ_{As}	recovery rate from strain Asian
δ_{H}	recovery rate from strain DHF
α	progression rate to DHF from strain Asian
μ_{m}	natural mortality rate of vectors
θ_{Am}	infectious rate from hosts to vectors, strain American
θ_{As}	infectious rate from hosts to vectors, strain Asian
p	proportion of vectors infected via vertical transmission

$$\dot{S} = \mu N - \frac{\beta_{Am} S W_{Am}}{M} - \frac{\beta_{As} S W_{As}}{M} - \mu S \tag{6.1}$$

$$\dot{D}_{Am} = \frac{\beta_{Am} S W_{Am}}{M} - (\delta_{Am} + \mu) D_{Am} \tag{6.2}$$

$$\dot{D}_{As} = \frac{\beta_{As} S W_{As}}{M} - (\delta_{As} + \alpha + \mu) D_{As} \tag{6.3}$$

$$\dot{H} = \gamma_{As} \alpha_{As} D_{As} - (\delta_{H} + \mu) H \tag{6.4}$$

$$\dot{R} = \delta_{Am} D_{Am} + \delta_{As} D_{As} + \delta_{H} H - \mu R \tag{6.5}$$

$$\dot{V} = \mu_{m} M - p \mu_{m} W_{Am} - \frac{V \theta_{Am} D_{Am}}{N} - \frac{V \theta_{As} D_{As}}{N} - \mu_{m} V \tag{6.6}$$

$$\dot{W}_{Am} = \frac{V \theta_{Am} D_{Am}}{N} - \mu_{m} W_{Am} \tag{6.7}$$

$$\dot{W}_{As} = \frac{V \theta_{As} D_{As}}{N} + p \mu_{m} W_{As} - \mu_{m} W_{As} \tag{6.8}$$

Basic Reproductive Number

We rescale the model and will refer to each class as the proportion of the total population. Furthermore, we assume that all infected individuals recover at the same average rate δ. If we consider our model to contain infections from DENV-

2 American only, then the reproductive number is

$$\mathscr{R}_0^{Am} = \sqrt{\frac{\beta_{Am}}{\delta+\mu}\frac{\theta_{Am}}{\mu_m}},$$

derived using the next generation operator (see Appendix 6.4). The square root indicates that this is a “two-step" process, i.e. in order for a human to cause another human to be infected, a mosquito must first be infected. $\frac{1}{\delta+\mu}$, is the average infectious period and β_{Am} is the transmission rate (host to vector). Similarly, θ_{Am} is the transmission rate from vectors to hosts. If $\mathscr{R}_0 > 1$ we expect an outbreak of DF in our population.

If DENV-2 Asian is the only genotype present, the reproductive number is

$$\mathscr{R}_0^{As} = \frac{p}{2} + \sqrt{\left(\frac{p}{2}\right)^2 + \frac{\beta_{As}}{(\delta+\alpha+\mu)}\frac{\theta_{As}}{\mu_m}}.$$

There are four components to $\mathscr{R}_0^{As}$: $\frac{\theta_{As}}{\mu_m}$ is the contribution to the reproductive number from infected mosquitoes, the infectious force of mosquitoes times the average time spent in the infectious class; $\frac{\beta_{As}}{\delta+\alpha+\mu}$ is likewise the infectious force of humans times the average time spent in the infectious class; $\left(\frac{p}{2}\right)^2$ is the indirect contribution from vertical transmission, that is, from infections caused by mosquitoes that were born with dengue; $\frac{p}{2}$ is the direct contribution from vertical transmission infectious mosquitoes create more infectious mosquitoes by giving birth to them, not through infecting humans. When we had only DENV-2 American, dengue transmission was “two step" process because in order for an infected mosquito to infect more mosquitoes, it had to first infect a human. Now, when we have DENV-2 Asian, dengue transmission has contributions from a “two step" and “one step processes. The “one step," or direct, transmission is due to vertical transmission alone and includes the direct generation of infected mosquitoes by other infected mosquitoes via birth. The “two step," or indirect transmission is due to both vertical transmission and horizontal transmission (infection via vector-host transmission). The impact of vertical transmission has been split in

half, averaged, into direct and indirect components with the “two step" process being the *geometric* average of the vertical and horizontal components.

Then the basic reproductive number of our entire model, defined as the average number of secondary cases produced by a typical infectious individual in a *mostly susceptible* population, is the maximum of the two reproductive numbers

$$\mathcal{R}_0 = max[\mathcal{R}_0^{Am}, \mathcal{R}_0^{As}].$$

We compare the two reproductive numbers and find the critical value of the vertical transmission coefficient p_{crit} that dictates when DENV-2 Asian dominates, $\mathcal{R}_0^{As} > \mathcal{R}_0^{Am}$. First let us define the reproductive number for Asian as a function of p

$$\mathcal{R}_0^{As}(p) = \frac{p}{2} + \sqrt{\left(\frac{p}{2}\right)^2 + \frac{\beta_{As}}{(\delta+\alpha+\mu)}\frac{\theta_{As}}{\mu_m}}. \tag{6.9}$$

Then,

$$\mathcal{R}_0^{As}(0) = \sqrt{\frac{\beta_{As}}{(\delta+\alpha+\mu)}\frac{\theta_{As}}{\mu_m}}.$$

If we assume that DENV-2 American and DENV-2 Asian are equally virulent *ceteris paribus*, then

$$p_{crit} = \frac{\alpha}{\delta+\alpha+\mu}\mathcal{R}_0^{Am}.$$

Thus vertical transmission must balance the proportion of individuals who progress to DHF (since we assume they do not transmit infection). Note that if $\alpha = 0$, then any level of vertical transmission would cause DENV-2 Asian to dominate. This is as expected since if they are completely identical except one strain has an additional mechanism to spread, then it will out compete the other strain. However, if we assume DENV-2 Asian is more virulent, as the data suggests, then it becomes even less likely that DENV -2 American will dominate DENV-2 Asian and this may explain why DENV-2 Asian tends to out compete DENV-2 American wherever the two strains co-circulate [Rico-Hesse, R. *et al* 1997, Montoya, Y. *et al* 2003]. In this case, the general form for the critical value of vertical transmission

is

$$p_{crit} = \frac{\left(\mathcal{R}_0^{Am}\right)^2 - \left(\mathcal{R}_0^{As}(0)\right)^2}{\mathcal{R}_0^{Am}}, \tag{6.10}$$

and whenever $p > p_{crit}$, $\mathcal{R}_0^{As} > \mathcal{R}_0^{Am}$. For a fixed value of $\mathcal{R}_0^{As}$ and $\mathcal{R}_0^{Am}$, Figure 6.3 shows how large p must be for $\mathcal{R}_0^{As} > \mathcal{R}_0^{Am}$. Alternately we can fix p at some value and for a given value of $\mathcal{R}_0^{Am}$, if the value of $\mathcal{R}_0^{As}$ is above the line, then $\mathcal{R}_0^{As} > \mathcal{R}_0^{Am}$. If $p = 0$ (solid line), then we need $\mathcal{R}_0^{As}(0) > \mathcal{R}_0^{Am}$. However, as we increase p to 0.5 (dotted line), or even to 1 (dashed line), then we see $\mathcal{R}_0^{As}(0) < \mathcal{R}_0^{Am}$ and still $\mathcal{R}_0^{As} > \mathcal{R}_0^{Am}$, since $\mathcal{R}_0^{As}$ needs to only be above the line. Thus increases p can decrease the threshold required for DENV-2 Asian to outcompete DENV-2 American.

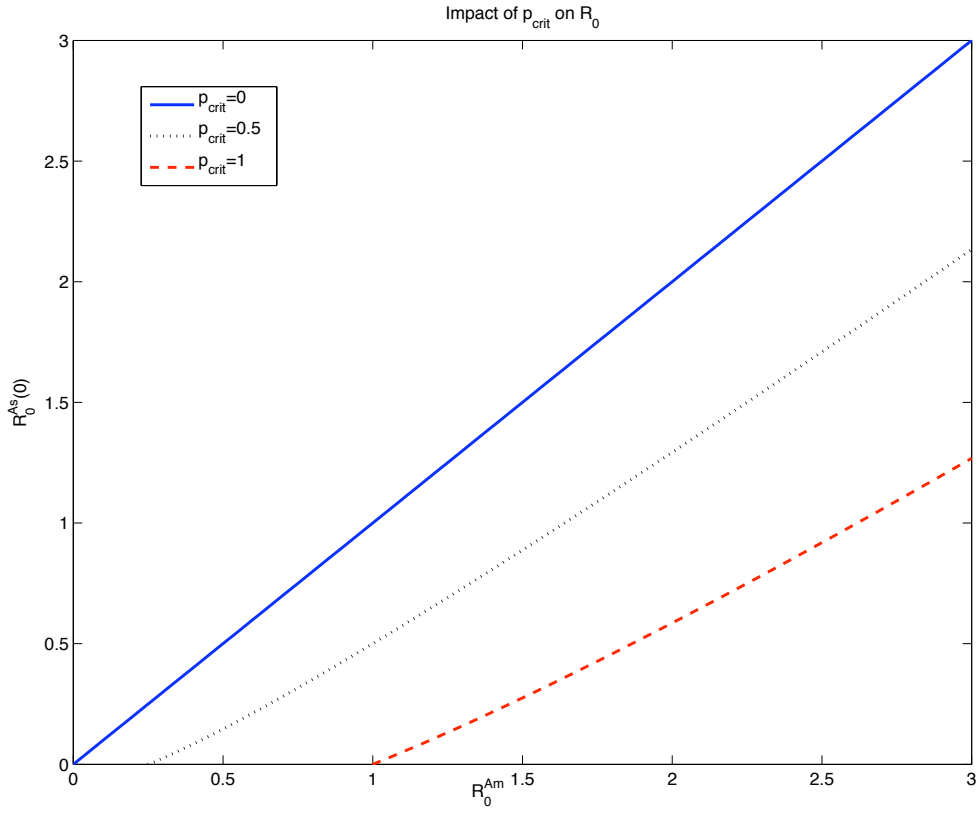


Figure 6.3: The region where DENV-2 Asian genotype outcompetes DENV-2 American genotype is represented by the area above the line for a fixed p_{crit}. For a fixed $\mathcal{R}_0^{As}(0)$ and $\mathcal{R}_0^{Am}$, if p is greater than p_{crit}, graphed, then DENV-2 Asian dominates DENV-2 American. Conversely, if $p = 0$ (the solid line), then $\mathcal{R}_0^{As} > \mathcal{R}_0^{Am}$ if $\mathcal{R}_0^{As}(0) > \mathcal{R}_0^{Am}$. As we increase p to 0.5 (the dotted line), we see that $\mathcal{R}_0^{As}(0)$ can be less than $\mathcal{R}_0^{Am}$ and still $\mathcal{R}_0^{As} > \mathcal{R}_0^{Am}$. If we further increase p to 1 (the dashed line), then DENV-2 American must be much much stronger than DENV-2 Asian in order for DENV-2 American to outcompete DENV-2 Asian.

Equilibria

There are three equilibria in our system. Competitive exclusion precludes a coexistence equilibrium. We have a disease free equilibrium (DFE), an DENV-2 American equilibrium (EAM) and an DENV-2 Asian equilibrium (EAS). The DFE is

$$\begin{aligned} S^* &= 1 \\ D_{Am}^* &= 0 \\ D_{As}^* &= 0 \\ H^* &= 0 \\ R^* &= 0 \\ V^* &= 1 \\ W_{Am}^* &= 0 \\ W_{As}^* &= 0. \end{aligned} \tag{6.11}$$

The DFE always exists and is locally asymptotically stable whenever $\mathcal{R}_0 < 1$, see Appendix 6.4. Further, we can use a Lyapunov function to show that the DFE is globally asymptotically stable if $\mathcal{R}_0 < 1$, see Appendix 6.6. For the EAM,

$$\begin{aligned} S^* &= \frac{\mu\beta_{Am} + \mu_m(\delta+\mu)}{\theta_{Am}(\beta_{Am}+\mu)} \\ D_{Am}^* &= \frac{\mu\mu_m\left(\left(\mathcal{R}_0^{Am}\right)^2 - 1\right)}{\theta_{Am}(\beta_{Am}+\mu)} \\ D_{As}^* &= 0 \\ H^* &= 0 \\ R^* &= 1 - S^* - D_{Am}^* \\ V^* &= 1 - W_{Am}^* \\ W_{Am}^* &= \frac{\mu\left(\left(\mathcal{R}_0^{Am}\right)^2 - 1\right)}{\theta_{Am}\mu\left(\mathcal{R}_0^{Am}\right)^2 + \beta_{Am}} \\ W_{As}^* &= 0. \end{aligned} \tag{6.12}$$

The EAM only exists if $\mathscr{R}_0^{Am} > 1$ and Section 6.2 will determine its stability. For EAS,

$$\begin{aligned}
S^* &= \frac{\beta_{m2}\mu + \mu_m(\delta+\alpha+\mu)(1-p)}{\beta_{m2}(\beta_{As}+\mu)} \\
D_{Am}^* &= 0 \\
D_{As}^* &= \frac{\mu\mu_m\mathscr{R}_0^{As}(0)^2 + p - 1}{\beta_{m2}(\beta_{As}+\mu)} \\
H^* &= \frac{\mu\mu_m\alpha\mathscr{R}_0^{As}(0)^2 + p - 1}{\beta_{m2}(\beta_{As}+\mu)(\delta+\mu)} \\
R^* &= 1 - S^* - D_{As}^* - H^* \\
V^* &= 1 - W_{As}^* \\
W_{Am}^* &= 0 \\
W_{As}^* &= \frac{\mu\mu_m\mathscr{R}_0^{As}(0)^2 + p - 1}{\mu\mathscr{R}_0^{As}(0)^2(1+\frac{\mu_m}{\beta_{As}}) + 1 - p}.
\end{aligned} \tag{6.13}$$

The EAS only exists if $\left(\mathscr{R}_0^{As}\right)^2(0) > 1$ and its stability is determined below.

Invasion Reproductive Numbers

The invasion reproductive number (derived in Appendix 6.5) for DENV-2 Asian invading DENV-2 American is

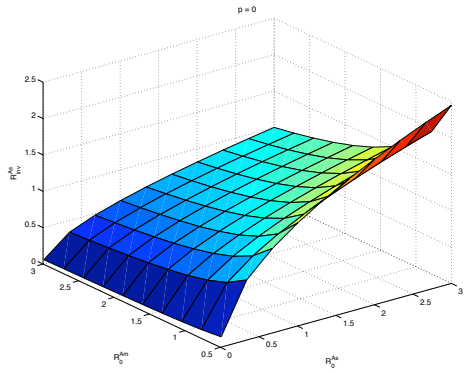
$$\mathscr{R}_{inv}^{As} = \frac{p}{2} + \sqrt{\left(\frac{p}{2}\right)^2 + \left(\frac{\mathscr{R}_0^{As}(0)}{\mathscr{R}_0^{Am}}\right)^2}. \tag{6.14}$$

Note, if $p = 0$, then the invasion reproductive number is simply the ratio of the DENV-2 Asian and DENV-2 American reproductive numbers, as we would expect in a simple competition model. In order for EAM to be locally asymptotically stable, $\mathscr{R}_0^{Am} > 1$ and $\mathscr{R}_{inv}^{As} < 1$. The invasion reproductive number for DENV-2 American invading DENV-2 Asian is

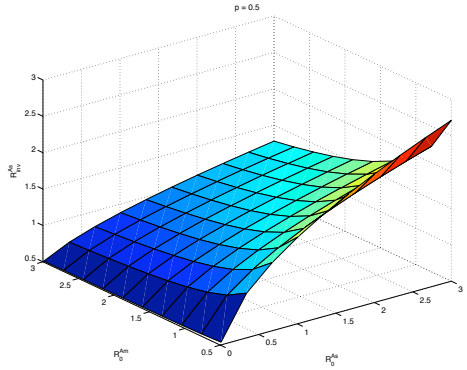
$$\mathscr{R}_{inv}^{Am} = \frac{\mathscr{R}_0^{Am}}{\mathscr{R}_0^{As}(0)}\sqrt{(1-p)}. \tag{6.15}$$

Furthermore, if $p = 1$, then DENV-2 American could never invade. This is because there would always be a reservoir of DENV-2 Asian if the probability of vertical transmission was 100%, although this is highly unlikely. Then EAS is locally asymptotically stable if $\mathcal{R}_0^{As} > 1$ and $\mathcal{R}_{inv}^{Am} < 1$.

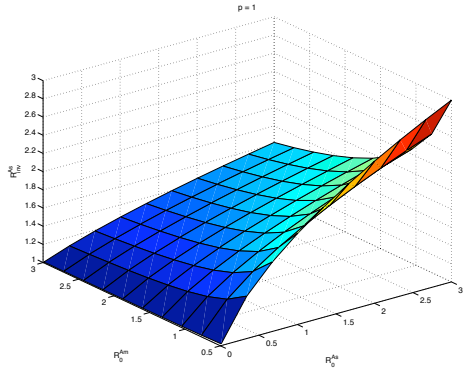
Figure 6.4a shows how $\mathcal{R}_{inv}^{As} < 1$ varies as a function of $\mathcal{R}_0^{Am}$ and $\mathcal{R}_0^{As}(0)$ for $p = 0$. Note that $\mathcal{R}_{inv}^{As} = 1$ when $\mathcal{R}_0^{Am} = \mathcal{R}_0^{As}$. In Figure 6.4b $p = 0.5$ and note how the curve has shifted upwards, making it easier for $\mathcal{R}_{inv}^{As} > 1$. In Figure 6.4c, $p = 1$ and notice how the lowest point of the graph is at 1.



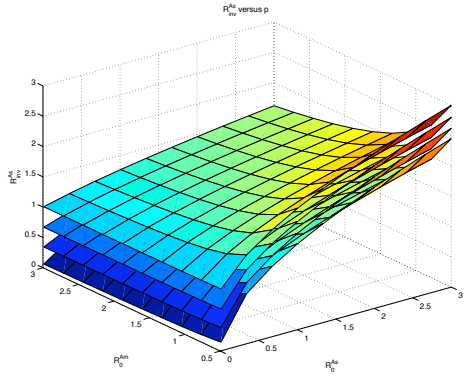
(a) p=0, DENV-2 Asian invades if $\mathcal{R}_0^{As}(0) > \mathcal{R}_0^{Am}$.



(b) Increasing p to 0.5, facilitates DENV-2 Asian to invading as noted by the upward shift of the graph.



(c) As p is further increased to 1, it becomes much easier for DENV-2 Asian to invade.



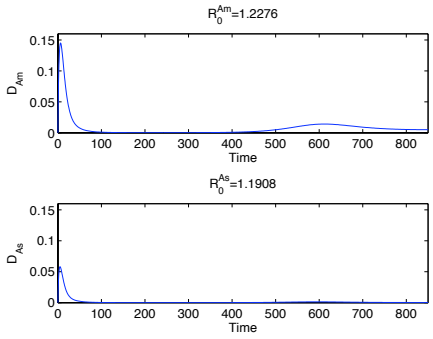
(d) Increasing p shifts upward the manifold for $\mathcal{R}_{inv}^{As}$ as a function of $\mathcal{R}_0^{As}(0)$ and $\mathcal{R}_0^{Am}$.

Figure 6.4: Invasion reproductive number for DENV-2 Asian into DENV-2 American. As p is increased, it becomes easier for DENV-2 Asian to invade DENV-2 American, represented by the upward shift of the graph.

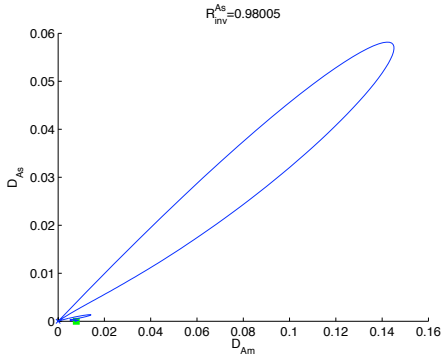
To further illustrate the impact of the invasion reproductive number, we will

play out a scenario where DENV-2 American is endemic in a population and DENV-2 Asian tries to invade. Suppose DENV-2 American is introduced into a region and $\mathcal{R}_0^{Am} > 1$, then we would expect an outbreak and DENV-2 American would remain endemic in the population. This is the situation in Peru prior to 2000. Then suppose DENV-2 Asian is introduced into that same region. It is not enough for $\mathcal{R}_0^{As} > 1$ for there to be an outbreak of DF because not all of the population is suscetible. There is a segment of the population that has been exposed to DF and thus is protected from DENV-2 Asian. Therefore, for there to be an outbreak of DF, $\mathcal{R}_{inv}^{As} > 1$, the situation in Peru after 2000. This scenario is shown in Figures 6.5 and 6.6. We introduce a few infected people with DENV-2 American in a population of mostly susceptible individuals. The DFE (x) is unstable because $\mathcal{R}_0^{Am} > 1$ and the outbreak is dominated by genotype American since $\mathcal{R}_0^{Am} > \mathcal{R}_0^{As}$ (Figure 6.5b). Genotype American is endemic and genotype Asian dies out in this scenario (Figure 6.5a). Then we increase β_{As} such that $\mathcal{R}_{inv}^{As} > 1$. Another outbreak is triggered, but this time it is dominated by genotype Asian (Figure 6.6b. The population started near an endemic level of genotype American (EAM), but now genotype Asian tends to an endemic level (EAS) and genotype American tends to zero (Figure 6.6a).

Similarly, we can illustrate how $\mathcal{R}_{inv}^{Am}$ varies as a function of $\mathcal{R}_0^{Am}$ and $\mathcal{R}_0^{As}(0)$ for fixed p, see Figure 6.7. The top most manifold is when $p = 0$. As $\mathcal{R}_0^{Am}$ increases, $\mathcal{R}_{inv}^{Am}$ increases. When we increase p, the manifold lowers and flattens out until the point when it is flat at $p = 0$. At this point, DENV-2 American is no longer able to invade DENV-2 Asian as no value for $\mathcal{R}_0^{Am}$ will make $\mathcal{R}_{inv}^{Am} > 1$

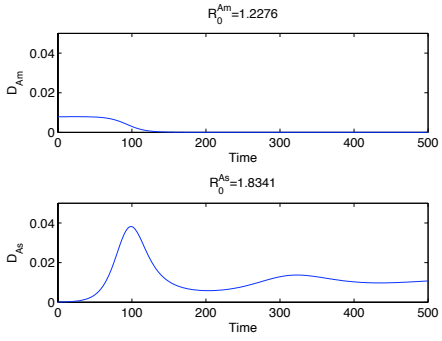


(a) First outbreak is dominated by genotype American since $\mathscr{R}_0^{Am} > \mathscr{R}_0^{As}$.

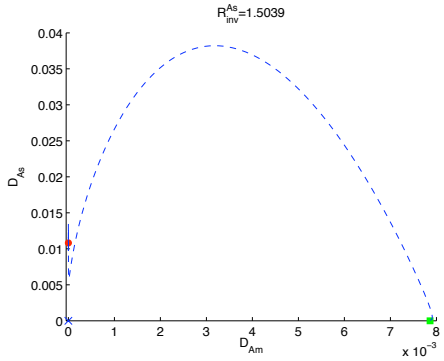


(b) After the initial outbreak, there is an endemic level of genotype American.

Figure 6.5: If $\mathscr{R}_0^{As} < 1$, $\mathscr{R}_0^{Am} > 1$, then EAM is stable as genotype American tends to some endemic level and genotype Asian tends to zero (a). The phase portrait shows the relative prevalence of each genotype (b). The outbreak starts near the origin and eventually tends towards EAM (square).



(a) Second outbreak is dominated by genotype Asian since $\mathscr{R}_0^{As} > \mathscr{R}_0^{Am}$.



(b) After the initial outbreak, there is an endemic level of genotype Asian.

Figure 6.6: If the outbreaks starts near EAM and $\mathscr{R}_{inv}^{As} > 1$, then genotype American tends to zero and genotype Asian tends to an endemic level (a). The phase portrait shows the relative prevalence of each genotype (b). The outbreak starts near EAM (square) and eventually tends towards EAS (circle).

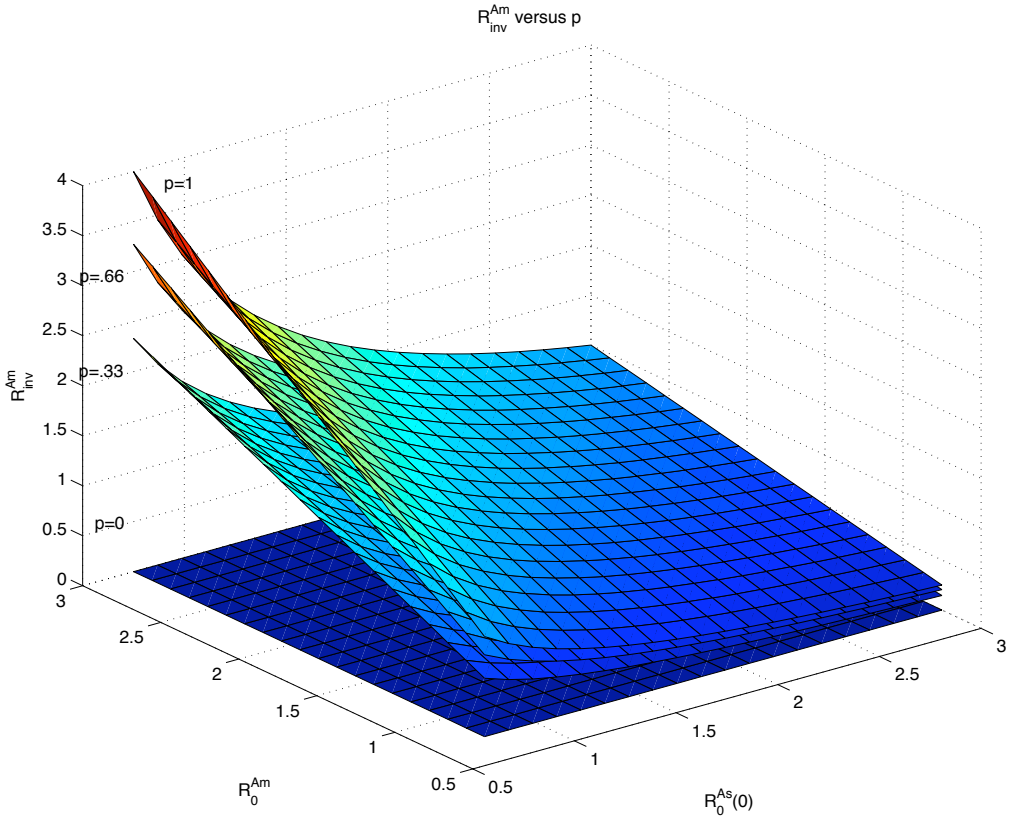


Figure 6.7: As p increases, it becomes more difficult for DENV-2 American to invade DENV-2 Asian, as indicated by the manifold decreasing and flattening out. Ultimately, when $p = 1$, DENV-2 American is no longer able to invade as represented by the bottom most, flat graph.

6.3 Discussion

We have shown that vertical transmission makes a disease more likely to both spread in an area without prior infection, but also to invade an area that is already endemic to that disease. This work builds on an epidemiological framework that shows vertical transmission may be a viable transmission mechanism for dengue in the wild. It also advances mathematical modeling of dengue in particular, and vector-borne diseases in general. Despite the evidence that vertical transmission may be important in dengue, few models have incorporated this feature.

Bernoulli, in 1760, was one of the earliest scholars to mathematically model a disease [Murray, J.D., 2002]. It would be a century later when Ross used his models to study the novel idea of mosquitoes spreading Malaria in 1900's, and a couple more decades before the seminal work of Kermack McKendrick in 1927 [Brauer, F. and Castillo-Chavez, C., 2001, Gumel, A. *et al* 2006]. Over a century after the ground breaking work of Ross, models are still being used to study Malaria [McKenzie and Samba, 2004], dengue [Nishiura, H., 2006], and other vector-borne disease such as West Nile Virus [Cruz-Pacheco, G., *et al* 2004, Bowman, C. *et al* 2005]. However, vertical transmission in these models is rarely studied, whereas HIV has become the canonical example of vertical transmission in an infectious disease [Anderson, R.M., 1988, Blower and Dowlatabadi, 1994, Soderlund et al., 1999].

Vertical transmission of dengue has been demonstrated to occur both in the wild as well as in laboratory settings [Rosen, L. *et al* 1983, Bosio, C.F. *et al* 1992, Kow, C.Y. *et al* 2001, Gunther, J. *et al* 2007, Arunachalam, N. *et al* 2008, Cecõlio, A.B. *et al* 2009], although the percentage of transovarial transmission in *Ae. aegypti* is low [Hutamai, S. *et al* 2007, Akbar, M.R. *et al* 2008]. Another study showed that mosquitoes infected with DENV-2 through vertical transmission are not only capable of horizontally transmit the virus but that also there was a higher vertical transmission rate of the virus when eggs were incubated for longer times

at room temperature [Mourya et al., 2001]. Overall these studies showed the epidemiological importance of *Ae. aegypti* not only as a vector but also in the maintenance of virus through transovarial passage in nature. Our results show that even a low probability of vertical transmission can have a major impact on the long term dynamics of DF. In the situation where we have two competing genotypes, vertical transmission can make the difference between a failed outbreak and a successful invasion and ability to become endemic in a population.

Our model was inspired by the 2000-2001 dengue epidemic in the northwest region of Peru. This was the first time that DHF cases were observed in Peru, and DENV-2 Asian genotype was introduced into the country [Montoya, Y. *et al* 2003]. Despite the endemic presence of both DENV-1 and DENV-2 American genotype in Peru, no DHF cases were previously detected, this could be explained by cross-immunity conferred by DENV-1 against DENV-2 American genotype and not the Asian genotype [Kochel, T.J. *et al* 2002]. Moreover, data from the 2000-2001 outbreak in Peru showed that the DENV-2 Asian genotype displaced the DENV-2 American as observed by Restriction Fragment Length Polymorphism (RFLP) analysis and corroborated by partial sequence analysis [Montoya, Y. *et al* 2003]. Displacement of DENV-2 American by the Asian genotype has previously been documented in the Americas to be associated to the appearance of DHF in Cuba [Guzman, M.G. *et al* 1995], , Jamaica, Venezuela, Colombia, Brazil and Mexico [Rico-Hesse, R. *et al* 1997]. [Rico-Hesse et al., 1997] We proposed that displacement of the DENV-2 American genotype could be in part due to vertical transmission of the virus to the progeny, eggs could survive the inter-epidemic season and hatch already containing the virus. This proposition is supported by both the basic and invasion reproductive numbers calculated in this paper.

In an area where neither DENV-2 genotype Asian or American is present, the basic reproductive number is simply the maximum of the two, genotype specific,

reproductive numbers

$$\begin{aligned}
\mathscr{R}_0 &= \max\left[\mathscr{R}_0^{Am}, \mathscr{R}_0^{As}\right] \\
\mathscr{R}_0^{Am} &= \sqrt{\frac{\beta_{Am}}{\delta+\mu}\frac{\theta_{Am}}{\mu_m}} \\
\mathscr{R}_0^{As} &= \frac{p}{2} + \sqrt{\left(\frac{p}{2}\right)^2 + \frac{\beta_{As}}{(\delta+\alpha+\mu)}\frac{\theta_{As}}{\mu_m}},
\end{aligned}$$

where we note $\mathscr{R}_0^{As}$ is a strictly increasing function of the vertical transmission parameter, p. In a completely susceptible population, vertical transmission can improve the chances of a DENV-2 Asian outbreak. Furthermore, in an area already endemic with DENV-2 genotype American, vertical transmission facilitates the invasion, and replacement by DENV-2 genotype Asian if the invasion reproductive number is greater than one

$$\mathscr{R}_{inv}^{As} = \frac{p}{2} + \sqrt{\left(\frac{p}{2}\right)^2 + \left(\frac{\mathscr{R}_0^{As}(0)}{\mathscr{R}_0^{Am}}\right)^2}.$$

Similarly, if DENV-2 genotype Asian is endemic in a region, then vertical transmission makes it more difficult for DENV-2 American to invade

$$\mathscr{R}_{inv}^{Am} = \frac{\mathscr{R}_0^{Am}}{\mathscr{R}_0^{As}(0)}\sqrt{(1-p)}.$$

Invasion reproductive numbers generally arise in the context of two species competing for the same niche leading to competitive exclusion [Zhang et al., 2007].

In the absence of an effective vaccine, worldwide efforts should be made in order to monitor not only the disease but also *Aedes* mosquitoes, both males and females, and the DENV serotypes and genotypes that are being carried and transmitted. Our model is intended not only to highlight the importance of vertical transmission in a dengue outbreak but also the importance of epidemiological

surveillance incorporating molecular genotyping. Routine detection of the virus in both mosquitoes and hosts in endemic areas with dengue will be valuable in order to prevent major outbreaks and gauge the severity of the response that is required to combat any potential outbreak. Interdisciplinary efforts should be encouraged in order to validate theoretical models with real life data.

6.4 Appendix: $\mathcal{R}_0$ via Next Generation Operator

We use the next generation operator to calculate the basic reproductive number. This method has several advantages over other methods especially in the context of vector-borne diseases, see [Van den Driessche and Watmough, 2002] or [Diekmann et al., 1990] for a more complete discussion and proof of the method. In this section we outline how this method is applied. First we must identify the infected classes: D_{Am}, D_{As}, W_{Am}, W_{As} and H. Then we must identify the "new" infections. Infections coming into D_{Am}, D_{As}, W_{Am} and W_{As} are new while infections coming into H are "old" since individuals must first be infected via D_{As}. Then we form two vectors, $\mathcal{F}$ which consists of only the new infection terms, and $\mathcal{V}$ that is the negation of the remaining terms in our infected classes, that is

$$\mathcal{F} - \mathcal{V} = \begin{bmatrix} \dot{D_{Am}} \\ \dot{D_{As}} \\ \dot{W_{Am}} \\ \dot{W_{As}} \\ \dot{H} \end{bmatrix}$$

Then

$$\mathcal{F} = \begin{bmatrix} \frac{\beta_{Am} S W_{Am}}{M} \\ \frac{\beta_{As} S W_{As}}{M} \\ \frac{\theta_{Am} V D_{Am}}{N} \\ \frac{\beta_{m2} V D_{As}}{N} + p \mu_m W_{As} \\ 0 \end{bmatrix}, \tag{6.16}$$

and

$$\mathcal{V} = \begin{bmatrix} (\delta+\mu)D_{Am} \\ (\delta+\alpha+\mu)D_{As} \\ \mu_m W_{Am} \\ \mu_m W_{As} \\ (\delta+\mu)H - \alpha D_{As} \end{bmatrix}. \tag{6.17}$$

Next we calculate the Jacobian Matrices

$$\mathbf{F} = \begin{bmatrix} 0 & 0 & \frac{\beta_{Am}S}{M} & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{As}S}{M} & 0 \\ \frac{\theta_{Am}V}{N} & 0 & 0 & 0 & 0 \\ 0 & \frac{\theta_{Am}V}{N} & 0 & p\mu_m & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \tag{6.18}$$

$$\mathbf{V} = \begin{bmatrix} \delta+\mu & 0 & 0 & 0 & 0 \\ 0 & \delta+\alpha+\mu & 0 & 0 & 0 \\ 0 & 0 & \mu_m & 0 & 0 \\ 0 & 0 & 0 & \mu_m & 0 \\ 0 & -\alpha & 0 & 0 & \delta+\mu \end{bmatrix}. \tag{6.19}$$

Next we must evaluate the Jacobian matrices at the disease free equilibrium (Equation 6.11), keeping in mind that we have normalized both the human and mosquito populations. Then it only remains to find the eigenvalues of $\mathbf{FV}^{-1}$ since the basic reproductive number is the spectral radius, or largest eigenvalue of the next generation matrix

$$\mathcal{R}_0 = \rho(\mathbf{FV}^{-1}). \tag{6.20}$$

Carrying out the calculation yields two candidates (the other eigenvalues are zero or strictly smaller than these candidates)

$$\mathscr{R}_0^{Am} = \sqrt{\frac{\beta_{Am}}{\delta+\mu}\frac{\theta_{Am}}{\mu_m}} \text{ and} \tag{6.21}$$

$$\mathscr{R}_0^{As} = \frac{p}{2}+\sqrt{\left(\frac{p}{2}\right)^2+\frac{\beta_{As}}{\delta+\alpha+\mu}\frac{\theta_{As}}{\mu_m}} \tag{6.22}$$

where

$$\mathscr{R}_0 = \max\{\mathscr{R}_0^{Am}, \mathscr{R}_0^{As}\} \tag{6.23}$$

as required.

6.5 Appendix: Invasion Reproductive Numbers

To find the invasion reproductive number, we follow the same methodology as in finding the basic reproductive number. However, instead of assuming the entire population is susceptible to infection, we assume that one genotype is already established, endemic, in the population. Then “new" infection are only those infections associated with the invading strain. Then for Asian invading American, only classes D_{As}, W_{As} and H are of interest with new infections in the D_{As} and W_{As} classes:

$$\mathscr{F} = \begin{bmatrix} \frac{\beta_{As} S W_{As}}{M} \\ \frac{\beta_{m2} V D_{As}}{N} + p\mu_m W_{As} \\ 0 \end{bmatrix}, \tag{6.24}$$

and

$$\mathscr{V} = \begin{bmatrix} (\delta+\alpha+\mu)D_{As} \\ \mu_m W_{As} \\ (\delta+\mu)H - \alpha D_{As} \end{bmatrix}. \tag{6.25}$$

Next we calculate the Jacobian Matrices

$$\mathbf{F} = \begin{bmatrix} 0 & \frac{\beta_{As} S}{M} & 0 \\ \frac{\theta_{As} V}{N} & p\mu_m & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{6.26}$$

$$\mathbf{V} = \begin{bmatrix} \delta + \alpha + \mu & 0 & 0 \\ 0 & \mu_m & 0 \\ -\alpha & 0 & \delta + \mu \end{bmatrix}. \tag{6.27}$$

Next we evaluate these Jacobian matrices at the *American* equilibrium (Equation 6.12) since we assumed stain 1 was endemic prior to the introduction of Asian. Then it only remains to find the eigenvalues of $\mathbf{FV}^{-1}$ yields only one candidate

$$\mathscr{R}_{inv}^{As} = \frac{p}{2} + \sqrt{\left(\frac{p}{2}\right)^2 + \left(\frac{\left(\mathscr{R}_0^{As}(0)\right)^2}{\left(\mathscr{R}_0^{Am}\right)^2}\right)^2}. \tag{6.28}$$

Similarly for American invading Asian, D_{Am} and W_{Am} are the classes of interest.

$$\mathscr{F} = \begin{bmatrix} \frac{\beta_{Am} S W_{Am}}{M} \\ \frac{\theta_{Am} V D_{Am}}{N} \end{bmatrix}, \tag{6.29}$$

and

$$\mathscr{V} = \begin{bmatrix} (\delta + \mu) D_{Am} \\ \mu_m W_{Am} \end{bmatrix}. \tag{6.30}$$

Next we calculate the Jacobian Matrices

$$\mathbf{F} = \begin{bmatrix} 0 & \frac{\beta_{Am} S}{M} & 0 \\ \frac{\theta_{Am} V}{N} & 0 & \end{bmatrix} \tag{6.31}$$

$$\mathbf{V} = \begin{bmatrix} \delta + \mu & 0 \\ 0 & \mu_m \end{bmatrix}, \tag{6.32}$$

and we evaluate these Jacobian matrices at the *Asian* equilibrium (Equation 6.13) since we assumed stain 2 was endemic. Then the dominant eigenvalue of $\mathbf{FV}^{-1}$ is

$$\mathscr{R}_{inv}^{Am} = \sqrt{\left(\frac{\left(\mathscr{R}_0^{Am}\right)^2 (1-p)}{\left(\mathscr{R}_0^{As}(0)\right)^2} \right)^2}. \tag{6.33}$$

6.6 Appendix: Global stability of $\mathscr{R}_0$

Using the rescaled system of equations, let

$$L = D_{2Am} + D_{2As} + \frac{\beta_{2Am}}{\mu_m} W_{Am} + \frac{\beta_{2As}}{\mu_m} W_{As}.$$

Clearly L is positive definite and radially unbounded. The orbital derivative of L is

$$\begin{aligned}
\dot{L} &= \beta_{Am} W_{Am} S - (\delta_{Am} + \mu) D_{Am} + \beta_{As} W_{As} S - (\delta_{Am} + \mu) D_{Am} \\
&\quad \theta_{Am} D_{Am} V - \mu_m W_{Am} + \theta_{As} D_{As} V - \mu_m W_{As} + p \mu_m W_{As} \\
&= -\beta_{Am} W_{Am} (1 - S) - (\delta_{Am} + \mu) D_{Am} (1 - \mathscr{R}_0^{Am} V) \\
&\quad -\beta_{As} W_{As} (1 - S - p W_{As}) - (\delta_{As} + \mu) D_{As} (1 - \mathscr{R}_0^{As}(0) V)
\end{aligned}$$

If $\mathscr{R}_0 < 0$, then clearly $\dot{L} \leq 0$. Next we must show that the DFE is the maximal invariant subspace of $\dot{L} = 0$. From above we have four conditions that must be simultaneously satisfied for $\dot{L} = 0$,

$$W_{Am}(1 - S) = 0 \tag{6.34}$$

$$W_{As}(1 - S - p W_{As}) = 0 \tag{6.35}$$

$$D_{Am}(1 - \mathscr{R}_0^{Am} V) = 0 \tag{6.36}$$

$$D_{As}(1 - \mathscr{R}_0^{As}(0) V) = 0 \tag{6.37}$$

Equation 6.34 implies that either $W_{Am} = 0$ or $S = 1$. Suppose $W_{Am} \neq 0$, then $S = 1$ and $\dot{S} = 0$ but

$$\dot{S} = -\beta_{Am} W_{Am} - \beta_{As} W_{As} < 0,$$

which is a contradiction, thus $W_{Am} = 0$. From Equation 6.36 either $D_{Am} = 0$ or $V = \frac{1}{\mathscr{R}_0^{Am}}$. Suppose $D_{Am} \neq 0$, since $\mathscr{R}_0^{Am} < 1$, $V < 0$ which is impossible since $V \in [0,1]$. Therefore $D_{Am} = 0$. Similarly, Equation 6.37 implies that either $D_{As} = 0$ or $V = \frac{1}{\mathscr{R}_0^{As}(0)}$, but if $\mathscr{R}_0^{As} < 1$, then $\mathscr{R}_0^{As}(0) < 1$ and we conclude $D_{As} = 0$. Finally, condition 6.35 implies that either $W_{As} = 0$ or $S = 1 - p\,W_{As} > 0$ if $p < 1$. Suppose $W_{As} \neq 0$. Since $D_{As} = 0$, $\dot{D}_{As} = 0$ and

$$\dot{D}_{As} = \beta_{As} S W_{As} > 0,$$

thus we conclude $W_{As} = 0$. Also note that since $\dot{D}_{As} = 0$, $\dot{H} = -(\delta_H + \mu)H$ which implies $H \to 0$, thus the maximal invariant set is the DFE which is globally asymptotically stable the the Lyapunov-LaSalle Theorem.

Chapter 7

Final Epidemic Size

In this section we present a relationship between the basic reproductive number and the final epidemic size for a vector-borne disease. This type of relationship was first presented by Kermack and McKendrick in 1927 for an age of infection model (see [Arino, J. *et al* 2007] and references therein for a review of this type of formulation). This is the first application of the final epidemic size to a model of a vector disease with vertical transmission. Consider a single strain vector transmitted disease

7.1 Extension of the Final Size Relation to Simple Host-Vector Models

Suppose we have a vector-host system characterized by an SIR with out vital dynamics for the host and SI with vital dynamics for the vector. This system is described by the following equations:

$$\dot{S} = -\beta S\frac{W}{M} \tag{7.1}$$

$$\dot{I} = \beta S\frac{W}{M} - \gamma I \tag{7.2}$$

$$\dot{R} = \gamma I \tag{7.3}$$

$$\dot{V} = \Lambda - \theta V\frac{I}{N} - \mu V \tag{7.4}$$

$$\dot{W} = \theta V\frac{I}{N} - \mu W \tag{7.5}$$

where S is the class of susceptible hosts, I is infectious hosts, R is recovered hosts, V is susceptible vectors and W is infectious vectors. We note that the total host population is conserved and the total vector population can be written as $\dot{M} = \Lambda - \mu M$. This expression can be explicitly solved and we see $M \to \frac{\Lambda}{\mu}$ exponentially. If we assume the time-scale of the vector vital dynamics is much faster than the epidemiological time-scale, then we can take the asymptotic approxima-

tion that dynamics of the whole system is equivalent to the dynamics considering the vector system at equilibrium, $V \to V^*$, $W \to W^*$, and $M \to \frac{\Lambda}{\mu}$. Then we can rescale the host equations by N and the vector equations by $\frac{\Lambda}{\mu}$ and use lower case letters to denote fractions of the relevant population size to write:

$$\dot{s} = -\beta s w \tag{7.6}$$

$$\dot{i} = \beta s w - \gamma i \tag{7.7}$$

$$\dot{r} = \gamma i \tag{7.8}$$

$$\dot{v} = \mu - \theta v i - \mu v \tag{7.9}$$

$$\dot{w} = \theta v i - \mu w. \tag{7.10}$$

We can then solve the vector system for the equilibrium infected population proportion as a function of the infected host proportion

$$w^* = \frac{\theta i}{\theta i + \mu}.$$

If we add equations 7.6 and 7.7 yields

$$\dot{s} + \dot{i} = -\gamma i$$

from which we conclude that $i_\infty \to 0$. Since v is bounded, we can conclude from equation 7.10 that $w_\infty \to 0$. Then integrating equation 7.6 yields

$$\ln \frac{s_0}{s_\infty} = \beta \int_0^\infty w \, dt.$$

The right hand side is bounded which implies $s_\infty > 0$. Then we can take the ratio of equations 7.6 and 7.7 to calculate the final epidemic size of the model

$$\frac{di}{ds} = -1+\frac{\gamma i}{\beta s w} \tag{7.11}$$

$$= -1+\frac{\gamma i}{\beta s \frac{\theta i}{\theta i+\mu}} \tag{7.12}$$

$$= -1+\frac{\gamma i}{\beta s}+\frac{\mu}{\beta\theta s} \tag{7.13}$$

$$\frac{di}{ds}-\frac{\gamma}{\beta s}i = -1+\frac{\gamma\mu}{\beta\theta s} \tag{7.14}$$

$$\left(\frac{di}{ds}-\frac{\gamma}{\beta s}i\right)s^{-\frac{\gamma}{\beta}} = \left(-1+\frac{\gamma\mu}{\beta\theta s}\right)s^{-\frac{\gamma}{\beta}} \tag{7.15}$$

$$\frac{d}{ds}\left(is^{-\frac{\gamma}{\beta}}\right) = -s^{-\frac{\gamma}{\beta}}+\frac{\gamma\mu}{\beta\theta}s^{-\frac{\gamma}{\beta}-1} \tag{7.16}$$

$$\int\frac{d}{ds}\left(is^{-\frac{\gamma}{\beta}}\right) = \int -s^{-\frac{\gamma}{\beta}}+\int\frac{\gamma\mu}{\beta\theta}s^{-\frac{\gamma}{\beta}-1} \tag{7.17}$$

$$is^{-\frac{\gamma}{\beta}} = \frac{-s^{1-\frac{\gamma}{\beta}}}{1-\frac{\gamma}{\beta}}-\frac{\mu}{\theta}s^{-\frac{\gamma}{\beta}}+C \tag{7.18}$$

$$i = \frac{-s}{1-\frac{\gamma}{\beta}}-\frac{\mu}{\theta}+Cs^{\frac{\gamma}{\beta}} \tag{7.19}$$

$$C = i_0 s_0^{-\frac{\gamma}{\beta}}+\frac{s_0^{1-\frac{\gamma}{\beta}}}{1-\frac{\gamma}{\beta}}+\frac{\mu}{\theta}s_0^{-\frac{\gamma}{\beta}} \tag{7.20}$$

Now if we allow for vertical transmission in the vectors, we arrive at the following set of differential equations

$$\dot{S} = -\beta S\frac{W}{M} \tag{7.21}$$

$$\dot{I} = \beta S\frac{W}{M}-\gamma I \tag{7.22}$$

$$\dot{R} = \gamma I \tag{7.23}$$

$$\dot{V} = \Lambda-\theta V\frac{I}{N}-\mu V-p\mu W \tag{7.24}$$

$$\dot{W} = \theta V\frac{I}{N}-\mu W+p\mu W \tag{7.25}$$

where p is the proportion of female mosquitoes that become infectious vertically (through birth). Then we can rescaled system as before to get

$$\dot{s} = -\beta s w \tag{7.26}$$

$$\dot{i} = \beta s w - \gamma i \tag{7.27}$$

$$\dot{r} = \gamma i \tag{7.28}$$

$$\dot{v} = \mu - \theta v i - \mu v - p\mu w \tag{7.29}$$

$$\dot{w} = \theta v i - \mu w + p\mu w. \tag{7.30}$$

Solving the final equation gives

$$w^* = \frac{\theta i}{\theta i + \mu(1-p)}.$$

If we let $\hat{\mu} = \mu(1-p)$, we recover the same solution as before, but with a modified death/birth rate. Additionally, if we replace the constant recruitment rate, Λ with proportional recruitment that keeps the total vector size constant, μM, then we also recover the same final size relation.

Chapter 8

Optimal Control of Dengue Fever

8.1 Introduction

Dengue fever is one of the most important reemerging vector-borne diseases. The primary vector, *Aedes Aegypti* has endured several attempted eradication campaigns, but both the vector and the disease have revealed themselves to be extremely resilient to control measures. We suggest that vertical transmission, an often overlooked transmission pathway for dengue fever, may contribute to the difficulty of controlling the disease. As the number and severity of outbreaks increases worldwide, we need to be both effective and efficient in how we implement campaigns to mitigate or prevent disease outbreaks. Our modeling efforts show that ignoring vertical transmission may undercut the effectiveness of any control program.

There are only two disease that has been successfully eradicated: smallpox in 1979 and just recently rinderpest has been declared eradicated by the UN, due in large part to an effective vaccine and aggressive vaccination program [Nations, 2011]. Although vaccines exist for many other diseases, there are many barriers to widespread vaccine coverage including costs, side effects and even public perception. WIthout a broad vaccine coverage “herd immunity," the first step in disease eradication, is difficult to establish [Amanna and Slifka, 2005, Anderson and May, 1985, Shim et al., 2009]. There is no vaccine for dengue fever, thus the mitigation and prevention policies have focused on site reduction (elimination of mosquito breeding sites) and spraying programs; that is, they have focused on controlling the vector. This shift in strategy has the advantage of transforming the disease control problem into one of eliminating an easier to visualize, and villianize, insect rather than a virus. However, the primary driver of extinction is habitat disturbance

and direct elimination (harvesting, hunting, etc.) [Ceballos and Ehrlich, 2002, Sodhi et al., 2009]. Unfortunately, *Ae. Aegypti* has demonstrated an affinity to the urban landscape and ability to thrive even in countries with strict control programs [Goh, 1998].

Of the several attempts to eradicate dengue via eliminating the vector, the most notable dengue eradication campaign has been the attempt by the then called Pan American Sanitary Board using DDT. Political, logistic and ecological issues prevented the full eradication of *A*e. aegypti in 1952 in a campaign initiated by the Pan American Sanitary Board [Reiter and Gubler, 1997]. Although the program was declared a success at the time, as the campaign waned, re-infestation begin in the mid $1960's$ [Arias, J.R., 2002, Soper, F.L., 1967]. The surviving *A*e. aegypti population developed increased levels of resistance to DDT and other insecticides that has made its eradication or control of the mosquito via chemical means difficult [Reiter, P. *et al* 1997, Polson, K.A. *et al* 2006, Polson, K.A. *et al* 2010]. Botanical extracts have been pursued as an alternative means of vector control, but their effectiveness (as part of a dengue control strategy) has yet to be ascertained [Govindarajan, M. *et al* 2011, Koodalingam, A. *et al* 2011]. .

Although relatively unheard of in North America, dengue fever is a growing concern and the World Health Organization estimates that 40% of the global population is at risk for dengue infection. It has been estimated that between 50 and 100 million new infections are generated each year, a group that includes approximately $500,000$ cases of the more severe manifestation dengue hemorrhagic fever, DHF, and $22,000$ deaths (mostly children) [WHO, 2010]. The range of *Ae. Aegypti* have traditionally been limited by weather, but increased urbanization and climate change facilitate the spread of the mosquito. The challenges that we face in isolating and controlling dengue not only come from climate changes but also from global transportation flows. The FAA (Federal Aviation Administration) estimates that American air traffic will double [FAA, 2011] over the next 20

years with the largest share of the international growth coming from the Asian and Latin American, regions where dengue is endemic. Mass transportation is indeed an important factor in the long range dispersal of dengue [Harrington, L.C. *et al* 2005, Farrar, J. *et al* 2007, Gomez-Dantes, H. and Willoquet, J.R., 2009] and the always increasing numbers of Americans globally engaged puts the U.S. at risk of dengue especially, in the 28 US states where *A*e. aegypti is already established; a group that includes the states of Arizona and Florida, among others [CDC, 2010, Knowlton et al., 2011].

While we have mentioned some of the political and ecological reasons for the failure of previous eradication campaigns [Reiter and Gubler, 1997], this paper aims to elucidate some implications of vertical transmission on an attempt to control an outbreak of dengue fever. Because vertical transmission is often considered to not be a major factor in dengue transmission, we model the effect of a control measure that does not directly impact vertical transmission. We then compare situations where vertical transmission is and is not a significant mode of dengue transmission. In the next session we will develop the system with control and develop conditions for the existence of an optimal control. Then we present some numerical results and finally we discuss the implications of optimal control in a model of an infectious disease with vertical transmission.

8.2 Mathematical Model

Although vertical transmission has been mostly understudied in models of dengue, recent results [Murillo et al., 2012b] have demonstrated that vertical (transovarial) transmission has both primary and secondary effects in facilitating the invasion and persistence of novel strains of dengue. Dengue management policies exist virtually everywhere dengue fever is a major health concern, yet the fact that dengue outbreaks are increasing in severity and frequency suggests we need to better understand control strategies and how to evaluate them [Knowl-

ton, K., *et al* 2011]. The model presented here is based on a previous model [Murillo et al., 2012b] and we will highlight the features that are relevant to the formation of the optimal control problem.

Among these features is vertical transmission which will be explored by considering a population that is impacted by two variants of the same strain of dengue simultaneously: one that exhibits vertical transmission as a significant mode of disease transmission and one that does not[1]. We use a compartmental modeling framework where each compartment, shown in Figures 8.1 and 8.2 by a letter within a box, denotes a class of individuals. Then the arrows represent the flows of individuals between different states [Brauer and Castillo-Chavez, 2001]. Let S represent the number of susceptible hosts (humans). These individuals are antigenically naive to the particular strain of dengue being modeled, but may have had previous exposures to other strains. D_{Am} and D_{As} are individuals infected with genotypes of dengue strain 2, DENV-2 Asian and DENV-2 American, respectively. H represents individuals who have developed DHF, R and is recovered individuals. V is the class of susceptible vectors (female mosquitoes). W_{Am} and W_{As} are mosquitoes that carry strain DENV-2 American and DENV-2 Asian, respectively. Then we can write the system of equations representing our model as:

[1]For an example of this particular context, see [Murillo et al., 2012a]. In that paper DENV-2 American was endemic in Peru prior to the 2000 outbreak that saw the invasion of DENV-2 Asian.

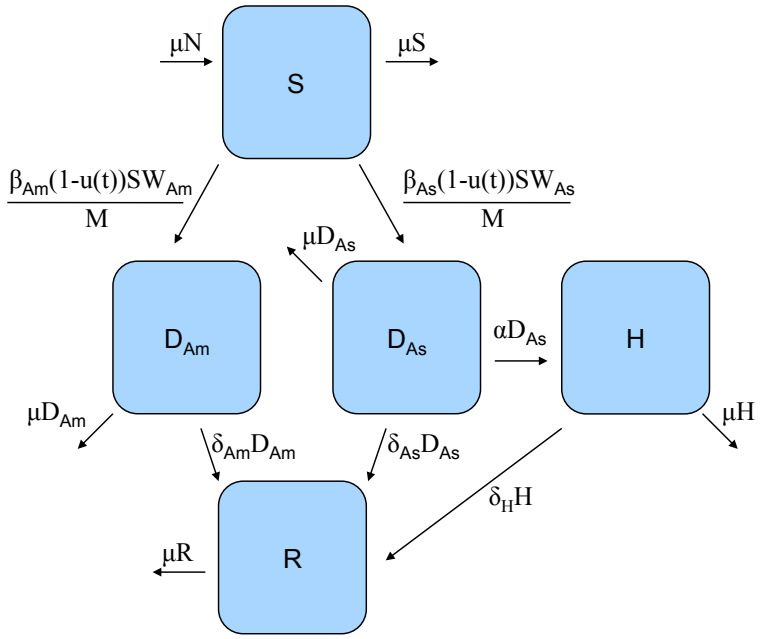


Figure 8.1: Host model. S is the class of susceptible individuals who can become infectious with either DENV-2 American genotype, D_{Am}, or DENV-2 Asian genotype D_{As} via infectious female mosquitoes W carrying the corresponding strain. In this model, only individuals infected with the Asian genotype can progress to DHF, H, and all infected individuals can recover, R. The control is given by u(t).

$$
\begin{aligned}
\dot{S} &= \mu N - \frac{\beta_{Am}(1-u(t))SW_{Am}}{M} - \frac{\beta_{As}SW_{As}}{M} - \mu S \\
\dot{D}_{Am} &= \frac{\beta_{Am}(1-u(t))SW_{Am}}{M} - (\delta+\mu)D_{Am} \\
\dot{D}_{As} &= \frac{\beta_{As}SW_{As}}{M} - (\delta+\alpha+\mu)D_{As} \\
\dot{H} &= \alpha D_{As} - (\delta+\mu)H \\
\dot{R} &= \delta D_{Am} + \delta D_{As} + \delta H - \mu R \\
\dot{V} &= \mu_m M - p\mu_m W_{As} - \frac{\theta_{Am}(1-u(t))VD_{Am}}{N} - \frac{\theta_{As}(1-u(t))VD_{As}}{N} - \mu_m V \\
\dot{W}_{Am} &= \frac{\theta_{Am}(1-u(t))VD_{Am}}{N} - \mu_m W_{Am} \\
\dot{W}_{As} &= \frac{\theta_{As}(1-u(t))VD_{As}}{N} + p\mu_m W_{As} - \mu_m W_{As}
\end{aligned}
\tag{8.1}
$$

Where $u(t)$ is the percentage reduction in infection due to the effect of control

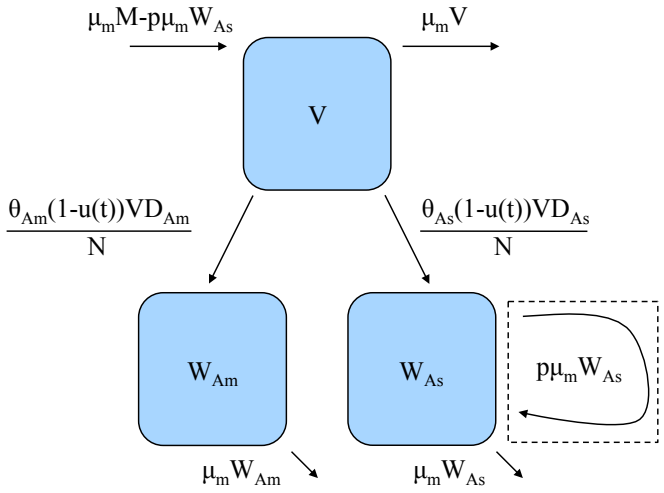


Figure 8.2: Vector model. V is the class of susceptible female mosquitoes that can become infected with either DENV-2 American genotype W_{Am} or DENV-2 Asian genotype W_{As} via contact with an infectious human, D carrying the corresponding genotype. Vertical transmission only occurs in mosquitoes infected with genotype Asian. In this model, there is a constant birth rate, but a proportion, p, of those births by mosquitoes carrying genotype Asian, W_{As}, enter directly into the infectious class. The control is given by u(t).

measures. Then $\beta_i(1-u)$ is the effective transmission force for strain i. Note we assume no *a priori* knowledge of what strain a particular individual has, thus the control measure is independent of the strain. Furthermore, since we are primarily interested in modeling the *effect* of a control measure, we assume that the reduction in effective contacts impacts mosquitoes equally well as humans. Thus, their effective force of infection is also reduced by $u(t)$. We also assume that one strain, DENV-2 Asian, is more virulent, leading to cases of DHF and also exhibiting vertical transmission with some probability p times the basic fecundity function while the other strain, DENV-2 American, does not.

When the control function $u(t) \equiv 0$, system 8.1 is said to be autonomous. The basic reproductive number of an epidemiological model generally determines whether or not the disease will die out or persist [Brauer and Castillo-Chavez, 2001]. For the autonomous system, if we consider each strain independently, then the

reproductive number for DENV-2 American is $\mathscr{R}_0^{Am} = \sqrt{\frac{\beta_{Am}}{(\delta+\mu)}\frac{\theta_{Am}}{\mu_m}}$, and the reproductive number for DENV-2 Asian is $\mathscr{R}_0^{As} = \frac{p}{2} + \sqrt{\left(\frac{p}{2}\right)^2 + \frac{\beta_{As}}{(\delta+\alpha+\mu)}\frac{\theta_{As}}{\mu_m}}$. Then the basic reproductive number is $\mathscr{R}_0 = max[\mathscr{R}_0^{Am}, \mathscr{R}_0^{As}]$ [Murillo et al., 2012b]. The basic reproductive number is a central component of the model that can distinguish between different qualitative behavior in the autonomous system.

A central component of the control problem is the optimization, in this case minimization, of an objective function. We are interested in controlling an outbreak of dengue, thus we want to minimize the number of infective individuals. However, we are also interested in preventing future outbreaks, thus we want to minimize the number of infected mosquitoes and individuals both during the course of our control measure and when our control policy has ended: at time $t = T$. Then the corresponding objective function is:

$$\begin{aligned} J(u_1(t)) \;=\; & \int_0^T \left(w_1(D_{Am}(t) + D_{As}(t)) + w_2(W_{Am}(t) + W_{As}(t)) + \frac{1}{2} w_3 u^2(t) \right) dt \\ & + w_4(D_{Am}(T) + D_{As}(T)) + w_5(W_{Am}(T) + W_{As}(T)) \end{aligned} \tag{8.2}$$

where w_1 is the weight constants for host infections, w_2 is the weight constant for vector infections, $\frac{1}{2} w_3 u^2(t)$ is the cost of control and included as a quadratic term for technical reasons, and w_4 and w_5 are the weight constant for the payoff term (at time $t = T$). If we let X be the vector of our state variables which is restricted to the positive orthant, $X \in \mathbb{R}_+^8$, then X^* is the optimal solution that corresponds to the optimal control function u^* such that

$$J(u^*) = \min\{J(u) | u \in \Omega\},$$

where $\Omega = \{(u(t) \in L^1 \,|\, 0 \leq u(t) \leq 1, t \in [0, T]\}$. Then the Hamiltonian of our system is

$$
\begin{aligned}
\hat{H}(X,u) \;=\;& w_1(D_{Am}(t)+D_{As}(t))+w_2(W_{Am}(t)+W_{As}(t))+\frac{1}{2}w_3u^2(t) \qquad (8.3)\\
&+\lambda_1\left(\mu N-\frac{\beta_{Am}(1-u(t))SW_{Am}}{M}-\frac{\beta_{As}(1-u(t))SW_{As}}{M}-\mu S\right)\\
&+\lambda_2\left(\frac{\beta_{Am}(1-u(t))SW_{Am}}{M}-(\delta+\mu)D_{Am}\right)\\
&+\lambda_3\left(\frac{\beta_{As}(1-u(t))SW_{As}}{M}-(\delta+\alpha+\mu)D_{As}\right)\\
&+\lambda_4\left(\alpha D_{As}-(\delta+\mu)H\right)\\
&+\lambda_5\left(\delta D_{Am}+\delta D_{As}+\delta H-\mu R\right)\\
&+\lambda_6\left(\mu_m M-p\mu_m W_{As}-\frac{\theta_{Am}(1-u(t))VD_{Am}}{N}-\frac{\theta_{As}(1-u(t))VD_{As}}{N}-\mu_m V\right)\\
&+\lambda_7\left(\frac{\theta_{Am}(1-u(t))VD_{Am}}{N}-\mu_m W_{Am}\right)\\
&+\lambda_8\left(\frac{\theta_{As}(1-u(t))VD_{As}}{N}+p\mu_m W_{As}-\mu_m W_{As}\right), \qquad (8.4)
\end{aligned}
$$

where λ_i are the co-state or adjoint variables [Lenhard and Workman, 2007]. Then, by Pontryagin's Maximum Principle [Pontryagin et al., 1962], our optimal solution can be found by simultaneously solving the adjoint system:

$$
\begin{aligned}
\frac{d\lambda_1(t)}{dt} &= -\frac{\partial \hat{H}}{\partial S} = & (\lambda_1-\lambda_2)\beta_{Am}(1-u)\frac{W_{Am}}{M} + (\lambda_1-\lambda_3)\beta_{As}(1-u)\frac{W_{As}}{M} + \lambda_1\mu \\
\frac{d\lambda_2(t)}{dt} &= -\frac{\partial \hat{H}}{\partial D_{Am}} = & (\lambda_6-\lambda_7)\theta_{Am}(1-u)\frac{V}{N} + (\lambda_2-\lambda_5)\delta + \lambda_2\mu - w_1 \\
\frac{d\lambda_3(t)}{dt} &= -\frac{\partial \hat{H}}{\partial D_{As}} = & (\lambda_6-\lambda_8)\theta_{As}(1-u)\frac{V}{N} + (\lambda_3-\lambda_5)\delta + (\lambda_3-\lambda_4)\alpha + \lambda_3\mu - w_1 \\
\frac{d\lambda_4(t)}{dt} &= -\frac{\partial \hat{H}}{\partial H} = & (\lambda_4-\lambda_5)\delta + \lambda_4\mu \\
\frac{d\lambda_5(t)}{dt} &= -\frac{\partial \hat{H}}{\partial R} = & \lambda_5\mu \\
\frac{d\lambda_6(t)}{dt} &= -\frac{\partial \hat{H}}{\partial V} = & (\lambda_6-\lambda_7)\theta_{Am}(1-u)\frac{D_{Am}}{N} + (\lambda_6-\lambda_8)\theta_{As}(1-u)\frac{D_{As}}{N} + \lambda_6\mu_m \\
\frac{d\lambda_7(t)}{dt} &= -\frac{\partial \hat{H}}{\partial W_{Am}} = & (\lambda_1-\lambda_2)\beta_{Am}(1-u)\frac{S}{N} + \lambda_7\mu_m - w_2 \\
\frac{d\lambda_8(t)}{dt} &= -\frac{\partial \hat{H}}{\partial W_{As}} = & (\lambda_1-\lambda_3)\beta_{As}(1-u)\frac{S}{N} + (\lambda_6-\lambda_8)p\mu_m + \lambda_8\mu_m - w_2,
\end{aligned}
$$

with the transversality conditions

$$
\begin{aligned}
&\lambda_1 = \lambda_4 = \lambda_5 = \lambda_6 = 0 \\
&\lambda_2 = \lambda_3 = w1 \\
&\lambda_7 = \lambda_8 = w2,
\end{aligned}
$$

and the optimality condition

$$
\begin{aligned}
\frac{\partial \hat{H}}{\partial u} &= w_3 u + (\lambda_1-\lambda_2)\beta_{Am}S\frac{W_{Am}}{M} + (\lambda_1-\lambda_3)\beta_{As}S\frac{W_{As}}{M} \\
&\quad + (\lambda_6-\lambda_7)\theta_{Am}V\frac{D_{Am}}{N} + (\lambda_6-\lambda_8)\theta_{As}V\frac{D_{As}}{N},
\end{aligned} \tag{8.5}
$$

where $\frac{\partial \hat{H}}{\partial u} = 0$ at $u = u^*$. We can solve this for the optimal control function u^* with the constraint that u must be between 0 and 1 to get

$$u^* = \min\left\{\max\left\{0,(\lambda_2-\lambda_1)\beta_{Am}S\frac{W_{Am}}{w_3M}+(\lambda_3-\lambda_1)\beta_{As}S\frac{W_{As}}{w_3M}\right.\right.$$
$$\left.\left.+(\lambda_7-\lambda_6)\theta_{Am}V\frac{D_{Am}}{w_3N}+(\lambda_8-\lambda_6)\theta_{As}V\frac{D_{As}}{w_3N}\right\},1\right\}.$$

This type of optimal control formulation has several application in mathematical biology [Blayneh et al., 2009, Lee et al., 2010a, Lee et al., 2010b, Lee et al., 2011, Lenhard and Workman, 2007]. Although a proof of the existence of an optimal control is left to the Appendix, the solution to our control problem will be a piecewise smooth control function. For the purposes of this article, what is important is the qualitative shape of this control function. Because it is unclear what the costs of these control policies are relative to the effective reduction in transmission, more insight may be gleaned by examining the qualitative features of the control function as the relative costs are changed.

8.3 Numerical Results

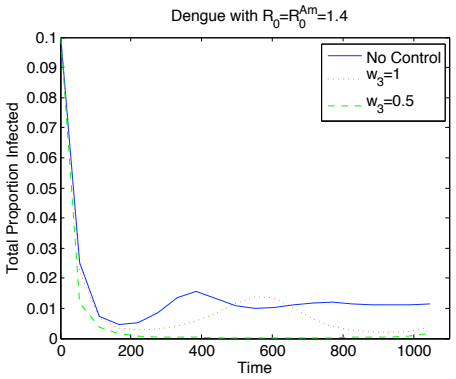
Each numerical solution is ran over a period of three years to give account for transient dynamics. In reality, a control policy would also be evaluated over short, medium and long term time periods, and three years seemed sufficient for our numerical results. The default parameters for all simulations are listed in Table 8.1 unless otherwise indicated.

If the cost of the control function is comparable, on the same order of magnitude, to the costs incurred from the disease, then there is no incentive to invest heavily on control. We see this in Figure 8.3 where not much effort is spent on the control function. However, if the control because less expensive, or analogously the costs from disease become more expensive, then it is worthwhile to invest in eliminating the disease and preventing an outbreak. Note that with sufficient effort the control function can mitigate the current outbreak and prevent future ones (the damped oscillations predicted in the autonomous model) as seen

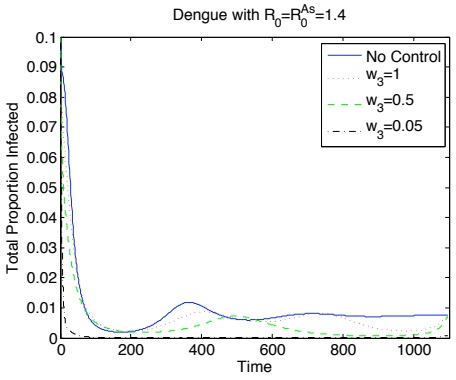
Table 8.1: Default Parameter Values for Dengue.

parameter	default value	units	source
α	0.113	per day	Watts et al
μ_m	0.0958	per day	Rodhain and Rosen
p	0.0133	dimensionless	Chunge et al
mu	0.000038	per day	WHO[2]
θ_{As}	0.28	per day	estimated
θAm	0.28	per day	estimated
β_{As}	0.75	per day	estimated
β_{Am}	0.25	per day	estimated
δ	.2	per day	estimated

in Figure 8.3. This is the case where the reproductive number, $\mathcal{R}_0$, is greater than one (1.4), otherwise there would be no outbreak and control would be moot. However, the left panels in Figures 8.3 and 8.4 are when $\mathcal{R}_0^{As} < \mathcal{R}_0^{Am}$, i.e. the strain without vertical transmission is the dominant strain during an outbreak. If we keep the same basic reproductive number, but instead chose the outbreak to be dominated by the strain *with* vertical transmission, $\mathcal{R}_0^{As} > \mathcal{R}_0^{Am}$, then we get the scenarios depicted in the right panels of Figures 8.3 and 8.4. Here we see that when the cost of control is comparable to the cost of the disease, we get the same results as before. When the cost of control is too high, we cannot completely control the outbreak and we must respond to rises in prevalence, Figure 8.4. However, at the same level of relative costs where the outbreak was controlled before, here we are unable to fully control the outbreak. The total number of cases is larger and there is a small secondary outbreak. In order to fully control the outbreak, we have to reduce the relative costs even further than in the previous case. Vertical transmission made the outbreak more difficult to control because the control function did not prevent the development of new infected mosquitoes from infected eggs.

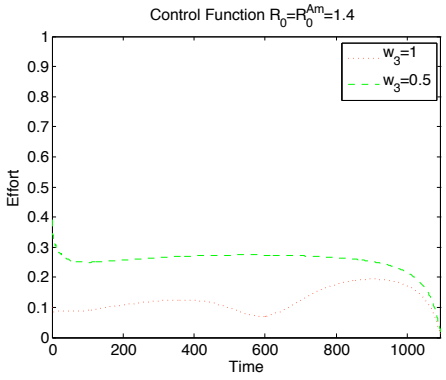


(a) Proportion of the total population infected with either strain DENV-2 American or DENV-2 Asian when the dominant strain is DENV-2 American, $\beta_{American} = .1948$ and $\beta_{Asian} = .185$.

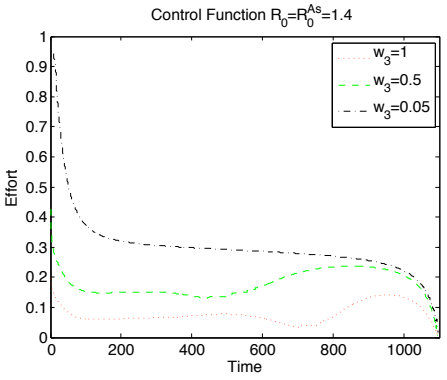


(b) Proportion of the total population infected with either strain DENV-2 American or DENV-2 Asian when the dominant strain is DENV-2 Asian, $\beta_{American} = .15$ and $\beta_{Asian} = .3$.

Figure 8.3: As the relative cost of the control function, w_3, is reduced, the proportion of infected people decreases. However when the outbreak is dominated by the strain without vertical transmission, (a), then the outbreak can be controlled more easily than when the outbreak is dominated by the strain with vertical transmission, (b). In the latter case, the cost of control must be reduced even further to effectively control the outbreak.



(a) The effort is the percentage of all infections prevented when the dominant strain is DENV-2 American, $\beta_{American} = .1948$ and $\beta_{Asian} = .185$.



(b) The effort is the percentage of all infections prevented when the dominant strain is DENV-2 Asian, $\beta_{American} = .15$ and $\beta_{Asian} = .3$.

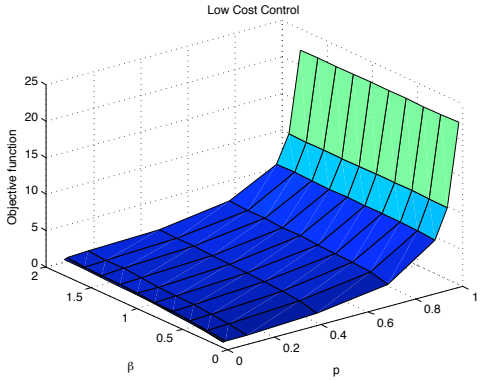
Figure 8.4: As the relative cost of the control function decreases, it is used more frequently and is able to control the outbreak. If the relative cost is expensive, then it is used sparingly and in response to outbreaks. Notice the peaks occur right after an increase in the prevalence of dengue in the corresponding panel of Figure 8.3.

To further see the impact of vertical transmission, we measured the total value of the objective function and the cumulative costs as functions of p, the proportion of eggs hatched infected with dengue. Regardless of the costs of control, having a large force of vertical transmission makes an outbreak extremely expensive to control, Figure 8.5b. This is due to the fact that the control policy cannot directly stop the generation of infected mosquitoes via vertical transmission, and thus are penalized by the number of new infections those mosquitoes cause, Figure 8.6b. If the relative cost of control is higher, then the total costs are proportionally higher as well.

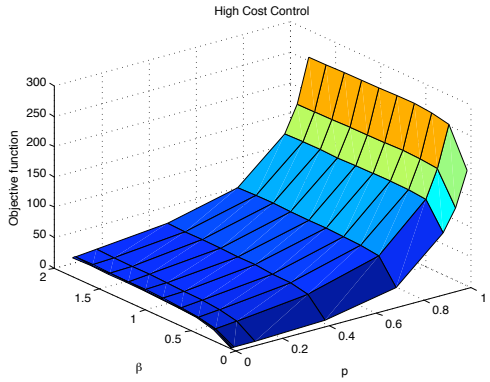
For a fixed force of horizontal transmission, β, we can see how the total costs of control and the severity of an outbreak vary directly with changes in the force of vertical transmission, p, and relative cost of control, w_3, in Figure 8.7. As the horizontal transmission increases, we notice that larger outbreaks occur for smaller values of vertical transmission. Large values of vertical transmission can cause larger outbreaks with associated larger costs.

8.4 Discussion

Diseases have been and continue to be a major public health challenge, with outbreaks of infectious diseases capable of causing tremendous loss of life in relatively short time periods. There are various strategies to controlling an epidemic (including vaccination, isolation, and social distancing) that have been used to study disease prevention/mitigation in various contexts (see [Anderson and May, 1985, Brauer and Castillo-Chavez, 2001, Lee et al., 2010a, Lenhard and Workman, 2007, Reiter and Gubler, 1997] and references therein). If the disease is environmental, then policy makers can, in theory, impose restrictions on how the environmental conditions are created (regulate polluters, etc) or regulate how individuals come in contact with the environment (storage of radioactive material, for example). If the disease is infectious, then regulators can try to inform the public on how the



(a) If the control function is inexpensive, $w_3 = .01$, then outbreak can be controlled while keeping the objective function small unless there is a high proportion of mosquitoes becoming infected vertically.

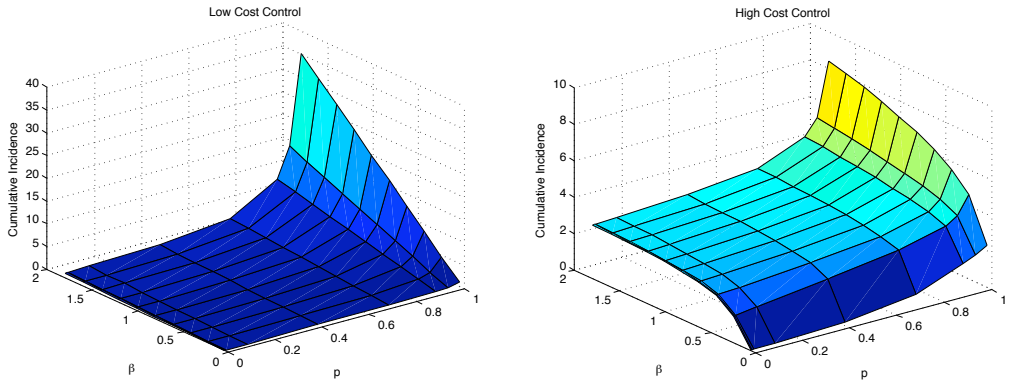


(b) If the control is expensive $w_3 = 2$, but not prohibitively so, then the control function will still be effective, but the objective function will be very expensive, especially for large values of vertical transmission.

Figure 8.5: Even with an “effective" control program, a high vertical transmission rate can render the health policy moot regardless of the cost of additional control is low, left panel, or high, right panel.

disease is transmitted and how to prevent transmission (washing hands, practicing safe sexual contact, needle sharing programs, voluntary isolation, etc). However, if the disease is vector transmitted, then we often have little recourse in trying to reason with the vectors.

Vectors are often harbored in poor environmental quality/sanitation conditions [Gubler and Kuno, 1997] and those with the socioeconomic means will often choose to live in environments where the vector is well controlled or they can afford to modify their environment to prevent the vector from becoming es-



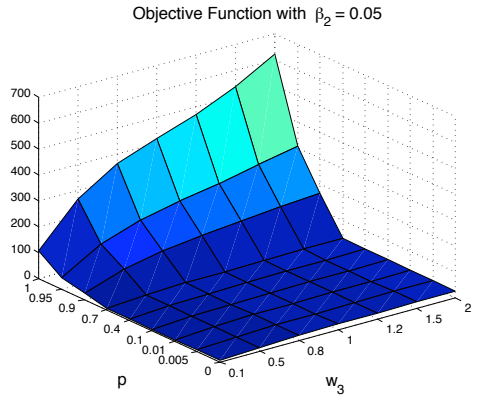
(a) If the control function is inexpensive, then incidence can be controlled unless there is a high proportion of mosquitoes becoming infected vertically and the transmission rate is high.

(b) If the control is expensive, then the control function can only reduce incidence by a limited factor.

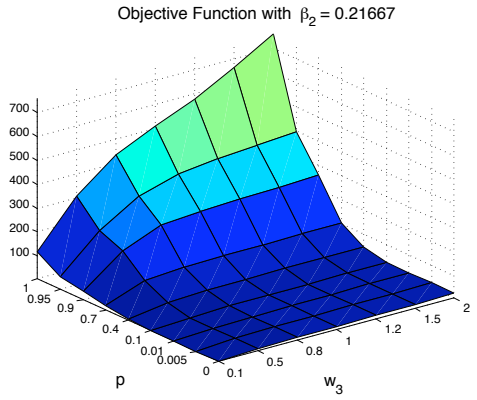
Figure 8.6: The outbreak can be well controlled except when vertical transmission is extremely high. Although this situation is unrealistic, it highlights the importance of a control strategy, whether highly cost efficient, left, or otherwise to take into consideration all possible transmission pathways.

tablished in these communities. This perverse form of Tiebot sorting can lead to a segregation of the population where the most vulnerable live in areas that facilitate the proliferation of the vector and hence the disease. However, people do not live in isolated communities and the introduction of dengue from endemic areas can undermine even the most effective control strategies [Goh, 1998, Gómez-Dantés and Willoquet, 2009, Gubler and Kuno, 1997]. This is particularly true of dengue where there is no vaccine, and hence no way to establish herd immunity [Anderson and May, 1985]. This is true on the global scale as well as the local scale. Although we consider mosquitoes to be the “vector" of dengue, their limited flying ability has made it clear that humans play a substantial role in the long range dispersal of dengue fever [Harrington, L.C. *et al* 2005]. Dengue has spread to many new countries and increased global engagement [FAA, 2011] makes the U.S. particularly vulnerable to future outbreaks considering that the vector is already endemic in many states [Knowlton, K., *et al* 2011].

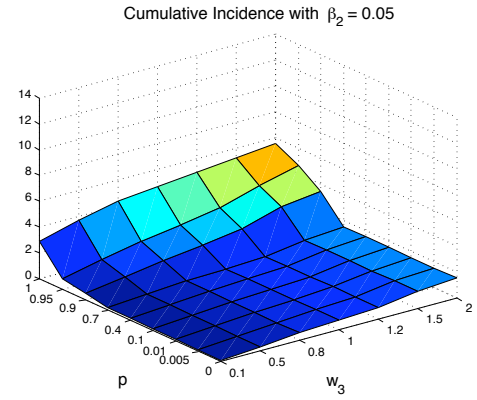
This gloomy outlook is exacerbated by the fact that we sill do not understand



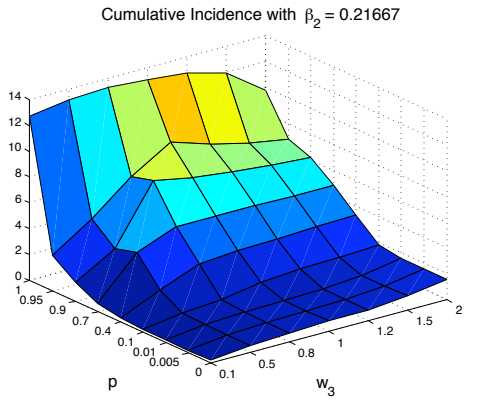
(a) If the force of horizontal transmission is small, β_{Am}, then the force of vertical transmission may be relatively large before an outbreak occurs.



(b) Even if the force of horizontal transmission is moderate, β_{Am}, the force of vertical transmission can create larger outbreaks.



(c) If the relative costs of control, w_3, are high, then it is cheaper not to strongly implement a control measure and the number of dengue cases increases. However, as vertical transmission becomes high, the any control policy becomes inadequate.



(d) As the force of transmission increases, we observe biologically unrealistic rates of infection. These results are included here for illustration of the strong effect low levels of vertical transmission may have if the force of horizontal transmission is large.

Figure 8.7: Regardless of whether horizontal transmission is low, left panels, or moderate, right panels, a high level of vertical transmission can create extremely large, and costly outbreaks, top panels. If the relative costs of controlling the outbreak are low, w_3, then the epidemic can still be controlled, bottom panels. However, if the cost is high, then the outbreak will be extremely expensive and impossible to control.

the role vertical transmission plays in the spread (of some or potentially all strains) of dengue and how particular strains contribute to more severe manifestations of dengue including DHF and DSS. This paper illuminates some of the implications of a control strategy that ignores the role of vertical transmission. If horizontal transmission is the dominant mode of transmission, *and* the reproductive number is not near its threshold value, then vertical transmission may be negligible. However, if any of those conditions are not met, vertical transmission may render a perfectly adequate control policy useless. There is some evidence that genetic changes in either the vector or the virus may facilitate vertical transmission [Bosio, C.F. *et al* 1992, Mourya *et al*, 2001, Gunther, J. *et al* 2007, Arunachalam, N. *et al* 2008,]. The unbeknownst proliferation of these genetic mutants can establish an alternative pathway of dengue transmission leading to unexpected outbreaks and perplexing regulators using policies that should be effective. Thus now knowing the force of vertical transmission can increase both the costs associated with controlling the vector and the burden of dengue cases. While control is still possible, ignoring the role of vertical transmission can only subvert an otherwise effective policy.

8.5 Appendix: Existence of Optimal Control

To prove the existence we use Theorem 4.1 from Fleming and Rishel, but first note the system 1 is clearly well-posed. In particular, the total host and vector populations are constant, $\frac{dN}{dt} = 0$, $\frac{dM}{dt} = 0$, and thus the solutions are bounded in the positive orthant. Then, to use the Theorem from Fleming and Rishel we require the following 5 conditions:

1. The set of controls and corresponding state variables is non-empty
2. The control set, Ω, is convex and closed
3. The right hand side of system 8.1 is bounded by a linear function in the state and control
4. The integrand of the objective functional is convex and bounded below by $c_1(|u_1|^2 + |u_2|^2)^{\frac{\beta}{2}} - c_2$, the Lipschitz condition
5. The payoff function is continuous

To show these we note

1. If we consider the vector of state variables $\mathbf{x} = [S, D_{Am}, D_{As}, H, R, V, W_{Am}, W_{As}]^T$, then we can write our system of equations as

$$\dot{\mathbf{x}} = f(\mathbf{x}, u).$$

   Since we know our state variables are bounded in the positive orthant, the particular form of our system of equations dictates that $f(\mathbf{x}, u)$ is bounded. Thus there exists a unique solution to our system given suitable initial data (cite fred or luke, cauchy or IVP).

2. By construction of Ω, this condition is clearly met.

3. The total population for both the host and vector systems is constant, thus all solutions are bounded. The control function is also bounded thus the right hand side can be bounded by a linear function in the state and control.

4. The integrand is linear in the state variable and quadratic in the control function, and thus clearly convex. Furthermore, the Lipschitz is condition is clearly satisfied as the integrand is bounded below since both the state and control are non-negative.

5. The payoff function is clearly continuous by construction.

Thus we have satisfied the conditions of the Theorem and an optimal control exits.

Chapter 9

Cities in Ecology: Synthesis

We have constructed a framework to conceptualize the city along the dimensions of population and built infrastructure. In our framework the city had its dynamics governed by net migration mediated through the effects of the economic, social and natural environments of the city. We discovered that there were multiple stable states for our city given a fixed set of parameters and that changes in initial conditions, path dependence, had the potential to alter the long term trajectory of our city. However, exogenous forces such as shocks and disturbances or changes in parameters could also qualitatively change the long term equilibrium state of the city. The interplay of human amenity, natural amenity, and economic productivity in a city allowed us to describe the suite of possible trajectories for a set of disparate city types.

Although cities are human dominated habitats, many species have become well adapted to our urban areas. In particular, *Ae. aegypti*, the mosquitoes primarily responsible for large outbreaks of dengue, have adapted to city life. Dengue outbreaks impact primarily children and are often spread in areas that are rapidly urbanizing and lack the social or financial resources to control the mosquito. Thus it is not just the human, natural and economic environment within a city that drives the time evolution of the city, but also the distribution of the human, natural and economic resources that drives the well being of the denizens of the city. The urbanization patterns (and inequality) in a city may drive disease prevalence, and disease prevalence is a signal that could shape the migrations patterns of cities (especially who moves where).

We must understand how we can merge natural, social, and economic resources to drive our cities towards equilibrium states that are desirable, but we must also understand how to distribute those resources to ensure that our cities

are equitable and livable. We want people to come to our cities because they are great, and we want them to stay in our cities because they will have great lives.

BIBLIOGRAPHY

[Akbar et al., 2008] Akbar, M., Agoes, R., Djatie, T., and Kodyat, S. (2008). Pcr detection of dengue transovarial transmissibility in *a*edes aegypti in bandung, indonesia. *Proc ASEAN Congr Trop Med Parasitol*, 3:84–9.

[Aldstadt et al., 2011] Aldstadt, J., Koenraadt, C., Fansiri, T., Kijchalao, U., Richardson, J., Jones, J., and Scott, T. (2011). Ecological modeling of *a*edes aegypti (l.) pupal production in rural kamphaeng phet, thailand. *PLoS Neglected Tropical Diseases*, 5(1):425–462.

[Allen, L.J.S., 2003] Allen, L.J.S. (2003). *An introduction to stochastic processes with applications to biology*. Pearson Education.

[Amanna and Slifka, 2005] Amanna, I. and Slifka, M. (2005). Public fear of vaccination: separating fact from fiction. *Viral Immunology*, 18(2):307–315.

[Amcroft and von Bertele, 2001] Amcroft, D. and von Bertele, M. (2001). An evidence-based vector control strategy for military deployments: the british army experience. *Medecine tropicale*, 61:91–98.

[Amson, J.C., 1975] Amson, J.C. (1975). Catastrophe theory: a contribution to the study of urban systems? *Environment and Planning B*, 2:177–221.

[Anderies, 1998] Anderies, J. (1998). Culture and human agro-ecosystem dynamics: the tsembaga of new guinea. *Journal of theoretical biology*, 192(4):515–530.

[Anderies et al., 2002] Anderies, J., Janssen, M., and Walker, B. (2002). Grazing management, resilience, and the dynamics of a fire-driven rangeland system. *Ecosystems*, 5(1):23–44.

[Anderies et al., 2006] Anderies, J., Walker, B., and Kinzig, A. (2006). Fifteen weddings and a funeral: case studies and resilience-based management. *Ecology and Society*, 11(1):21.

[Anderson and May, 1985] Anderson, R. and May, R. (1985). Vaccination and herd immunity to infectious diseases. *Nature*, 318(6044):323–329.

[Anderson, R.M., 1988] Anderson, R.M. (1988). The role of mathematical models in the study of hiv transmission and the epidemiology of aids. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 1(3):241.

[Arias, J.R., 2002] Arias, J.R. (2002). Dengue: How are we doing?

[Arino et al., 2007] Arino, J., Brauer, F., van den Driessche, P., Watmough, J., and Wu, J. (2007). A final size relation for epidemic models. *Mathematical Biosciences and Engineering*, 4(2):159.

[Arunachalam et al., 2008] Arunachalam, N., Tewari, S., Thenmozhi, V., Rajendran, R., Paramasivan, R., Manavalan, R., Ayanar, K., and Tyagi, B. (2008). Natural vertical transmission of dengue viruses by *a*edes aegypti in chennai, tamil nadu, india. *Indian J Med Res*, 127:395–397.

[Barnes and Rosen, 1974] Barnes, W. and Rosen, L. (1974). Fatal hemorrhagic disease and shock associated with primary dengue infection on a pacific island. *The American Journal of Tropical Medicine and Hygiene*, 23(3):495.

[Batty, 2005] Batty, M. (2005). *Cities and complexity*. MIT Press.

[Batty, 2008] Batty, M. (2008). The size, scale, and shape of cities. *Science*, 319(5864):769.

[Berkes et al., 2000] Berkes, F., Folke, C., and Colding, J. (2000). *Linking social and ecological systems: management practices and social mechanisms for building resilience*. Cambridge Univ Pr.

[Bettencourt et al., 2007] Bettencourt, L., Lobo, J., Helbing, D., Kühnert, C., and West, G. (2007). Growth, innovation, scaling, and the pace of life in cities. *Proceedings of the National Academy of Sciences*, 104(17):7301.

[Blayneh et al., 2009] Blayneh, K., Cao, Y., and Kwon, H. (2009). Optimal control of vector-borne diseases: treatment and prevention. *Discrete and Continuous Dynamical Systems*, Series B(11).

[Blower and Dowlatabadi, 1994] Blower, S. and Dowlatabadi, H. (1994). Sensitivity and uncertainty analysis of complex models of disease transmission: an hiv model, as an example. *International Statistical Review/Revue Internationale de Statistique*, 62(2):229–243.

[Bosio et al., 1992] Bosio, C., Thomas, R., Grimstad, P., and Rai, K. (1992). Variation in the efficiency of vertical transmission of dengue-1 virus by strains of *a*edes albopictus (diptera: Culicidae). *Journal of medical entomology*, 29(6):985–989.

[Bowman et al., 2005] Bowman, C., Gumel, A., Van den Driessche, P., Wu, J., and Zhu, H. (2005). A mathematical model for assessing control strategies against west nile virus. *Bulletin of mathematical biology*, 67(5):1107–1133.

[Brauer and Castillo-Chavez, 2001] Brauer, F. and Castillo-Chavez, C. (2001). *Mathematical models in population biology and epidemiology*. Springer Verlag.

[Burke et al., 1988] Burke, D., Nisalak, A., Johnson, D., and Scott, R. (1988). A prospective study of dengue infections in bangkok. *The American journal of tropical medicine and hygiene*, 38(1):172.

[Carpenter et al., 2001] Carpenter, S., Walker, B., Anderies, J., and Abel, N. (2001). From metaphor to measurement: resilience of what to what? *Ecosystems*, 4(8):765–781.

[Castillo-Chavez and Song, 2004] Castillo-Chavez, C. and Song, B. (2004). Dynamical models of tuberculosis and their applications. *Mathematical biosciences and engineering: MBE*, 1(2):361.

[CDC, 2010] CDC (2010). Report Suggests Nearly 5 Percent Exposed to Dengue Virus in Key West.

[Ceballos and Ehrlich, 2002] Ceballos, G. and Ehrlich, P. (2002). Mammal population losses and the extinction crisis. *Science*, 296(5569):904.

[Cecílio et al., 2009] Cecílio, A., Campanelli, E., Souza, K., Figueiredo, L., and Resende, M. (2009). Natural vertical transmission by stegomyia albopicta as dengue vector in brazil. *Brazilian Journal of Biology*, 69:123–127.

[Center, 2008] Center, P. R. (2008). American Mobility: Who Moves? Who Stays Put? Where's Home? *Social and Demographic Trends*.

[Center, 2009] Center, P. R. (2009). Denver Tops List of Favorite Cities: For Nearly Half of America, Grass Is Greener Somewhere Else. *Social and Demographic Trends*.

[Chowell and Sanchez, 2006] Chowell, G. and Sanchez, F. (2006). Climate-based descriptive models of dengue fever: the 2002 epidemic in colima, mexico. *Journal of environmental health*, 68(10):40.

[Chowell et al., 2008] Chowell, G., Torre, C., Munayco-Escate, C., Suarez-Ognio, L., López-Cruz, R., Hyman, J., and Castillo-Chavez, C. (2008). Spatial and temporal dynamics of dengue fever in peru: 1994–2006. *Epidemiology and infection*, 136(12):1667–1677.

[Clapp et al., 1997] Clapp, J., Rodriguez, M., and Thrall, G. (1997). How GIS can put urban economic analysis on the map. *Journal of Housing Economics*, 6:368–386.

[Clark, 1985] Clark, C. (1985). *Bioeconomic modelling and fisheries management*. Wiley.

[Clarke and Gaydos, 1998] Clarke, K. and Gaydos, L. (1998). Long term urban growth prediction using a cellular automaton model and gis: Applications in san francisco and washington/baltimore. *International Journal of Geographical Information Science*, 12(7):699–714.

[Córdoba, 2008] Córdoba, J. (2008). On the distribution of city sizes. *Journal of Urban Economics*, 63(1):177–197.

[Cruz-Pacheco et al., 2004] Cruz-Pacheco, G., Esteva, L., Montano, J., and Vargas, C. (2004). A mathematical model for the dynamics of west nile virus.

[De Groot et al., 2002] De Groot, R., Wilson, M., and Boumans, R. (2002). A typology for the classification, description and valuation of ecosystem functions, goods and services. *Ecological economics*, 41(3):393–408.

[Dendrinos and Mullally, 1981] Dendrinos, D. and Mullally, H. (1981). Evolutionary patterns of urban populations. *Geographical Analysis*, 13(4):328–344.

[Dendrinos and Mullally, 1985] Dendrinos, D. and Mullally, H. (1985). *Urban evolution: studies in the mathematical ecology of cities*. Oxford Univ Pr.

[Deubel et al., 1986] Deubel, V., Kinney, R., and Trent, D. (1986). Nucleotide sequence and deduced amino acid sequence of the structural proteins of dengue type 2 virus, jamaica genotype. *Virology (USA)*.

[Diamond et al., 2005] Diamond, J., Ltd, L. T., Film, N. G. T. ., and (US), N. G. S. (2005). *Guns, germs, and steel*. National Geographic.

[Diekmann et al., 1990] Diekmann, O., Heesterbeek, J., and Metz, J. (1990). On the definition and the computation of the basic reproduction ratio r_0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28(4):365–382.

[Edelstein-Keshet, L., 1988] Edelstein-Keshet, L. (1988). Mathematical models in biology. *Birkh*
"auser mathematics series.

[Eisen and Eisen, 2008] Eisen, R. and Eisen, L. (2008). Spatial modeling of human risk of exposure to vector-borne pathogens based on epidemiological versus arthropod vector data. *Journal of medical entomology*, 45(2):181–192.

[FAA, 2011] FAA (2011). FAA Forcast Fact Sheet[1]-Fiscal Years 2011-31.

[Farrar et al., 2007] Farrar, J., Focks, D., Gubler, D., Barrera, R., Guzman, M., Simmons, C., Kalayanarooj, S., Lum, L., McCall, P., Lloyd, L., et al. (2007). Editorial: Towards a global dengue research agenda. *Tropical Medicine & International Health*, 12(6):695–699.

[Fleming and Rishel, 1975] Fleming, W. and Rishel, R. (1975). *Deterministic and stochastic optimal control*. Springer-Verlag, New York.

[Focks and Alexander, 2006] Focks, D. and Alexander, N. (2006). Multicountry study of *a*edes aegypti pupal productivity survey methodology: findings and recommendations. *Geneva: WHO*.

[Forrester, 1969] Forrester, J. (1969). *Urban Dynamics*. The MIT Press.

[Gladwell, 2000] Gladwell, M. (2000). *The tipping point: How little things can make a big difference*. Little, Brown and Company.

[Goh, 1998] Goh, K. (1998). Dengue-a re-emerging infectious disease in singapore. *Dengue in Singapore.*, pages 33–49.

[Goldfrank et al., 1999] Goldfrank, W., Goodman, D., and Szasz, A. (1999). *Ecology and the world-system*. Praeger Pub Text.

[Gómez-Dantés and Willoquet, 2009] Gómez-Dantés, H. and Willoquet, J. (2009). Dengue in the americas: challenges for prevention and control. *Cadernos de Saúde Pública*, 25:19–31.

[Govindarajan et al., 2011] Govindarajan, M., Mathivanan, T., Elumalai, K., Krishnappa, K., and Anandan, A. (2011). Mosquito larvicidal, ovicidal, and repellent properties of botanical extracts against anopheles stephensi, *a*edes aegypti, and culex quinquefasciatus (diptera: Culicidae). *Parasitology Research*, pages 1–15. 10.1007/s00436-011-2263-1.

[Graves and Linneman, 1979] Graves, P. and Linneman, P. (1979). Household migration: Theoretical and empirical results. *Journal of urban economics*, 6(3):383–404.

[Greenwood, 1985] Greenwood, M. (1985). Human migration: theory, models, and empirical studies. *Journal of Regional Science*, 25(4):521–544.

[Gubler and Clark, 1996] Gubler, D. and Clark, G. (1996). Community involvement in the control of *a*edes aegypti. *Acta Tropica*, 61(2):169–179.

[Gubler and Kuno, 1997] Gubler, D. and Kuno, G. (1997). *Dengue and Dengue Hemorrhagic Fever*. CABI.

[Gubler et al., 1978] Gubler, D., Reed, D., Rosen, L., and Hitchcock Jr, J. (1978). Epidemiologic, clinical, and virologic observations on dengue in the kingdom of tonga. *The American Journal of Tropical Medicine and Hygiene*, 27(3):581.

[Gubler, D., 2005] Gubler, D. (2005). The emergence of epidemic dengue fever and dengue hemorrhagic fever in the americas: a case of failed public health policy. *Revista Panamericana de Salud Pública*, 17:221–224.

[Gumel et al., 2006] Gumel, A., Castillo-Chavez, C., Mickens, R., and Clemence, D. (2006). *Mathematical studies on human disease dynamics: emerging paradigms and challenges*. American Mathematical Society.

[Günther et al., 2007] Günther, J., Martínez-Muñoz, J., Pérez-Ishiwara, D., and Salas-Benito, J. (2007). Evidence of vertical transmission of dengue virus in two endemic localities in the state of oaxaca, mexico. *Intervirology*, 50(5):347–352.

[Guzman et al., 1995] Guzman, M., Deubel, V., Pelegrino, J., Rosario, D., Marrero, M., Sariol, C., and Kouri, G. (1995). Partial nucleotide and amino acid sequences of the envelope and the envelope/nonstructural protein-1 gene junction of four dengue-2 virus strains isolated during the 1981 cuban epidemic. *The American journal of tropical medicine and hygiene*, 52(3):241.

[Haken, 1983] Haken, H. (1983). *Synergetics: an introduction: nonequilibrium phase transitions and self-organization in physics, chemistry and biology*. Springer Berlin:.

[Halstead et al., 2002] Halstead, S., Lan, N., Myint, T., Shwe, T., Nisalak, A., Kalyanarooj, S., Nimmannitya, S., Soegijanto, S., Vaughn, D., and Endy, T.

(2002). Dengue hemorrhagic fever in infants: research opportunities ignored. *Centers for Disease Control*.

[Halstead et al., 1970] Halstead, S., Nimmannitya, S., and Cohen, S. (1970). Observations related to pathogenesis of dengue hemorrhagic fever. iv. relation of disease severity to antibody response and virus recovered. *The Yale Journal of Biology and Medicine*, 42(5):311.

[Halstead, S.B., 1988] Halstead, S.B. (1988). Pathogenesis of dengue: challenges to molecular biology. *Science*, 239(4839):476.

[Halstead, S.B., 2006] Halstead, S.B. (2006). Dengue in the americas and southeast asia: do they differ? *Revista Panamericana de Salud Pública*, 20:407–415.

[Harrington et al., 2005] Harrington, L., Scott, T., Lerdthusnee, K., Coleman, R., Costero, A., Clark, G., Jones, J., Kitthawee, S., Kittayapong, P., Sithiprasasna, R., et al. (2005). Dispersal of the dengue vector *a*edes aegypti within and between rural communities. *The American journal of tropical medicine and hygiene*, 72(2):209.

[Harris et al., 2000] Harris, E., Videa, E., Perez, L., Sandoval, E., Tellez, Y., Perez, M., Cuadra, R., Rocha, J., Idiaquez, W., Alonso, R., et al. (2000). Clinical, epidemiologic, and virologic features of dengue in the 1998 epidemic in nicaragua. *The American journal of tropical medicine and hygiene*, 63(1):5.

[Hawley, 1981] Hawley, A. (1981). *Urban Society: an ecological approach*. Wiley and Sons, Inc., NY, NY.

[Hawley et al., 1987] Hawley, W., Reiter, P., Copeland, R., Pumpuni, C., and Craig Jr, G. (1987). *A*edes albopictus in north america: probable introduction in used tires from northern asia. *Science*, 236(4805):1114.

[Hemingway and Ranson, 2000] Hemingway, J. and Ranson, H. (2000). Insecticide resistance in insect vectors of human disease. *Annual Review of Entomology*, 45(1):371–391.

[Hernandez-Suarez, C.M., 2009] Hernandez-Suarez, C.M. (2009). Dengue in colima.

[Holling, 1973] Holling, C. (1973). Resilience and stability of ecological systems. *Annual review of ecology and systematics*, 4:1–23.

[Hopkins et al., 1982] Hopkins, T., Wallerstein, I., Bach, R., et al. (1982). *World-systems analysis: theory and methodology*. Sage Publications.

[Hutamai et al., 2007] Hutamai, S., Suwonkerd, W., Suwannchote, N., Somboon, P., and Prapanthadara, L. (2007). A survey of dengue viral infection in *a*edes aegypti and *a*edes albopictus from re-epidemic areas in the north of thailand using nucleic acid sequence based amplification assay. *Southeast Asian journal of tropical medicine and public health*, 38(3):448.

[Jacobs, 1992] Jacobs, J. (1992). *The death and life of great American cities*. Vintage.

[Judson, 2009] Judson, O. (2009). Math and the City. *The New York Times*, The Wild Side, Guest Column.

[Karatzas and Shreve, 1991] Karatzas, I. and Shreve, S. (1991). *Brownian motion and stochastic calculus*. Springer.

[Karlin and Taylor, 1975] Karlin, S. and Taylor, H. (1975). *A first course in stochastic processes*. Academic Press New York.

[Kermack and McKendrick, 1927] Kermack, W. and McKendrick, A. (1927). A contribution to the mathematical theory of epidemics. *Proc. R. Soc. London*, 115:700.

[Knowlton et al., 2011] Knowlton, K., Solomon, G., and Rotkin-Ellman, M. (2009, assessed February 2011). Fever pitch: Mosquito-borne dengue fever threat spreading in the americas. http://www.nrdc.org/health/dengue/files/dengue.pdf NRDC Issue Paper, July.

[Knox, 1995] Knox, P. (1995). *World cities in a world-system*. Cambridge Univ Pr.

[Knox and McCarthy, 1994] Knox, P. and McCarthy, L. (1994). *Urbanization: An introduction to urban geography*. Prentice-Hall.

[Kochel et al., 2002] Kochel, T., Watts, D., Halstead, S., Hayes, C., Espinoza, A., Felices, V., Caceda, R., Bautista, C., Montoya, Y., Douglas, S., et al. (2002). Effect of dengue-1 antibodies on american dengue-2 viral infection and dengue haemorrhagic fever. *The Lancet*, 360(9329):310–312.

[Kok, Y., 2010] Kok, Y. (2010). Dengue fever cases reach record highs, in *Time*.

[Koodalingam et al., 2011] Koodalingam, A., Mullainadhan, P., and Arumugam, M. (2011). Effects of extract of soapnut sapindus emarginatus on esterases and phosphatases of the vector mosquito, *a*edes aegypti (diptera: Culicidae). *Acta Tropica*.

[Kow et al., 2001] Kow, C., Koon, L., and Yin, P. (2001). Detection of dengue viruses in field caught male *a*edes aegypti and *a*edes albopictus (diptera: Culicidae) in singapore by type-specific pcr. *Journal of medical entomology*, 38(4):475–479.

[Kribs-Zaleta, 2002] Kribs-Zaleta, C. (2002). Center manifolds and normal forms in epidemic models. *IMA VOLUMES IN MATHEMATICS AND ITS APPLICATIONS*, 125:269–286.

[Krugman, P., 1996] Krugman, P. (1996). *The Self Organizing Economy (Mitsui Lectures in Economics)*. Blackwell Pub.

[Kurtz, T.G., 1978] Kurtz, T.G. (1978). Strong approximation theorems for density dependent markov chains. *Stochastic Processes and their Applications*, 6(3):223–240.

[Kuske et al., 2007] Kuske, R., Gordillo, L., and Greenwood, P. (2007). Sustained oscillations via coherence resonance in SIR. *Journal of theoretical biology*, 245(3):459–469.

[Kuznetsov et al., 1998] Kuznetsov, Y., Kuznetsov, I., and Kuznetsov, Y. (1998). *Elements of applied bifurcation theory*. Springer New York.

[Kyle and Harris, 2008] Kyle, J. and Harris, E. (2008). Global spread and persistence of dengue. *Annual Reviews*.

[Lancaster, 1971] Lancaster, K. (1971). *Consumer demand: a new approach*. Columbia University Press New York.

[Larson et al., 2010] Larson, L., Murillo, D., Shutters, S., Miller, T., and Garduno, G. (2010). Proximity IsnÕt Everything: A Hedonic Model to Estimate the Value of Public Parks to Single- and Multi-Family Residences in the Phoenix Metropolitan Area. *In Preparation*.

[Lee, 1973] Lee, D. (1973). Requiem for large-scale models. *Journal of the American Planning Association*, 39(3):163–178.

[Lee et al., 2010a] Lee, S., Chowell, G., and Castillo-Chavez, C. (2010a). Optimal control of inSSuenza pandemics: The role of antiviral treatment and isolation. *Journal Theoretical Biology*, 265:136–150.

[Lee et al., 2010b] Lee, S., Jung, E., and Castillo-Chávez, C. (2010b). Optimal control intervention strategies in low- and high-risk problem drinking populations. *Socio-Economic Planning Sciences*, 44:258–265.

[Lee et al., 2011] Lee, S., Morales, R., and Castillo-Chávez, C. (2011). A note on the use of inSSuenza vaccination strategies when supply is limited. *Mathematical Biosciences and Engineering*, 8(1):172–182.

[Leitmeyer et al., 1999] Leitmeyer, K., Vaughn, D., Watts, D., Salas, R., Villalobos, I., et al. (1999). Dengue virus structural differences that correlate with pathogenesis. *Journal of Virology*, 73(6):4738.

[Lenhard and Workman, 2007] Lenhard, S. and Workman, J. (2007). *Optimal control applied to biological models*. Chapman and Hall, CRC Press, New York.

[Lewis et al., 1993] Lewis, J., Chang, G., Lanciotti, R., Kinney, R., Mayer, L., and Trent, D. (1993). Phylogenetic relationships of dengue-2 viruses. *Virology (New York, NY)*, 197(1):216–224.

[Lloyd, R., 2008] Lloyd, R. (2008). Bones reveal oldest case of tb. http://www.livescience.com/history/081014-tb-skeleton.html.

[Macdonald, G., 1957] Macdonald, G. (1957). *The epidemiology and control of malaria*. Oxford University Press.

[Malthus and edited by Appleman, 2004] Malthus, T. and edited by Appleman, P. (2004). *An essay on the principle of population : influences on Malthus' work nineteenth-century comment, Malthus in the twenty-first century*. New York: Norton.

[Massey, 1990] Massey, D. (1990). Social structure, household strategies, and the cumulative causation of migration. *Population index*, 56(1):3–26.

[Massey et al., 1993] Massey, D., Arango, J., Hugo, G., Kouaouci, A., Pellegrino, A., and Taylor, J. (1993). Theories of international migration: a review and appraisal. *Population and development review*, pages 431–466.

[Massey et al., 1994] Massey, D., Arango, J., Hugo, G., Kouaouci, A., Pellegrino, A., and Taylor, J. (1994). An evaluation of international migration theory: the North American case. *Population and Development Review*, 20(4):699–751.

[McKenzie and Samba, 2004] McKenzie, F. and Samba, E. (2004). The role of mathematical modeling in evidence-based malaria control. *The American journal of tropical medicine and hygiene*, 71(2 Suppl):94.

[McNeill, 1976] McNeill, W. (1976). *Plagues and peoples*. Anchor.

[Montoya et al., 2003] Montoya, Y., Holechek, S., Caceres, O., Palacios, A., Burans, J., Guevara, C., Quintana, F., Herrera, V., Pozo, E., Anaya, E., et al. (2003). Circulation of dengue viruses in north-western peru, 2000-2001. *World Health Organization Regional Office for South-East Asia*.

[Morens and Fauci, 2008] Morens, D. and Fauci, A. (2008). Dengue and hemorrhagic fever: A potential threat to public health in the united states. *Jama*, 299(2):214.

[Mount et al., 1996] Mount, G., Biery, T., and Haile, D. (1996). A review of ultralow-volume aerial sprays of insecticide for mosquito control. *Journal of the American Mosquito Control Association-Mosquito News*, 12(4):601–618.

[Mourya et al., 2001] Mourya, D., Gokhale, M., Basu, A., Barde, P., Sapkal, G., Padbidri, V., and Gore, M. (2001). Horizontal and vertical transmission of dengue virus type 2 in highly and lowly susceptible strains of *A*edes aegypti mosquitoes. *Acta virologica*, 45(2):67–72.

[Mulligan, 1984] Mulligan, G. (1984). Agglomeration and central place theory: a review of the literature. *International Regional Science Review*, 9(1):1–42.

[Mulligan, 2009] Mulligan, G. (2009). Urban Amenities. *SciTopics*, Retrieved May 8, 2010, from http://www.scitopics.com/Urban_Amenities.html.

[Mumford, 1997] Mumford, L. (1997). *The culture of cities*. Routledge.

[Murillo et al., 2012a] Murillo, D., Holechek, S., Sánchez, F., Edwar, P., and Castillo-Chávez, C. (2012a). The 2000 dengue outbreak in peru: A case for vertical transmission. *in preperation*.

[Murillo et al., 2012b] Murillo, D., Sánchez, F., Holechek, S., and Castillo-Chávez, C. (2012b). Vertical transmission in a two-strain model of dengue fever. *in preperation*.

[Murray, J.D., 2002] Murray, J.D. (2002). *Mathematical biology*. Springer.

[Nations, 2011] Nations, U. (2011). Un lauds international cooperation in eradicating deadly cattle plague.

[Nguyen et al., 2006] Nguyen, H., Nguyen, L., Lei, H., Lin, Y., Lien, L., Huang, K., Lin, C., Do, Q., Vo, H., Lam, M., Yeh, T., Huang, J., Liu, C., and Halstead, S. (2006). Volume replacement in infants with dengue hemorrhagic fever/dengue shock syndrome. *The American journal of tropical medicine and hygiene*, 74(4):684.

[Nishiura, H., 2006] Nishiura, H. (2006). Mathematical and statistical analyses of the spread of dengue. *Dengue Bulletin*, 30:51.

[Ooi et al., 2006] Ooi, E., Goh, K., and Gubler, D. (2006). Dengue prevention and 35 years of vector control in singapore. *Shouxi*, 12(6).

[Pacheco-Coral et al., 2010] Pacheco-Coral, A., Quiñones-Pinzón, M., Serrato-Pomar, I., and Rivas-Muñoz, F. (2010). Evaluating an information, education and communication (iec) strategy which was adopted for *a*edes aegypti control in la dorada, colombia. *Revista de Salud Pública*, 12(3):380–390.

[Page, 2011] Page, S. (2011). Diversity and Collective Wisdom. Presentation.

[Park, 1951] Park, R. (1951). The city: Suggestions for the investigation of human behavior in the urban environment. In Hatt, P. and Reiss Jr., A., editors, *Reader in Urban Sociology*, pages 2–32. The Free Press, Glencoe, IL.

[Paz-Soldan et al., 2011] Paz-Soldan, V., Plasai, V., Morrison, A., Rios-Lopez, E., Guedez-Gonzales, S., Grieco, J., Mundal, K., Chareonviriyaphap, T., and Achee, N. (2011). Initial assessment of the acceptability of a push-pull *a*edes aegypti control strategy in iquitos, peru and kanchanaburi, thailand. *The American Journal of Tropical Medicine and Hygiene*, 84(2):208.

[Pettit et al., 2010] Pettit, W., Whelan, P., McDonnell, J., and Jacups, S. (2010). Efficacy of alpha-cypermethrin and lambda-cyhalothrin applications to prevent *a*edes breeding in tires. *Journal of the American Mosquito Control Association*, 26(4):387–397.

[Polson et al., 2006] Polson, K., Rawlins, S., Brogdon, W., and Chadee, D. (2006). Characterisation of ddt and pyrethroid resistance in trinidad and tobago populations of *a*edes aegypti. *Bulletin of Entomological Research*, pages 1–7.

[Polson et al., 2010] Polson, K., Rawlins, S., Brogdon, W., and Chadee, D. (2010). Organophosphate resistance in trinidad and tobago strains of *a*edes aegypti. *Journal of the American Mosquito Control Association*, 26(4):403–410.

[Pontryagin et al., 1962] Pontryagin, L., Boltyanskii, V., Gamkrelidze, R., and Mishchenko, E. (1962). The mathematical theory of optimal control processes. *Interscience, New York*.

[Prietula et al., 1998] Prietula, M., Carley, K., and Gasser, L. (1998). *Simulating organizations: Computational models of institutions and groups*, volume 1. The MIT Press.

[Reisner, 1993] Reisner, M. (1993). *Cadillac desert: The American West and its disappearing water*. Penguin Group USA.

[Reiter and Gubler, 1997] Reiter, P. and Gubler, D. (1997). Surveillance and control of urban dengue vectors. *Dengue and dengue hemorragic fever. New York: CAB International*, pages 45–60.

[Richardson, H. W., 1973] Richardson, H. W. (1973). Theory of the distribution of city sizes: Review and prospects. *Regional Studies*, 7:239–251.

[Rico-Hesse et al., 1998] Rico-Hesse, R., Harrison, L., Nisalak, A., Vaughn, D., Kalayanarooj, S., Green, S., Rothman, A., and Ennis, F. (1998). Molecular evolution of dengue type 2 virus in thailand. *The American journal of tropical medicine and hygiene*, 58(1):96.

[Rico-Hesse et al., 1997] Rico-Hesse, R., Harrison, L., Salas, R., Tovar, D., Nisalak, A., Ramos, C., Boshell, J., de Mesa, M., Nogueira, R., and Rosa, A. (1997). Origins of dengue type 2 viruses associated with increased pathogenicity in the americas. *Virology*, 230(2):244–251.

[Rodhain and Rosen, 1997] Rodhain, F. and Rosen, L. (1997). Mosquito vectors and dengue virus-vector relationships. *Dengue and dengue hemorrhagic fever*, pages 112–134.

[Rogers and Murillo, 2010] Rogers, B. and Murillo, D. (2010). Pigs, Parties and Noise: How Stochasticity Impacts the Robustness of the Tsembaga Cultural Practices. *In Review*.

[Rosen et al., 1983] Rosen, L., Shroyer, D., Tesh, R., Freier, J., and Lien, J. (1983). Transovarial transmission of dengue viruses by mosquitoes: *A*edes albopictus and *a*edes aegypti. *The American journal of tropical medicine and hygiene*, 32(5):1108–1119.

[Rosen, 1974] Rosen, S. (1974). Hedonic prices and implicit markets: product differentiation in pure competition. *Journal of political economy*, 82(1).

[Rosen, L., 1977] Rosen, L. (1977). The emperor's new clothes revisited, or reflections on the pathogenesis of dengue hemorrhagic fever. *The American Journal of Tropical Medicine and Hygiene*, 26(3):337.

[Ross, R., 1910] Ross, R. (1910). *The prevention of malaria*. Dutton.

[Samuelson, 1971] Samuelson, P. (1971). Generalized predator-prey oscillations in ecological and economic equilibrium. *Proceedings of the National Academy of Sciences of the United States of America*, 68(5):980.

[Sanchez et al., 2006] Sanchez, F., Engman, M., Harrington, L., and Castillo-Chavez, C. (2006). Models for dengue transmission and control. In *Mathematical studies on human disease dynamics: emerging paradigms and challenges: AMS-IMS-SIAM Joint Summer Research Conference on modeling the dynamics of human diseases: emerging paradigms and challenges, July 17-21, 2005, Snowbird, Utah*, volume 410, page 311. Amer Mathematical Society.

[Sanchez, F., 2007] Sanchez, F. (2007). Studies in epidemiology and social dynamics. *D., Cornell University*.

[Sangkawibha et al., 1984] Sangkawibha, N., Rojanasuphot, S., Ahandrik, S., Viriyapongse, S., Jatanasen, S., Salitul, V., Phanthumachinda, B., and Halstead, S. (1984). Risk factors in dengue shock syndrome: a prospective epidemiologic study in rayong, thailand: I. the 1980 outbreak. *American Journal of Epidemiology*, 120(5):653.

[Scott et al., 1976] Scott, R., Nimmannitya, S., Bancroft, W., and Mansuwan, P. (1976). Shock syndrome in primary dengue infections. *The American Journal of Tropical Medicine and Hygiene*, 25(6):866.

[Scott et al., 2000] Scott, T., Amerasinghe, P., Morrison, A., Lorenz, L., Clark, G., Strickman, D., Kittayapong, P., and Edman, J. (2000). Longitudinal studies of *a*edes aegypti (diptera: Culicidae) in thailand and puerto rico: blood feeding frequency. *Journal of Medical Entomology*, 37(1):89–101.

[Shah, 2010] Shah, S. (2010). *The Fever: how malaria has ruled humankind for 500,000 years*. Farrar, Straus and Giroux.

[Shah, S., 2010] Shah, S. (2010). The tenacious buzz of malaria. http://online.wsj.com/article/SB10001424052748704111704575354911834340450.html.

[Shim et al., 2009] Shim, E., Kochin, B., and Galvani, A. (2009). Insights from epidemiological game theory into gender-specific vaccination against rubella. *Math Biosci Eng*, 6(4):839–854.

[Shiode and Torrens, 2008] Shiode, N. and Torrens, P. (2008). Comparing the Growth Dynamics of Real and Virtual Cities. *Understanding dynamics of geographic domains*, page 187.

[Shreve, 2004] Shreve, S. (2004). *Stochastic calculus for finance: Continuous-time models*. Springer Verlag.

[Siler et al., 1926] Siler, J., Hall, M., Hitchens, A., et al. (1926). Dengue: its history, epidemiology, mechanism of transmission, etiology, clinical manifestations, immunity, and prevention. *Philippine Journal of Science*, 29:1–302.

[Simmons et al., 1931] Simmons, J., St John, J., and Reynolds, F. (1931). Experimental studies of dengue. *Philippine Journal of Science*, 44:424–428.

[Sittisombut et al., 1997] Sittisombut, N., Sistayanarain, A., Cardosa, M., Salminen, M., Damrongdachakul, S., Kalayanarooj, S., Rojanasuphot, S., Supawadee, J., and Maneekarn, N. (1997). Possible occurrence of a genetic bottleneck in dengue serotype 2 viruses between the 1980 and 1987 epidemic seasons in bangkok, thailand. *The American journal of tropical medicine and hygiene*, 57(1):100.

[Soderlund et al., 1999] Soderlund, N., Zwi, K., Kinghorn, A., and Gray, G. (1999). Prevention of vertical transmission of hiv: analysis of cost effectiveness of options available in south africa. *Bmj*, 318(7199):1650.

[Sodhi et al., 2009] Sodhi, N., Brook, B., and Bradshaw, C. (2009). Causes and consequences of species extinctions. *The Princeton Guide to Ecology*, pages 514–520.

[Soper, F.L., 1967] Soper, F.L. (1967). *A*edes aegypti and yellow fever. *Bulletin of the World Health Organization*, 36(4):521.

[Strogatz, 1994] Strogatz, S. (1994). *Nonlinear dynamics and chaos*. Addison-Wesley Reading, MA.

[The College of Physicians of Philedelphia, 2012] The College of Physicians of Philedelphia (2012). History of vaccines. http://www.historyofvaccines.org.

[Troy and Grove, 2008] Troy, A. and Grove, J. (2008). Property values, parks, and crime: A hedonic analysis in Baltimore, MD. *Landscape and Urban Planning*, 87(3):233–245.

[Van den Driessche and Watmough, 2002] Van den Driessche, P. and Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180(1):29–48.

[Weidlich, 1991] Weidlich, W. (1991). Physics and social science–The approach of synergetics. *Physics Reports*, 204(1):1–163.

[Weidlich, 2000] Weidlich, W. (2000). *Sociodynamics*. Harwood Academic Publishers.

[White and Engelen, 2000] White, R. and Engelen, G. (2000). High-resolution integrated modelling of the spatial dynamics of urban and regional systems. *Computers, environment and urban systems*, 24(5):383–400.

[WHO, 2010] WHO (2010). Dengue and Dengue Hemorrhagic Fever. Fact sheet No. 117. [cited December 22, 2009].

[Wilson, 1981] Wilson, A. (1981). *Catastrophe theory and bifurcation: applications to urban and regional systems*. University of California Press.

[Wimberley et al., 2007] Wimberley, R., Morris, L., and Fulkerson, G. (2007). World population takes a turn. *The News and Observer*.

[Zhang et al., 2006] Zhang, C., Mammen Jr, M., Chinnawirotpisan, P., Klungthong, C., Rodpradit, P., Nisalak, A., Vaughn, D., Nimmannitya, S., Kalayanarooj, S., and Holmes, E. (2006). Structure and age of genetic diversity of dengue virus type 2 in thailand. *Journal of General Virology*, 87(4):873.

[Zhang et al., 2007] Zhang, P., Sandland, G., Feng, Z., Xu, D., and Minchella, D. (2007). Evolutionary implications for interactions between multiple strains of host and parasite. *Journal of theoretical biology*, 248(2):225–240.

[Zipf, 1972] Zipf, G. (1972). *Human behavior and the principle of least effort*. Hafner New York.