NOVEL APPLICATIONS OF EXPECTED UTILITY THEORY TO EPIGENETICS, SIGNAL DETECTION AND EPIDEMIOLOGY

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ABSTRACT OF THE DISSERTATION

Novel Applications of Expected Utility Theory to Epigenetics, Signal Detection and Epidemiology

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Trade-offs occur at every level of ecological organization and are sensitive to changing environments and sudden perturbations to systems. To study trade-offs, it is necessary to characterize the costs and benefits of traits under conditions of environmental change, however this can be challenging to accomplish empirically. Economic theory has a long history of examining optimal strategies in games, gambles and investments.¹ An economic framework that characterizes costs and benefits of a particular strategy is called expected utility theory.²,³ Within the body of this work, we propose that expected utility theory may be applied to anticipate how an individual or population will respond to changing environmental conditions.

We apply this expected utility theory framework to three biological systems to explore optimal decision making in the face of trade-offs to individuals and populations in the face of changing environmental conditions. Specifically, we model expected utility of epigenetic gene regulation, expected utility of signal detection criteria in social populations, and expected utility of social isolation during a pandemic in populations with heterogeneous immunocompromise.

Our first application of expected utility theory answers: under which frequencies of environmental change is epigenetic regulation of gene expression likely to emerge? To
answer this question, we propose that epigenetic modulation is itself a trait with benefits such as enabling rapid acclimation to environmental conditions and costs such as establishing and controlling epigenetic machinery. We then introduce the concept of epiallelic redundancy as a means by which to increase the likelihood that an organism will express the optimal trait for the current environmental conditions. Next, we develop a model characterizing the expected utility of epigenetic modulation of phenotype. Our results show that epigenetic control is only likely to evolve in situations where the cost of control is small and environmental fluctuations are frequent, causing variations in the fitness of a phenotype across a range of environmental conditions.

Our next application of expected utility theory is to answer: can heterogeneity in signal detection criteria among individuals in a population facilitate or dissolve trade-offs in group decision making? To answer this question, we first invoke the framework of signal detection theory (SDT). In this framework, individuals vary in the criteria that they set to detect and respond to environmental signals. Individuals with high criterion values for signal detection have more hits (true positive detections) and fewer correct rejections (true negative detections), whereas individuals with lower criterion values will have fewer hits and more correct rejections. This difference in detection ability leads to trade-offs in signal detection. To answer our question at the population level, we expand the classical signal detection theory framework to include populations of individuals varying in their signal detection criterion choice. Further, we determine a net utility for each individual of participating in group consensus. We show that individual payoff for participating a population-level decision-making regarding the presence of a signal can affect the criterion choice utility each individual experiences. These results suggest that
coordination in decision-making regarding a signal can be advantageous in changing environmental conditions and can maintain individual variation in signal detection criteria in populations.

Our final application of expected utility theory answers: how does heterogeneous immunocompromise within a population affect the economic and epidemiological utility of social isolation? To answer this question, we develop a multi-group Susceptible-Exposed-Infected-Recovered (SEIR) model to compartmentalize individuals by immunocompetence. Next, we use expected utility theory to generate utilities of social isolation. These utilities of social isolation are then evaluated for various social isolation scenarios and provide a means by which to compare both macroeconomic and epidemiological effects of the social isolation scenarios. We show that in populations with high proportions of immunocompromised individuals, there is a higher expected utility of social isolation than in populations with smaller proportions of immunocompromised individuals. In populations with higher proportions of immunocompromised individuals, we find that the form of the expected utility curve is shifted such that more stringent social isolation is more favorable to economic and epidemiological outcomes.

Taken together, the three chapters of this dissertation represent successful applications of expected utility theory to ecological systems. The conceptual and computational simplicity of expected utility theory lends itself readily to application in a wide variety of biological systems and provides a reliable proxy for quantifying the trade-offs inherent to those systems.
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TABLE OF CONTENTS

ABSTRACT OF THE DISSERTATION ................................................................. ii

ACKNOWLEDGEMENTS .............................................................................. v

LIST OF TABLES ........................................................................................ vii

LIST OF ILLUSTRATIONS .......................................................................... viii

INTRODUCTION ........................................................................................... 1

CHAPTER 1: Expected Utility of Epigenetic Modulation of Gene Expression ........6

CHAPTER 2: Consensus Signaling as a Means to Preserve Heterogeneity in Signal Detection Criteria .......................................................... 30

CHAPTER 3: The Expected Utility of Social Isolation Can Inform Policy Decision-Making in a Pandemic ................................................................. 45

GENERAL DISCUSSION AND CONCLUDING REMARKS ................... 67

REFERENCES ............................................................................................ 71
LIST OF TABLES

Table 1: Proportion of criterion choices represented in each population distribution modeled ................................................................. 33

Table 2: Parameters used in multi-group SEIR model with economic impact ............. 54

Table 3: Parameters used in Gauteng province and Kigali City province runs of the model. ...................................................................................................................... 55

Table 4: Model results for Gauteng province, South Africa ...................................... 57

Table 5: Model results for Kigali City province, Rwanda ........................................ 57
LIST OF ILLUSTRATIONS

Figure 1: Expected relative utility of epigenetic modulation surface as a function of utility of target trait and environmental predictability window. .................................................16

Figure 2: Expected relative utility of epigenetic modulation surface as a function of utility of target trait and total number of genetic traits. ..........................................................17

Figure 3: Expected relative utility of epigenetic modulation surface as a function of utility of target trait and epiallelic redundancy. .................................................................18

Figure 4: Expected relative utility of epigenetic modulation surface as a function of utility of target trait and costs of epigenetic modulation. ....................................................19

Figure 5: Expected relative utility of epigenetic modulation surface as a function of cost of epigenetic modulation and epiallelic redundancy. ......................................................21

Figure 6: Expected relative utility of epigenetic modulation surface as a function of environmental predictability and number of traits. .........................................................22

Figure 7: Expected relative utility of epigenetic modulation surface as a function of environmental predictability and epiallelic redundancy. .....................................................23

Figure 8: Probabilities of hits, misses, correct rejections and false alarms associated with each of the 4 criteria modeled. .................................................................35

Figure 9: Utility of Population Mean Criterion (UPMC) under Consensus Requirement Conditions. .................................................................................................................36

Figure 10: Fractional change in utility of criterion location (FCIU) for each of the individuals modeled. ...........................................................................................................38

Figure 11: Total number of infections based on fraction of the population that is immunocompromised. ...........................................................................................................56
Figure 12: Infection levels of immunocompromised individuals in Kigali City province.

Figure 13: Infections levels of immunocompromised individuals in Gauteng province...

Figure 14: Changes in utility of isolation with workforce size in Kigali City province.

Figure 15: Changes in utility of isolation with workforce size in Gauteng province.
INTRODUCTION

Trade-offs arise at every level of biological organization and can be described as the advantage of a phenotypes in one ecological context accompanied by a disadvantage in the same or a different context.\textsuperscript{4} As an example of phenotypic trade-offs, consider the phenotypic plasticity of \textit{Daphnia}. Two distinct morphs have been characterized: a) the normal phenotype and the b) helmet-headed phenotype.\textsuperscript{5} In the absence or predators, the normal phenotype experiences maximal fitness, whereas in the presence of predators, the helmet-headed phenotype experiences maximal fitness.\textsuperscript{5} The trade-offs between allocation of energy to survival or fecundity in each phenotype, coupled with variability in predator abundance, prevent one phenotype from becoming fixed in the population.\textsuperscript{6}

Characterizing the trade-offs in these costs and benefits at every level of biological or organization remains challenging, especially within shifting environments.\textsuperscript{7} An early model of trade-offs comes from the principle of allocation, stating that the energy an organism allocates to one function, for example reproduction, cannot be allocated to another function, for example survival. One form of this model proposed by Van Noordwijk and de Jong in 1986 is shown below.\textsuperscript{8}

\[ A = R + S \]

In this formulation, A is the total energy to be allocated, R is the energy that is allocated to reproduction and S is the energy that is allocated to survival. However, this model does not provide a means by which to quantify the values R and S should take on in a given
circumstance, and therefore provides limited insight to the ways by which trade-offs influence evolutionary outcomes in biological systems.

Trade-offs in decision-making across games, gambles and investments are characterized in the economic literature as early as the 1700s. Expected utility theory is a framework developed by economists for quantifying rational decision-making in the face of risk. In expected utility theory, a decision-maker assigns a value to the net benefit of a decision, and this value is called the utility of that decision. Factoring in the probability of the outcome enables the decision-maker to calculate the expected utility of that decision. Plotting the expected utility over a range of strategies can be used to generate a utility curve which can then be used to characterize the optimal behavior of the decision-maker as risk-averse, risk-neutral or risk-seeking. When this utility curve is concave, this indicates that a decision-making strategy results in diminishing returns, and thereby implies that the decision-maker should be risk-averse. Conversely, when a utility curve is convex, this indicates that a decision-making strategy results in exponentially increasing returns and implies that the decision-maker should be risk-seeking. Lastly, a utility curve can be linear, indicating that a decision-making strategy provides the same net returns, implying that the decision-maker should be risk neutral.

An overarching goal of this dissertation is to develop a broadly applicable framework based on expected utility theory to provide insights to understanding the effects of current and future trade-offs in ecological systems. In this work, we apply the expected utility framework to three ecological systems: (1) evolution of epigenetic regulation of gene expression, (2) evolution of signal detection criterion variance within populations, and (3)
optimal control of a pandemic in populations with heterogeneous immunocompromise. These three systems were chosen because they reflect different layers of ecological organization and impact, ranging in scope from narrow to broad.

The first system we examine is the evolution of epigenetic regulation of gene expression. The evolution and occurrence of epigenetic gene regulation is widely observed in a variety of organisms ranging from bacteria to multicellular eukaryotes. However, epigenetic regulation is not universal, nor is it the case that every gene in an organism is epigenetically controlled. Relevant environmental constraints to the evolution of epigenetic control include availability of nutrients and cellular building blocks, ecological interactions, as well as selective pressures affecting phenotypic fitness in a particular environment. We use expected utility theory to examine the environmental constraints and selective pressures that facilitate the emergence of epigenetic gene regulation. The model we develop is unique in that it allows us to explore when evolution should favor epigenetic modulation of traits, whereas most previous models in epigenetics focus on evolutionary fitness of the traits themselves.

The next system we examine is the evolution of variance of signal detection criteria within populations. We examine signal detection at the population level, wherein individuals vary in their ability to detect signals in the environment. Factors that cause this variation in perceptive ability include individual differences in signal sensitivity, transduction, processing, and in some cases learning history. Association and communication between conspecifics or interspecifics allows the transmission of information regarding signal presence and accuracy. We apply expected utility theory to an existing, classical model of
signal detection theory, to examine the circumstances in which group decision-making regarding the presence or absence of a signal would be beneficial to individuals with differing signal detection abilities. This novel synthesis of the theories of expected utility and signal detection, then informs our understanding of the evolution of intraspecific and interspecific communication.

Lastly, staying at the population level, while moving to the specific example of humans, we apply expected utility theory to optimize recommendations for social isolation in the COVID-19 pandemic caused by the novel coronavirus, SARS-CoV-2. We present a novel extension to the current modeling literature where we include an immunocompromised class of individuals in addition to the commonly modeled non-immunocompromised class.\textsuperscript{20–22} We do this because immunocompromised individuals were identified early on in the course of the pandemic as more likely to suffer severe infection outcomes\textsuperscript{23–25} and because levels of immunocompromise are not evenly distributed amongst human populations.\textsuperscript{26} To tease apart these effects, we specifically examine two populations of people: (1) in the Kigali City province of Rwanda where acquired immunodeficiency syndrome (AIDS) causes immunocompromise in about four percent of the populations, and (2) in the Gauteng province of South Africa where about seventeen percent of the population is immunocompromised by AIDS. Another key feature of these populations is a low average rate of savings combined with high levels of unemployment. These factors combine to make balancing economic and epidemiological trade-offs challenging. To provide a novel objective measure that balances economic losses and rates of infection, we derive a utility of social isolation from the population-level susceptible-exposed-
infected-recovered (SEIR) model commonly used\textsuperscript{20–22,27,28} in forecasting the scale of the COVID-19 pandemic.

Together, the chapters of this dissertation present a compelling series of case studies exemplifying the applicability of expected utility theory from economics to three ecological and biological systems. Expected utility theory provides a simple framework by which to understand the maintenance of traits in populations in the face of shifting costs and benefits of expression, as well as to generate insight for policy to manage a pandemic.
CHAPTER 1: Expected Utility of Epigenetic Modulation of Gene Expression

Abstract

Epigenetic mechanisms alter gene expression in response to changing environmental conditions. However, not all genes are under epigenetic control. Due to the vast potential fitness benefits of epigenetic modulation of traits, it is important to consider whether the ability for such control might itself have been shaped by selection. What environmental selective pressures might favor the ability to use epigenetic processes to rapidly switch gene expression levels, resulting in different phenotypes? We employ the perspectives of utility theory and liquidity portfolio management from the field of economics to construct a model that quantifies the current and future expected utility of epigenetic control. Our general model makes key predictions that are in keeping with the natural intuition for both evolutionary theory and simulated and real-world empirical observations. We introduce the concept of epiallelic redundancy as a way to increase the likelihood that an organism will express a maximally beneficial trait for its current environment. We conclude that epigenetic control should evolve in situations where the cost of control is small and environmental fluctuations are frequent. These results suggest that epigenetic control evolved as a result of a natural solution of mixed portfolio management and demonstrate how the economic literature on balancing liquidity of assets is relevant to, and can provide an intuitive context for, understanding the evolution of epigenetic control.

Introduction

Epigenetic modulation of traits, the processes that underlie developmental phenotypic plasticity and canalization, bringing about persistent developmental effects, are seen
broadly across taxa. Some developmental effects are transient while others can persist across generations; effects that persist transgenerationally are known as epigenetic inheritance. These processes can act on DNA transcription and regulation in a wide variety of ways ranging from DNA methylation, histone modification, non-coding RNAs, to transcriptional gene silencing. Mechanisms of epigenetics can shift the expected genotype to phenotype ratio, altering our understanding of how allele frequencies in populations may change.

Epigenetic processes can lead to the production of more than 1 phenotype from 1 genotype, commonly referred to as pleiotropy. Further, epigenetic gene regulation has been implicated in generating phenotypic plasticity. These processes can be involved in developmental and regulatory mechanisms susceptible to rapid adaptation, as well as organism-environment interactions facilitating niche construction. In general, changes to location, timing, amount, and product of gene expression can create opportunities for evolution to act. This means that epigenetic mechanisms may provide multiple pathways towards fitness benefits. The nature of these potential benefits may include: a) directing phenotypes in response to selective pressures with finer resolution (i.e., during an individual’s lifetime) than evolution (i.e., which acts over generational time-scales), b) allowing genotypes to respond to information in the environment, and c) maintaining genetic diversity when epigenetic mechanisms decouple the underlying genotype from the phenotype under selection, among others.

There exist developmental and regulatory constraints to epigenetic control. These constraints can operate over an individual’s lifetime or via evolutionary processes over generations. These include constraints due to physics, chemistry, energetics,
morphogenetics, and phylogenetics. Epigenetic control may incur increased ontogenetic costs whereby a more complex regulatory system may require more nutritional or energetic resources to develop and maintain, increased genotype complexity, and costs associated with mismatching the environment. In some cases, epigenetic mechanisms are implicated in disease states when early environmental signals do not reflect the current environmental conditions. For example, consider individuals conceived during famine may have maladaptive traits expressed when food is plentiful in adulthood.

These costs and benefits set the stage for asking what conditions tip the scale so that the benefits of epigenetic regulation outweigh the costs. Specifically, what conditions select for developmental and regulatory canalization or plasticity?

West-Eberhard suggested that traits resulting from environment-genotype interactions come to characterize species by causing developmental variation to which organisms respond to via phenotypic accommodation to produce new variants. As these variants spread and are successful over successive generations genetic fixation will occur. This leads us to broaden our questions to include: which traits should be expected to evolve epigenetic control? To answer this and the previous questions, we look to economic theory.

A well-studied problem in economic theory is the maximization of monetary gain through balancing liquid and illiquid assets in an investment portfolio. Expected utility theory provides one framework for considering this balance. In this framework, the diversification of a portfolio is based on each asset’s expected utility. Each asset has a current monetary value as well as a future monetary value. This value plotted over time forms a utility function. The utility function can be projected into the future, transforming
it into an expected utility function. Investors can then use expected utility to reduce investment risk in the face of uncertainty.

Depreciation, where an asset’s value decreases over time, and volatility, where an asset’s value changes rapidly over time, affect the expected utility of an asset. In terms of life history, we can frame senescence as depreciation, and we can use this framework to consider the processes influencing the balance between reproduction and somatic repair. For our purposes, we can frame genetic encoding of traits as illiquid assets, and epigenetic control as a means of investing in liquid assets. We can then draw from the economic literature to modify the expected utility framework to consider the utility of genetic and epigenetic control of developmental processes across generations.

This framework allows us to consider how individuals should allocate resources to epigenetic modulation of traits with various frequencies of environmental change. We base this on the premise that evolution should favor individual maximization of the expected utility of investments in epigenetic or genetic control based on the frequency of environmental change. This means that evolution should produce developmental patterns increasing the mean utility of the phenotype, with guiding signals provided by the environment. Further, evolution should produce phenotypes that minimize the variance in utility of the phenotype across generations.

This perspective then allows us to express intuitive evolutionary insights as rigorous, quantitative predictions. For example, we should expect that environments that change predictably, or are constant, should favor developmental canalization while environments that are unpredictable should favor plasticity. We expect costs to epigenetic modulation to
influence the expected utility of the ability to modulate phenotype. We here present a mathematical model to characterize this behavior and make quantifiable, testable predictions for when or which traits should have evolved mechanisms of epigenetic modulation.

**Model Framework**

Starting with the economic concepts of benefit, cost, and utility, we derived a set of equations governing the probability that an organism will possess an optimal trait that provides a fitness benefit in a given environment. We assumed the organism could possess this particular trait as a result of genetic or epigenetic mechanisms. We used the descriptive equations regarding the trait in question to determine the benefit, cost, and utility to modulate phenotype by epigenetic processes. We also incorporated explicit impact of environmental variability. To capture the effect of phenotypic change due to epigenetics, we used a ‘redundancy factor’ which increases the probability of an organism possessing a trait that provides a fitness benefit in the environment. We assumed the existence of N genotypic traits, each leading to a different phenotypic outcome.

**Derivation of Model**

To enable us to consider direct heritable epigenetic variation, we need to consider the success of populations of individuals that may share the same genotype, but exhibit distinct phenotypes due to epigenetic modulation, and contrast the fitness of those populations with that of populations that instead include genetic diversity itself. In our case, we will focus on total population growth rate as a reasonable metric of fitness. Since fitness of a population is defined by the reproductive success of its individuals, we refer to all benefits, costs, and utilities as average values within entire populations, based on their genotypes.
and epialleles. If we assume that we can measure the changes to total population growth rate as a result of different traits, we can define the utility of particular traits. We define utility with respect to alternate traits or absence of the trait in question, so our definition becomes the relative utility of a trait that can be modified epigenetically. Epigenetic processes are often implicated in phenotypic plasticity, yet our model considers only epigenetic pathways that lead to phenotypes with differential fitness in the environment. To define a relative utility of epigenetic modulation, we first assume that the epigenetic trait itself is the only variable affecting the population growth rate. When this is true, the relative utility of an epigenetic trait is the change in growth rate for a population with the trait relative to the growth rate of a population without the trait. If we define the trait in question as $T$, the reference state, where there is no capacity for epigenetic modulation within the population of the trait as $O$, and the population growth rate as $G$, the equation for the relative utility of the trait becomes:

$$U_T = G_T - G_O = B_T - L_T$$

In this equation, $U_T$ is the relative utility of the trait, $G_T$ is the growth rate of individuals with trait $T$, and $G_O$ is the growth rate of individuals without trait $T$. Further, $B_T$ is the benefit of trait $T$ and $L_T$ is the cost of trait $T$.

We next define the probability with which one organism has the specific trait, $T$, (of $N$ possible traits in the population) that provides the best fitness outcomes given the environment at this time as:

$$P(T) = \frac{1}{N}$$

This equation works only for the cases where the trait is solely the result of the individual’s genotype and assumes a mathematically neutral uniform distribution of genotypes. It is
important to note that this assumption is likely to be biologically implausible since genotypes are not drawn from uniform distributions. However, this assumption makes analysis straightforward and simple.

If we wish to know the probability with which one organism has the trait that best matches the environment, not only at a particular time, but going forward through a window of environmental predictability per generation, $E_W$, we may write the following:

$$P(T) = \left( \frac{1}{N} \right)^{E_W}$$

We assume that there is one maximally optimal trait per environmental condition.

To introduce epigenetic mechanisms for phenotypic modulation, we then alter the equation by adding a redundancy factor, $\alpha, 0 \leq \alpha \leq N$. Mathematically, as alpha increases, the value of the fraction $\frac{\alpha}{N}$ increases, thereby increasing the probability of the organism having the best trait that matches the environment over the environmental predictability window.

We write this as:

$$P(T) = \left( \frac{\alpha}{N} \right)^{E_W}$$

We define the energetic cost of the trait to the organism as the benefit of possessing trait, $T$, with respect to the relative utility of trait $T$ and the cost of trait $T$:

$$B_T = U_T + L_T$$

To be able to predict the future value of relative utility of trait $T$, we multiply the probability of possessing trait $T$ by the relative utility of trait $T$:

$$E(U_T) = P(T)U_T$$
We can also consider the ability to epigenetically modulate a trait as a trait itself. Much as we saw previously, there can be a relative utility, a benefit, and a cost of the trait known as “trait modulation”, just as we defined them for any other trait.

If we wish to know the benefit the ability to modulate a trait confers, we consider the cost of the trait and the relative utility of the trait. We can write this in two forms:

\[ B_M = U_M + L_M \]

\[ B_M = \left[ \left( \frac{\alpha + 1}{N} \right)^{E_W} - \left( \frac{\alpha}{N} \right)^{E_W} \right] U_T \]

Where \( U_M \) is the relative utility of the ability to modulate a trait, \( L_M \) is the cost of modulating a trait, and \( U_T \) is the relative utility of T. The first form comes from viewing the benefit of the modulation with respect to the utility and cost of the modulation. However, if we do not know what the relative utility of the modulation or the cost of the modulation is, we can rewrite the equation in the second form, with respect to the difference in probability of possessing the trait as a result of an increase in the redundancy factor by one, the relative utility of the trait and the cost of the trait.

The value of the cost of modulation is then calculated by multiplying a constant cost factor, \( C_M \), by the value of the redundancy factor, \( \alpha \), and the duration of the environmental predictability window, \( E_W \), during which the modulation takes place. We write this as:

\[ L_M = C_M E_W \alpha \]

We define the relative utility of trait modulation to be the difference between the benefit of the modulation and the cost of the modulation.

\[ U_M = B_M - L_M \]

If the only information we have is regarding the relative utility, benefit of and cost of a trait and not its modulation, we instead define these terms with respect to the trait itself.
To do so, we say that the benefit of modulating a trait is equal to the benefit to the individual conferred by the trait subtracted by the cost of the trait. Mathematically, this becomes:

\[ U_M = \left( \left( \frac{\alpha + 1}{N} \right)^{E_W} - \left( \frac{\alpha}{N} \right)^{E_W} \right) U_T - L_M \]

To evaluate the relative expected utility of the trait modulation, we simply evaluate the above equation with respect to the probability that the organism currently possesses the trait due to modulation and the benefits and costs of the modulation, according to the equation below.

\[ E(U_M) = \left( \frac{\alpha}{N} \right)^{E_W} U_T - L_M \]

**Theoretical Considerations Regarding the Model**

**Epigenetic modulation of traits: considered on a per-trait basis or as one ‘meta trait’?**

In this model, we consider epigenetic modulation of genetic traits as a ‘meta trait’ on which selection can act. This concept is not new and was originally proposed by West-Eberhard in the context of phenotypic plasticity.\(^{38}\)

The model does not consider the intricacies of the molecular and biochemical processes involved in various types of epigenetic control (DNA methylation, histone modification, siRNAs, etc.). However, it does provide a means for considering the potential costs to using and maintaining epigenetic machinery.

Viewing epigenetic mechanisms as a ‘meta trait’ allows us to evaluate how evolution may guide the development of epigenetic control of a specific trait as well as how evolution may guide the development of epigenetic control itself. This means that we can use this model to evaluate both which traits we expect to come under epigenetic control as well as the conditions that favor the emergence of epigenetic control across the genome.
**Shape of expected relative utility curves in our model**

Our model generates an equation for the expected utility of epigenetic modulation of traits. This equation is governed by parameters chosen to be biologically relevant (i.e., regions of the parameter space that generate negative expected utilities are not evaluated). Within the biologically relevant parameter space, the cost terms in the expected utility equation work to balance the benefit terms, thereby causing the resulting utility and expected utility functions to be concave.

**Results**

We restricted our evaluation of the system to regions of the parameter space that yielded non-negative values for both relative utility and expected utility. The output of the relative utility and relative expected utility equations is a value in ‘utils’, which are the common unit for utility in the economic literature. Because there is no standard for measuring the ‘utils’ of a trait or suite of traits, we can evaluate relative change in utils resulting from changes to input parameters to gain an understanding of the model dynamics. The equations for relative expected utility and relative expected utility are similar in form, and the resultant surfaces produced by these equations are similar. In this paper, we discuss the results of both equations, and use visualizations of relative expected utility.

For all cases, as utility of the target trait increases, relative expected utility of epigenetic modulation increases. Similarly, as cost of epigenetic modulation increases, relative expected utility of epigenetic modulation decreases.
Figure 1: Expected relative utility of epigenetic modulation surface as a function of utility of target trait and environmental predictability window.
Figure 2: Expected relative utility of epigenetic modulation surface as a function of utility of target trait and total number of genetic traits.
Figure 3: Expected relative utility of epigenetic modulation surface as a function of utility of target trait and epiallelic redundancy.
Figure 4: Expected relative utility of epigenetic modulation surface as a function of utility of target trait and costs of epigenetic modulation.

*Effects of Number of Traits and Environmental Predictability on Expected Utility of Epigenetic Modulation*

Our model enables us to examine the expected utility of possessing any number of traits, with one being optimal in the current environment. This is done by setting $\alpha = 1$.

An increase in $N$ in this model corresponds to a greater number of traits in a population’s gene pool. Our assumption that there is one maximally beneficial trait per environmental condition means that as N increases, the probability of an individual possessing the optimal trait for the current environmental condition decreases. As the window of environmental predictability increases, the expected relative utility of possessing the best trait increases.
Thus, the expected utility of epigenetic modulation is maximized for small $N$ and small $E_W$.

*Epiallelic Redundancy Ratio*

As the value of the fraction, $\frac{\alpha}{N}$, approaches 1, the number of epialleles which yield the phenotype which best matches the current environment increases. We refer to this increase in epialleles producing the same phenotypic result as epiallelic redundancy. Increasing epiallelic redundancy increases the probability that the phenotype expresses the optimal trait in the environment. However, as costs of epigenetic modulation increase, they can balance out benefits caused by increased epiallelic redundancy.
Figure 5: Expected relative utility of epigenetic modulation surface as a function of cost of epigenetic modulation and epiallelic redundancy.

**Conditions for Developmental Canalization or Plasticity**

We find that long windows of environmental predictability favor developmental canalization via genetic and/or epigenetic assimilation. In contrast, we find that short windows of environmental predictability favor developmental plasticity via genetic and/or epigenetic accommodation. We show that large costs of modulation favor canalization and low costs of modulation create conditions in which plasticity via epigenetic modulation can persist.
Figure 6: Expected relative utility of epigenetic modulation surface as a function of environmental predictability and number of traits.
Figure 7: Expected relative utility of epigenetic modulation surface as a function of environmental predictability and epiallelic redundancy.

Discussion

Epiallelic Redundancy

Redundancy in genes can allow an organism to compensate for a loss of function in a gene from the group.\textsuperscript{38} However, redundancy itself comes at a cost. As this cost of maintenance increases, each increase in redundancy provides less benefit. This means that redundancy is characterized as providing diminishing returns.

Epiallelic redundancy could enable the persistence of multiple genetic traits for adaptive phenotypic features in a population, despite the fact that some of those genetic traits may
be less optimal in particular environmental conditions. This means that epigenetic processes could produce a rescue effect, similar in principle to the concept of genetic rescue, where addition of new alleles to a population via immigration can counter loss of genetic diversity in a way that allows a population to persist, despite changing environmental conditions and selective pressures. We call this effect epigenetic rescue.

In instances where the cost of maintaining genes is greater than the cost of maintaining epialleles, epiallelic redundancy can help maximize the likelihood of an organism expressing a trait that is best suited to its current environment. Within a generation, organisms cannot change the genetic traits they possess, but the expression of these traits can be changed by epigenetic means. The fitness benefit of sensing changes in the environment and the utility of responding to such changes via changes to phenotype likely far outweighs the cost of epigenetic control and explains why epigenetic control is seen so broadly across taxa.\textsuperscript{12,29,44}

\textit{How Utility Relates to Waddington’s Epigenetic Landscape}

C.H. Waddington, considered the pioneer of epigenetics, coined the idea of the creode.\textsuperscript{45} In short, a creode is the developmental pathway followed by a cell as it grows to form part of a specialized organ. Waddington’s epigenetic landscape described the creodes as the trajectory from a developmental “hill” to a developmental “valley.” Much like water flowing into a watershed based on where it falls as precipitation, cell fate is tied to the ways in which environmental influences “push” a cell along a given creode. The concept of expected utility can help explain the topology of creodes. Valleys in Waddington’s epigenetic landscape can be thought of as areas of high utility of a given trait. A given unit of an organism (cell, organ, etc.) should maximize the expected utility of a trait and thus
follow a trajectory to reach a developmental state taking advantage of the high utility of the trait. In other words, any given unit of an organism seeks to optimize its trait investment portfolio to gain a maximum fitness return.

*How does this model fit into the existing literature of phenotypic plasticity?*

Epigenetic control has been shown to regulate phenotypes and has been implicated as a mechanism of phenotypic plasticity. Specifically, epigenetic mechanisms are the intermediary between genotype and environment. When one genotype produces multiple phenotypes via epigenetic mechanisms, the associated phenotypic traits are said to be plastic.\textsuperscript{34,46–48} However, it is important to note that epigenetic mechanisms are not the only drivers of phenotypic plasticity. Though the literature on modeling epigenetics is relatively new, the literature on modeling phenotypic plasticity is extensive.\textsuperscript{11,16–18,49–52} Theoretical models of evolution of phenotypic plasticity typically belong to three classes of models: optimality, quantitative genetics, and gametic.\textsuperscript{53} These models include numerous modeling and simulation methods: individual-based simulations\textsuperscript{54}, stochastic control theory\textsuperscript{39,55}, and information theory.\textsuperscript{56} Models of optimality and quantitative genetics tend to be general, while gametic models tend to be mathematically complex.\textsuperscript{39,50,57} Our model framework has the simplicity of optimality models, while retaining the possibility for modification to include the complexities gametic models address.

As a whole, the models of phenotypic plasticity exploring questions similar to ours have collectively shown four main results: 1) epigenetic inheritance will be adaptive when switching back and forth between states is costly,\textsuperscript{35} 2) adaptive plasticity evolves readily when populations disperse,\textsuperscript{58} 3) the nature of adaptive variations depends on the duration of the environmental predictability window, and 4) when environmental predictability is
high, developmental canalization is favored and, conversely, when environmental predictability is low, genotypic variations are suppressed and direct sensing of environmental conditions is preferable to any system of inheritance. These conclusions are echoed by our own findings regarding trade-offs between expected relative utility of modulation and cost of modulation, number of genetic alleles and duration of environmental predictability. When considered through the lens of evolution of phenotypic plasticity, our model extends the idea of redundancy from the idea of genetic redundancy to include epigenetic redundancy. This concept of epigenetic redundancy can be expanded into other mechanisms of phenotypic plasticity. While we do not explicitly model transmission of epigenetic states across generations, it can be inferred from our results that when environmental predictability windows are measured on the magnitude of an individual’s life, expected relative utility of epigenetic modulation will be maximized, and epigenetic control will evolve to respond to selective pressures on short time scales.

*How does this model fit into the existing literature of epigenetic control?*

Modelling efforts aimed at quantifying evolution of epigenetically controlled traits are often formulated as extensions of quantitative genetic models or evolutionary models such as the Price equation. These models typically consider the number of phenotypic traits present in populations after several generations. They find that epigenetic control enables more phenotypes to persist than genetic encoding alone, and that the variation of phenotypes created via epigenetic mechanisms has evolutionarily relevant outcomes. We see this in our model when we consider the case of low costs of maintenance of epigenetic machinery combined with low-to-intermediate levels of environmental predictability.
As a whole, models have collectively shown the following: large epigenetic resetting rates are favored in stochastic environments, continued environmental induction and epigenetic resetting prevent epigenetic fixation and maintain phenotypic variation\textsuperscript{59}, and epigenetic modulation is only useful when it enables an organism to respond rapidly to environmental changes.\textsuperscript{16–18} High fidelity inheritance of epiallele patterns leads to fixation of epiallelic expression, and low fidelity inheritance of epiallele patterns leads to genetic uniformity and variance in epiallelic expression.\textsuperscript{15} As shown in the aforementioned studies on phenotypic plasticity, studies of epigenetic evolution have shown that the environmental predictability window and cost of epigenetic modulation affect the evolution of epigenetic control.\textsuperscript{59} In addition, O’Dea et al. suggested the existence of epigenetic buffering, in which epigenetic mechanisms preserve phenotypic diversity, thereby limiting the loss of genes associated with a sudden change in selective pressure.\textsuperscript{57,60} Our framework also serves to explain these phenomena from a portfolio selection perspective, in place of a mechanistic quantitative genetic or classic evolutionary perspective.

\textit{Implications for conservation}

The world faces extinction crises across a wide variety of taxa due to changing environmental conditions.\textsuperscript{61,62} Our model highlights the importance of understanding the sources of adaptation in environments. Moving forward, conservation efforts should consider these sources when prioritizing species to target. Species that express epigenetically controlled traits that improve fitness in the face of changing environments may be at an advantage in reference to other species lacking these abilities, and prioritization that reflects this may lead to better outcomes.
Conclusions

We have developed a model for the evolution of epigenetic mechanisms of gene expression based on an expected utility framework borrowed from economic theory. Our model shows key factors influencing the evolution of epigenetic mechanisms include the utility of the trait being controlled by epigenetic mechanisms, the duration of environmental predictability, and the costs associated with maintaining and utilizing epigenetic machinery. This model predicts that traits with high utility are expected to come under epigenetic control when environmental fluctuations are frequent and costs to epigenetic machinery are low. Traits with low utility can only come under epigenetic control when costs to epigenetic machinery are miniscule. We find that plasticity as a result of epigenetic mechanisms evolves when the opportunity cost of plasticity is balanced with the benefits of plasticity. Specifically, plasticity is likely to evolve when relative utility of the target trait is high, windows of environmental predictability are short, and epiallelic redundancy is balanced with the cost of epigenetic modulation. We show that developmental canalization is favored when there are a small number of genomic traits for selection to act upon, when environments are predictable for several generations, and when costs to epigenetic machinery are large.

Our model is not a replacement for models of phenotypic plasticity or epigenetics. As we have demonstrated, our model captures many of the same biological phenomena that more complex models of phenotypic plasticity and epigenetics describe and can be adjusted to include more details of the biochemical processes involved in epigenetic mechanisms. There is extensive discussion of benefits, costs, and trade-offs of phenotypic and genomic traits\textsuperscript{1,3,4,7}, and our model adds nuance to this ongoing discussion by incorporating these
concepts into a formal framework, further tying in ideas from economic theory. This framework provides a novel and relatively simple mathematical means of addressing classic questions in evolution of phenotypic plasticity and the mechanisms that drive it.
CHAPTER 2: Consensus Signaling as a Means to Preserve Heterogeneity in Signal Detection Criteria

Abstract

Signal detection theory has been used in the fields of radar detection, psychology and neuroscience to describe the process of accurately discriminating signals from environmental noise. Integrated into the signal detection framework is the utility of a criterion choice. We expand the signal detection framework to include populations of individuals varying in their criterion choice. We then design populations that use a consensus measure to determine whether a signal is present. Our work shows that individual payoff for participating in a population-level decision regarding the presence of a signal can affect the criterion choice utility the individual experiences. This has implications for the evolution of social communication. Overall, we create a novel extension of signal detection theory with direct applications in the fields of ecology and evolution.

Introduction

Signal detection theory (SDT) was developed originally to optimize correct identification of signals within radar use cases. SDT assumes that there are two signal distributions: one noise distribution and one signal distribution. Both distributions are assumed to be normal, and the area under the curve for each is the probability of the decision associated with each. These distributions can overlap, meaning that four possibilities of detection outcome can be assigned – hit, miss, false alarm, and correct rejection. Another way to frame these four possibilities is to consider them as true positive detections (hits), false
negative detections (misses), false positive detections (false alarms), and true negative detections (correct rejections). For a given observer, signal detection theory can be used to identify that observer’s sensitivity to the signal, as well as the optimal criterion location that maximizes hits and correct rejections while also minimizing misses and false alarms. The optimization of criterion location is completed by identifying the distributions associated with the noise-only condition as well as the signal-only condition. Once these are plotted, the point at which the distributions overlap where the area under the curve is minimized is the optimal criterion location.

The mathematics involved in SDT have been extended to various fields including ecology, where the work has been extended to identify useful quantitative indicators of ecosystem properties, animal perception, the intersection of individual interactions with the environment, and optimal signal detection.

SDT can also explain how traits are acted on by selective pressures faced by organisms. For any signal used to make a fitness-influencing decision, a trait that optimizes the signal detection parameters is likely to be favored by natural selection. However, within populations, individuals possess variable traits that are ultimately used for signal detection. We propose that social communication regarding the presence of a signal may emerge in populations with a high between-individual variance in signal detection capacities. We suspect that in such populations, when the group makes decisions based on consensus reached via contribution from each individual’s perception, variation in signal detection criteria can be preserved, especially in individuals with poor signal detection capacities. As an example of this, some bacteria and oomycetes use consensus to drive the expression of genes that facilitate the infection of host organisms.
Further, we propose that there also exists a level of variance in signal detection ability of individuals that is detrimental to the cohesion of a social population as a whole, potentially facilitating the breakdown of future sociality.

Herein we propose a mathematical framework for expanding SDT to understand the evolution of social communication. Specifically, we consider the trade-offs for individuals with differing signal detection capacities and criteria to associate with other conspecifics to reach a consensus decision regarding the presence or absence of a signal. Such associations to reach a consensus decision can result in an increase in realized expected fitness of the individuals participating in the association. When there is an increase in realized expected fitness due to increased accuracy of signal detection by participating in group decision-making, social communication itself may allow the persistence of differing signal detection capacities within a population. In other words, individuals with less optimal criterion positions can continue to survive. To examine this possibility, we employ expected utility theory to determine if an individual benefits from being part of a social group and use this to project the likelihood of future emergence, or dissolution of, sociality.

Methods

We use the traditional signal detection theory (SDT) framework in MATLAB. An individual known as the receiver is tasked with attempting to detect a signal from two distributions – signal + noise and noise only. The signal + noise distribution is modeled as a normal distribution with a mean of 1 and a standard deviation of 1; the noise-only distribution is modeled as a normal distribution with a mean of 0 and a standard deviation
of 1. There are a total of 1000 random trials, with the yes-no presence of a signal determined by a random number generator, where a randomly generated value greater than or equal to 0.5 indicates the signal is present and a value less than 0.5 indicates the signal is not present.

An individual may choose 1 of 4 criteria (C) for signal detection: criterion 1 is a response threshold of 0.25, criterion 2 is a response threshold of 0.5, criterion 3 is a response threshold of 0.75 and criterion 4 is a response threshold of 1. Seven test populations comprised of 12 individuals each are modeled. Each population differed with respect to the proportion of individuals within the population that represented each of the 4 criterion choices. 1 baseline population comprising of 12 individuals with C = 0.25 was modeled as well. These populations are shown in Table 1.

Table 1: Proportion of criterion choices represented in each population distribution modeled.

<table>
<thead>
<tr>
<th>Population Distribution</th>
<th>Even</th>
<th>Middle Criteria Only</th>
<th>Mostly Low Criteria</th>
<th>Mostly End Criteria</th>
<th>Mostly Middle Criteria</th>
<th>Mostly High Criteria</th>
<th>End Criteria Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>C = 0.25</td>
<td>¼</td>
<td>n/a</td>
<td>5/12</td>
<td>5/12</td>
<td>1/12</td>
<td>1/12</td>
<td>½</td>
</tr>
<tr>
<td>C = 0.50</td>
<td>¼</td>
<td>½</td>
<td>5/12</td>
<td>1/12</td>
<td>5/12</td>
<td>1/12</td>
<td>n/a</td>
</tr>
<tr>
<td>C = 0.75</td>
<td>¼</td>
<td>½</td>
<td>1/12</td>
<td>1/12</td>
<td>5/12</td>
<td>5/12</td>
<td>n/a</td>
</tr>
<tr>
<td>C = 1.00</td>
<td>¼</td>
<td>n/a</td>
<td>1/12</td>
<td>5/12</td>
<td>1/12</td>
<td>5/12</td>
<td>½</td>
</tr>
</tbody>
</table>

Communication between individuals within a population was assumed to be faithful and instantaneous during each signal detection trial. Individuals were not modeled to distinguish whether a signal was a hit (correct detection) or a false alarm (false positive detection), meaning that there is no immediate fitness cost associated with false alarms. Four decision criteria were evaluated for each population: a) at least 25% of the population
agreed that a signal was present, b) at least 50% of the population agreed that a signal was present, c) at least 75% of the population agreed that a signal was present and d) 100% of the population agreed that a signal was present.

Utilities were calculated for each of the 4 response criteria (x).

\[ U(x) = \alpha P(\text{hit}) - \beta P(\text{miss}) + \gamma P(\text{correct rejection}) - \delta P(\text{false alarm}) \]

where \( \alpha \) is the benefit of a hit, \( \beta \) is the cost of a miss, \( \gamma \) is the benefit of a correct rejection and \( \delta \) is the cost of a false alarm. Utilities for the decision criteria (including population mean criteria/population criteria composition alternatives) were calculated using the mean population hits, misses, correct detections, and false alarms.

\[ U(\bar{x}) = \alpha P(\text{hit}) \bar{\bar{\,}} - \beta P(\text{miss}) \bar{\bar{\,}} + \gamma P(\text{correct rejection}) \bar{\bar{\,}} - \delta P(\text{false alarm}) \bar{\bar{\,}} \]

Each outcome was evaluated for a set of benefits of hits and correct detections and costs of misses and false alarms. The values in this set of benefits ranged from 0.6 to 1.1. The fractional change of response criterion utility as a result of associating with a population engaging in one decision rule was evaluated for each individual. These fractional changes in utility were then compared across individuals to describe preferential associations (or lack thereof) between individuals.

Results

The individual response criteria generated rates of hits (correct detections), misses (false negatives), correct rejections (true negatives), and false alarms (false positives) shown in Figure 8.
Figure 8: Probabilities of hits, misses, correct rejections and false alarms associated with each of the 4 criteria modeled. Note that hits and misses sum to 1 and correct rejections and false alarms sum to 1.

When $\alpha, \beta, \gamma, \text{ and } \delta$ were equivalent, at a value of 1.1, the individual response criterion of 0.75 generated the highest individual criterion utility at 0.7026. The individual response criterion of 1.00 generated the lowest individual criterion utility at 0.666.

When individuals were part of a population with a specific consensus requirement, the percent change in response criterion utility was different for each individual. Differences in response criterion utility resulted from: a) the response criteria represented within a population (population composition), and b) the consensus requirement employed by the population for signal detection. One example of this is shown in Figure 9.
Figure 9: Utility of Population Mean Criterion (UPMC) under Consensus Requirement Conditions. Individuals within each population may take on 1 of 4 criterion values: 0.25, 0.50, 0.75 and 1.00 for all population distributions when $\alpha$, $\beta$, $\gamma$, and $\delta$ were equivalent at a value of 0.6.

For all combinations of costs of false alarms and misses and benefits of correct rejections and hits, the consensus requirement that maximized utility for 1 individual maximizes utility for all individuals. One set of examples of this is shown in Figure 10.
Figure 10: Fractional change in utility of criterion location (FCIU) for each of the individuals modeled. A) FCIU for population distribution “even”. B) FCIU for population distribution “middle criteria only”. C) FCIU for population distribution “mostly low criteria”. D) FCIU for population distribution “mostly end criteria”. E) FCIU for population distribution “mostly middle criteria”. F) FCIU for population distribution “mostly high criteria”. G) FCIU for population distribution “end criteria only”. H) FCIU for a population with only one decision maker, with C = 0.25.

Discussion

Fundamentally, signal detection theory shows that, as an individual increases their response criterion value, hit (true positive detection) rates and false alarm (false positive detection) rates decrease while miss (false negative detection) rates and correct rejection (true negative detection) rates increase.\textsuperscript{64} Our work was inspired by the means by which bacteria and oomycetes accomplish quorum sensing and cooperative infection.\textsuperscript{75–77} In this work, we examined how participating in a group consensus for signal detection would affect the utility of criterion choice for individuals. We found that participating in a group consensus benefits some individuals by artificially increasing their hits and correct rejections while adversely affecting other individuals by artificially decreasing their hits and correct rejections.
When signal detection theory is applied to one individual, if the hit rate and false alarm rate are known, the correct rejection rate and miss rate can be calculated by subtracting either the hit rate or the false alarm rate from 1.\(^67,78\) It follows that if signal detection theory is applied to a population of individuals with known criteria, and if the average population hit rate and average population false alarm rate are known, the average population correct rejection and average population miss rates can be calculated in the manner described for one individual. Using this, we show that signal detection theory can also be applied to a population of individuals utilizing a consensus requirement to inform collective signal detection and that the relationships between average population hit and miss rates and average population false alarm and correct rejection rates hold.

Consensus requirements elevate the hit and correct rejection rates for individuals with otherwise low hit and correct rejection rates because agreement with other nearby individuals with higher hit and correct rejection rates is required to identify whether or not the group should react to a signal. Essentially, individuals with more stringent criteria shift the population mean criteria to be more stringent in a consensus requirement situation and vice versa. As a result, population composition with respect to the proportion of individuals with specific criteria affect the extent to which the population mean criteria is shifted. Population mean criteria determines the utility of both a decision criterion and a consensus requirement and is thus sufficient for use in evaluating changes to the aforementioned utilities. In other words, it is unnecessary to know the size of a population when evaluating population mean decision criteria and consensus requirements if the population composition with respect to criteria used by each portion of the population is known.
Population composition with respect to the criteria used by each portion of the population is enough to calculate the aforementioned utilities.

These results have implications for the evolution of populations facing selective pressures on sensory and perceptual parts and processes. When consensus signaling results in a positive fractional change in utility of criterion location (FCIU) for individuals in a population, consensus signaling can maintain a diversity of individual response criteria in a population. In this way, consensus signaling enables the silent perpetuation of a variety of response criteria within a population. Thus, a population may be able to recover from sudden changes in selective pressure resulting from changes in the differences between stimulus + noise and noise-only signal distributions. On the other hand, when consensus signaling results in a negative FCIU for individuals within a population, consensus signaling may be maladaptive for that population. Consensus signaling may be maladaptive because of a) the functional lowering of the mean population signal detection criterion causing increased false alarm rates, b) lack of consensus leading to increased miss rates, and c) when the signal to which the population responds is consistent. Basic evolutionary logic implies that consistent signals should produce stabilizing selection or directional selection depending on the population composition of the signal detection criterion being selected for.

In this work, we show that the FCIU measure alone is sufficient to predict the optimal composition of a population of individuals engaging in a signal detection task when communication about the presence or absence of a signal takes place. When the population distribution of criteria, signal detection parameters, and utility parameters are known, standard utilities from signal detection theory can be calculated and expanded upon as
described here to evaluate the potential evolutionary trajectories of a population. Thus, this work provides a means by which signal detection theory can be expanded to study the evolution of intraspecific and interspecific social behavior.

Signal detection theory comes into play anytime a signal is being detected. Environmental signals to which organisms may respond can change spatiotemporally, becoming more or less salient to individuals. When such changes occur, selection may favor differing response criteria. If we examine the case of signals becoming less salient, then the response criterion that natural selection favors will be one that maximizes correct detections and minimizes false alerts. Individuals with lower criterion values (C \approx 0.25) would have the maximum number of hits and would be favored by natural selection, while individuals with higher criterion values (C > 0.25) would experience lower fitness because of their inability to detect the signal and respond appropriately. However, if a population of individuals that require consensus signaling to respond to a signal includes individuals representative of low criteria, then since the mean population criterion decreases with increasing numbers of individuals with low criteria, such a population would be able to respond more frequently to the presence of the stimulus than another population comprised of individuals with higher mean criterion values. This would produce a rescue effect, similar in principle to the concept of genetic rescue, where addition of new alleles to a population via immigration can counter loss of genetic diversity in a way that allows a population to persist, despite changing environmental conditions and selective pressures. We call this effect consensus rescue.

In particular, the consensus signaling framework proposed in this study can be used to explain empirical observations at different levels of ecological interaction including
parasite-prey relations and human efforts to mitigate infectious diseases. As an example in the context of parasite-prey relationships, consider signaling by oomycetes attacking plants. At the initiation of the infection process, these pathogens release and respond to signal molecules. Once a quorum of signaling molecules is reached, even if the participating oomycetes are of different species, infection is triggered. At the beginning of the growing season, population densities of individual species are likely below those required for quorum. Responding to the signals of interspecific individuals would thereby provide the responding individual an advantage with early access to the plant host. Such early access to the host’s nutrition may provide a competitive advantage to species that are able to interpret interspecific signals and act on or just ahead of consensus-based decisions regarding timing of infection.

As an example of how the proposed consensus signaling framework can be applied to human efforts to mitigate infectious diseases, consider the effect of costs of coordination among neighboring districts in mitigating vector-borne spread within a human population. Lemanksi et al. showed that coordination with nearest neighbors in mosquito larvicide application keeps mosquito population sizes low, thereby preventing the transmission of Zika virus. Curiously, this work also showed that although coordination with nearest neighbors was successful, coordination with second nearest neighbors produced higher Zika virus transmission within the human population than no coordination at all. SDT, and specifically the work here presented, helps to make clear the reason behind that result: coordination to apply larvicide in multiple districts at the same time can be seen as a form of consensus requirement for detecting a signal. Since mosquito populations vary in their spatial distribution, only nearest neighbors are likely to experience a similar signal (larval
mosquito population size). This means that districts that are not immediately adjacent to each other may harbor distinct larval mosquito population sizes, and therefore districts may be responding to different signals. This can create a situation where the signal detection parameters used may be unique to each district and lead to variations in observed mean population criteria for treating patches with larvicides. When there are differences in district criteria for treatment, and districts are required to cooperatively decide when to treat, a signal detection with consensus situation arises. The current work lays out the theoretical framework for understanding why levels of coordination above nearest neighbors are not ideal in situations where Zika virus is being transmitted.

Signal detection can be more nuanced than the models presented herein. Future efforts to extend these models should at least include the effects of time-delays in signal detection and communication to determine consensus regarding the presence of a signal in the environment. It would be expected that time-delays shared by all individuals in a population would reduce the utility of a population wide criterion choice, and that in such situations some individuals may maximize their response criterion utility by making decisions alone. However, if some individuals in a population are faster in detecting signals and/or communicating about those signals, the resulting change in FCIU may be less intuitive. Another expansion of these models could also include the effects of changing signal + noise and noise-only distributions to capture the utility of group decision making and signal detection criteria in an unstable environment. Changing environments may select for plasticity on the level of the individual, rather than overall genetic variation in signal detection thresholds. In environments where signals are easily distinguished from
noise, the utility of consensus may decrease such that solitary behavior may have the highest fitness.

The signal detection theory framework has been extended to a variety of fields without requiring much change to the form of the component equations. Herein, we show that the traditional signal detection theory framework can be expanded from describing the optimal response criterion for one individual to describing the optimal response criteria for a social population. We show that, in cases where costs of missed detections and false alarms are not equal to the benefits of correct rejections and hits, populations comprised of individuals with a diversity of response criteria can detect signals more accurately than can individuals with a response criterion of maximal utility. This information can be used to project the likelihood of persistence in social groups.

Abstract

Immunocompromised individuals are more likely to catch, and experience severe outcomes from infectious pathogens, such as the SARS-CoV-2 responsible for the current COVID-19 pandemic. Populations across the globe can differ drastically in their relative representation of immunocompromised people, ranging, for example, from 3% in the US to 17% in South Africa and 4% in Rwanda. Such differences may require different prioritization of pandemic control measures by governments to achieve equivalent efficacy of epidemic control and equity in disease outcomes across the entire population. Herein, we develop a multi-group Susceptible-Exposed-Infected-Recovered model and use expected utility theory to evaluate outcomes of various social isolation schemes on the resulting number of infections and economic effects in two African populations (one with 4% and one with 17% immunocompromised individuals). We show that, while 100% isolation is a best practice for reducing infection load in the population, there is a threshold of isolation where 3% to 5% of the workforce can remain working to minimize both number of infections and GDP losses due to social isolation. In populations with higher proportions of immunocompromised individuals, the form of the expected utility curve is shifted such that more stringent social isolation yields more favorable economic outcomes and reduces disease incidence. This work can be used to inform pandemic decision-making.
Introduction

The COVID-19 pandemic has tested the preparedness of healthcare infrastructure, scientists, and policy makers worldwide. As healthcare professionals and policy makers rush to deliver treatments and protective policies, scientists rush to characterize economic and epidemiological outcomes of the pandemic. Impacts of the COVID-19 pandemic are far reaching and include effects to ecological services such as state and national parks in the US, which received funding cuts and reductions in income from visitation. Not only do there remain important open questions for the ongoing COVID-19 pandemic, but COVID-19 has highlighted the need to tackle challenging policy questions in advance of the next pandemic.

We therefore propose an extension of a general Susceptible-Exposed-Infected-Recovered (SEIR) model combined with a macroeconomic model to forecast the disproportionate influence of a pandemic on immunocompromised populations and to quantify the trade-offs between economic and epidemiological outcomes of a social isolation policy designed to reduce rates of infection.

Immunocompromised individuals are disproportionately affected by pandemics. In the case of COVID-19, immunocompromised individuals are more likely to develop severe disease, with longer duration of symptoms and higher likelihood of recurrent infection. Immunocompromise can result from various causes, including but not limited to autoimmune disorders, human immunodeficiency virus (HIV), cancer, and solid organ transplant. Much of the early narrative around social isolation measures such as mask-wearing, maintaining social distancing, and staying at home to avoid spreading COVID-
19 was centered around protecting immunocompromised groups and the elderly. However, despite this, immunocompromised status is often missing from the modeling literature on COVID-19.\textsuperscript{88–92}

The SEIR model is used to evaluate outcomes of a pandemic where exposed individuals are treated as a distinct subclass that represents the transition state from susceptible to infected.\textsuperscript{93} This model has been applied to the recent COVID-19 pandemic caused by SARS-CoV-2\textsuperscript{88–92,94}, although more recent efforts have shifted to more nuanced models as the etiology of the novel pathogen becomes clearer. SEIR models nonetheless remain insightful and important planning tools for the current and future pandemics. To evaluate economic outcomes, we adapt standard macroeconomic models of changes to GDP in populations.\textsuperscript{20,27,95–97} Lastly, to quantify and contrast the epidemiological and economic outcomes of policy decisions, we borrow expected utility from the economic literature.\textsuperscript{10}

A well-studied problem in economic theory is the maximization of monetary gain through balancing liquid and illiquid assets in an investment portfolio.\textsuperscript{10} Expected utility theory provides one framework for considering this balance via each asset’s value in a diversified portfolio.\textsuperscript{10} The monetary value of each asset can be plotted over time to form a utility function. The utility function can be projected into the future, transforming it into an expected utility function.\textsuperscript{98} Investors can use expected utility to reduce investment risk in the face of uncertainty. We modify this framework to derive an equation for the expected utility of social isolation, which can then be used in policy-making to balance economic and epidemiological trade-offs of gross domestic product (GDP) lost and total number of infections.
To our knowledge, no models exist that combine the SEIR framework, accounting for differences in infection duration or severity in immunocompromised and non-immunocompromised individuals that also quantify the expected utility of social isolation. We create a model to ask: (a) how does a pandemic spread through a population comprised of both immunocompromised and non-immunocompromised individuals and, (b) what level of social isolation leads to a maximization of the expected societal utility of isolation?

We present a multi-group SEIR model that differentiates between immunocompromised and non-immunocompromised individuals and quantifies the utility of social isolation, then using expected utility theory to evaluate the economic and epidemiological outcomes of various social isolation schemes. We choose to demonstrate our model for two locations in Africa, with differing fractions of immunocompromised individuals in the population. Specifically, these locations are the Kigali City province in Rwanda and Gauteng province in South Africa. Both provinces are affected strongly by high rates of HIV and acquired-immunodeficiency syndrome (AIDS) in the population\textsuperscript{81,99} and were chosen to highlight regions with differing levels of immunocompromise in the population. Simultaneously, both regions have large fractions of the population under-employed and working hourly positions to try and support themselves and their families at low-earning jobs.\textsuperscript{99,100}

**Methods**

To measure the effect of differing proportions of immunocompromised individuals in populations, we constructed a mathematical model to consider both epidemiological and economic outcomes. A modified multi-group SEIR model was simulated in MATLAB to model the spread of a pathogen through two populations, including 4% (Kigali city) and
17% (Gauteng) of the population being immunocompromised. A macroeconomic model was developed to reflect losses in GDP due to social isolation and cost of infection.

**Epidemiological model**

The epidemiological model used was a system of difference equations and was simulated for 2 years:

\[ N(t) = S(t) + E(t) + I(t) + Q(t) + R(t) \]

Where at time, \( t \), \( N(t) \) is the total population size, \( S(t) \) is the total number of susceptible individuals, \( E(t) \) is the total number of exposed individuals that are not yet infectious (i.e., exposed individuals are incapable of transmitting the pathogen to susceptible individuals), \( I(t) \) is the total number of infected individuals, \( Q(t) \) is the total number of socially isolated individuals and \( R(t) \) is the total number of recovered individuals. The transitions between SEIR compartments were modeled as follows:

\[
S(t) = S_{ic}(t) + S_{nic}(t)
\]

\[
S_{ic}(t + 1) = S_{ic}(t) - \frac{\beta S_{ic}(t)I(t)}{N(t)} + \delta_{ic} Q_{ic}(t) - \vartheta_{ic} S_{ic}(t)
\]

\[
S_{nic}(t + 1) = S_{nic}(t) - \frac{\beta S_{nic}(t)(t)}{N(t)} + \delta_{nic} Q_{nic}(t) - \vartheta_{nic} S_{nic}(t)
\]

\[
E(t) = E_{ic}(t) + E_{nic}(t)
\]

\[
E_{ic}(t + 1) = E_{ic}(t) + \frac{\beta S_{ic}(t)I(t)}{N(t)} - \sigma_{ic} E_{ic}(t)
\]

\[
E_{nic}(t + 1) = E_{nic}(t) + \frac{\beta S_{nic}(t)I(t)}{N(t)} - \sigma_{nic} E_{nic}(t)
\]
\[ I(t) = I_{ic}(t) + I_{nic}(t) \]

\[ I_{ic}(t + 1) = I_{ic}(t) + \sigma_{ic} E_{ic}(t) - \gamma_{ic} I_{ic}(t) \]

\[ I_{nic}(t + 1) = I_{nic}(t) + \sigma_{nic} E_{nic}(t) - \gamma_{nic} I_{nic}(t) \]

\[ Q(t) = Q_{ic}(t) + Q_{nic}(t) \]

\[ Q_{ic}(t + 1) = \begin{cases} & \text{if } I(t) < I_{\text{threshold}}, \\ & Q_{ic}(t) + \vartheta_{ic} S_{ic}(t) - \delta_{ic} Q_{ic}(t), \vartheta_{ic} < \delta_{ic} \\ & \text{if } I(t) \geq I_{\text{threshold}}, \\ & Q_{ic}(t) + \vartheta_{ic} S_{ic}(t) - \delta_{ic} Q_{ic}(t), \vartheta_{ic} \gg \delta_{ic} \end{cases} \]

\[ Q_{nic}(t + 1) = \begin{cases} & \text{if } I(t) < I_{\text{threshold}}, \\ & Q_{nic}(t) + \vartheta_{nic} S_{nic}(t) - \delta_{nic} Q_{nic}(t), \vartheta_{nic} < \delta_{nic} \\ & \text{if } I(t) \geq I_{\text{threshold}}, \\ & Q_{nic}(t) + \vartheta_{nic} S_{nic}(t) - \delta_{nic} Q_{nic}(t), \vartheta_{nic} \gg \delta_{nic} \end{cases} \]

\[ R(t) = R_{ic}(t) + R_{nic}(t) \]

\[ R_{ic}(t + 1) = R_{ic}(t) + \gamma_{ic} I_{ic}(t) \]

\[ R_{nic}(t + 1) = R_{nic}(t) + \gamma_{nic} I_{nic}(t) \]

Each SEIR category is split between immunocompromised (ic) and non-immunocompromised individuals (nic). Transition rates between compartments are separately defined depending on immunocompetency status and are listed in Table 2. Two individuals begin the infection: one immunocompromised individual and one non-immunocompromised individual. Immunocompromised individuals are parameterized to become infected at the same rate as non-immunocompromised individuals, with immunocompromised individuals taking longer to recover than immunocompetent individuals.25,85

In addition, a social isolation compartment, Q, was added to this model to capture the number of susceptible individuals who self-isolated according to government mandates of
personal preference, with immunocompromised individuals choosing to self-isolate more frequently than immunocompetent individuals. When the number of infections rose above a threshold value, $I_{\text{threshold}}$ (which was varied throughout the simulations), all individuals, excepting the subset of the essential workforce that could remain working, went into mandated social isolation. Social isolation rates were always $\leq 1$, to reflect the likelihood that some individuals are always likely to leave social isolation. When the number of infections was below the threshold value, immunocompromised individuals were assumed to enter social isolation at a rate higher than non-immunocompromised individuals due to the higher likelihood for severe disease outcomes in the pandemic for immunocompromised individuals. In addition, immunocompromised individuals were less likely to leave social isolation than non-immunocompromised individuals when infections were below threshold.

Participation in social isolation was a function of infection prevalence in the population, assuming instantaneous and accurate testing. We assume that all individuals in the population, except for essential workers, self-isolate in response to different population infection thresholds. The infection thresholds evaluated were 1%, 5% and 10% of the population infected, which is conservative and captures a more serious outbreak (~5% test positivity) than was required to issue stay-at-home orders in the US during the 2020 COVID-19 outbreak.²²

**Macroeconomic model**

The macroeconomic model used was a simple system of difference equations where, at time, $t$, the gross domestic product (GDP), $M(t)$, was modeled as a difference of the sum
of all gross income of individuals in the population and the sum of all gross costs of
individuals in the population.

\[ M(t) = M_{\text{in}}(t) - M_{\text{out}}(t) \]

\[ M_{\text{in}}(t + 1) = M_{\text{in}}(t) + sal(S_{lc}(t) + S_{nic}(t) + R_{lc}(t) + R_{nic}(t)) \]

\[ M_{\text{out}}(t + 1) = M_{\text{out}}(t) + c_q(Q_{lc}(t) + Q_{nic}(t)) + c_{ie}(E_{lc}(t) + E_{nic}(t)) + c_{il}(I_{lc}(t) + I_{nic}(t)) \]

Susceptible and recovered individuals contributed equally to GDP at a net benefit rate of
\( sal \), socially isolated individuals consumed assets at a rate, \( c_q \), and exposed and infected
individuals consumed assets as cost of personal maintenance and infection treatment at
net rates \( c_{ie} \) and \( c_{il} \), respectively. However, this model does not directly include deaths
resulting from infections and does not account for GDP loss resulting from a loss of life.
This framing allowed costs of a pandemic to be considered in terms of costs of social
isolation, treatment, and loss of people available to work.

Varying costs of treatment for infected individuals were evaluated in the model. These
costs ranged from a minimum of 1% of one worker’s salary per day to a maximum cost
of 100% of one worker’s salary per day.

**Fractional change in utility of social isolation**

Fractional changes in economic and epidemiological utilities were calculated for all runs.
These utilities were evaluated relative to a baseline run where individuals did not socially
isolate.
\[ U_M = \frac{M_q - M_{control}}{M_{control}} \]

Fractional change in economic utility of social isolation is denoted as \( U_M \) and represents the fractional utility of social isolation on changes in GDP over the course of the pandemic.

\[ U_L = \frac{I_q - I_{control}}{I_{control}} \]

Fractional change in epidemiological utility of social isolation is denoted as \( U_L \) and represents the fractional utility of social isolation on minimizing the total number of infections that occur over the course of the pandemic.

To calculate the overall utility of social isolation, we take the fractional changes in economic and epidemiological utilities together according to:

\[ U_{isolation} = (1 - \varepsilon)U_M + \varepsilon U_L \]

Where \( \varepsilon \) is a weighting coefficient, the optimal value of which was determined using a sensitivity analysis where the value of \( \varepsilon \) causes the midpoint of the \( U_{isolation} \) curve to reach a local maximum. This weighting allowed the comparison of \( U_{isolation} \) between outcomes in a way that reflects both the importance of changes to GDP, and the importance of maintaining a health human population.

Application of model to COVID-19 infections in two African provinces: Gauteng, South Africa and Kigali City, Rwanda

The overall model is parameterized according to Table 10. Calculation of essential workforce size was done according to the Guidance on Essential Critical Infrastructure Workers.\(^{101}\) Population statistics for Gauteng province were obtained from the 2011 South
African Census. Population statistics for Kigali City province were obtained the National Institute of Statistics of Rwanda. All other values were assumed or varied as part of the model.

Table 2: Parameters used in multi-group SEIR model with economic impact.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>Rate of infection</td>
<td>0.3</td>
</tr>
<tr>
<td>$\sigma_{nic}$</td>
<td>Rate of transition from exposure to infection</td>
<td>0.5</td>
</tr>
<tr>
<td>$\sigma_{ic}$</td>
<td>Rate of transition from exposure to infection</td>
<td>0.5</td>
</tr>
<tr>
<td>$\gamma_{nic}$</td>
<td>Rate of recovery for non-immunocompromised individuals</td>
<td>0.05</td>
</tr>
<tr>
<td>$\gamma_{ic}$</td>
<td>Rate of recovery for immunocompromised individuals</td>
<td>0.07</td>
</tr>
<tr>
<td>$\delta_{nic}$</td>
<td>Rate of non-immunocompromised individuals leaving social isolation</td>
<td>Varied from 0 to 1, dependent on individual choices and policymakers’ social isolation directives</td>
</tr>
<tr>
<td>$\delta_{ic}$</td>
<td>Rate of immunocompromised individuals leaving social isolation</td>
<td>Varied from 0 to 1, dependent on individual choices policymakers’ social isolation directives</td>
</tr>
<tr>
<td>$\theta_{nic}$</td>
<td>Rate of social isolation for non-immunocompromised individuals</td>
<td>Varied from 0 to .95, dependent on individual choices policymakers’ social isolation directives</td>
</tr>
<tr>
<td>$\theta_{ic}$</td>
<td>Rate of social isolation for immunocompromised individuals</td>
<td>Varied from 0 to .95, dependent on individual choices policymakers’ social isolation directives</td>
</tr>
<tr>
<td>$s_{al}$</td>
<td>Salary per person/day</td>
<td>Varied from 0.1 to 1</td>
</tr>
<tr>
<td>$c_q$</td>
<td>Cost of social isolation per day</td>
<td>0.1</td>
</tr>
<tr>
<td>$c_{le}$</td>
<td>Cost of treating exposed individuals per day</td>
<td>0.1</td>
</tr>
<tr>
<td>$c_{li}$</td>
<td>Cost of treating infected individuals per day</td>
<td>0.1</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Weighting coefficient for overall utility of social isolation</td>
<td>0.925</td>
</tr>
</tbody>
</table>

Table 3 represents parameterizations used for all Gauteng province and Kigali City province runs of the model.
Table 3: Parameters used in Gauteng province and Kigali City province runs of the model.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_{Gauteng}$</td>
<td>Total population size in Gauteng province</td>
<td>12,272,263</td>
</tr>
<tr>
<td>$W_{Gauteng}$</td>
<td>Percent of population that is part of the essential workforce in Gauteng province</td>
<td>18%</td>
</tr>
<tr>
<td>$N_{ic,Gauteng}$</td>
<td>Percent of population that is immunocompromised in Gauteng province</td>
<td>17%</td>
</tr>
<tr>
<td>$N_{Kigali}$</td>
<td>Total population size in Kigali City province</td>
<td>1,132,686</td>
</tr>
<tr>
<td>$W_{Kigali}$</td>
<td>Percent of population that is part of the essential workforce in Kigali City province</td>
<td>18%</td>
</tr>
<tr>
<td>$N_{ic,Kigali}$</td>
<td>Percent of population that is immunocompromised in Kigali City province</td>
<td>4%</td>
</tr>
</tbody>
</table>

Results

Selected model results for Gauteng are shown in Table 4 and selected model results for Kigali City are shown in Table 5.

Figure 11 shows that as immunocompromised individuals make up greater portions of the total population size, the number of overall infections increases.
Figure 11: Total number of infections based on fraction of the population that is immunocompromised.
Table 4: Model results for Gauteng province, South Africa

<table>
<thead>
<tr>
<th>Quarantine conditions</th>
<th>GDP lost to isolation and treatment</th>
<th>Final size of outbreak as a percentage of the population size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everyone except essential workforce (18% of population)</td>
<td>540 million units</td>
<td>34.6%</td>
</tr>
<tr>
<td>Everyone except 5% of essential workforce</td>
<td>750 million units</td>
<td>1.8%</td>
</tr>
<tr>
<td>Everyone except 1% of essential workforce</td>
<td>750 million units</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Table 5: Model results for Kigali City province, Rwanda

<table>
<thead>
<tr>
<th>Quarantine conditions</th>
<th>GDP lost to isolation and treatment</th>
<th>Final size of outbreak as a percentage of the population size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everyone except essential workforce (18% of population)</td>
<td>52 million units</td>
<td>33%</td>
</tr>
<tr>
<td>Everyone except 5% of essential workforce</td>
<td>72 million units</td>
<td>1.6%</td>
</tr>
<tr>
<td>Everyone except 1% of essential workforce</td>
<td>72 million units</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Across both provinces, two main patterns emerge: (1) as treatment costs increased, the pandemic’s effect on loss of GDP increased and (2) social isolation practices drastically reduced the total number of infections over the course of the pandemic, with isolation of larger proportions of the population leading to lower total infections.

Two less intuitive results emerged: (1) cost of isolation had a greater effect on GDP losses than cost of treatment and (2) the extent of social isolation had a stronger effect on total numbers of infections than the infection threshold that caused mass social isolation.

Figure 12 shows infection levels of immunocompromised individuals in Kigali City province increase with increasing essential workforce size. As less of the essential workforce is mandated to socially isolate, more immunocompromised infections occur.
Figure 12: Infection levels of immunocompromised individuals in Kigali City province. Infections increase as essential workforce size increases, effectively decreasing the fraction of the population capable of social isolation.

Figure 13 shows infection levels of immunocompromised individuals in Gauteng province increase when the fraction of essential workforce that must isolate is decreased. A larger number of people are infected in Gauteng because of the assumption of homogenous population distribution and mixing and the larger overall population size in Gauteng than in Kigali City. The results in Gauteng province echo the results in Kigali City province where, as less of the essential workforce is mandated to socially isolate, more immunocompromised infections occur.
Figure 13: Infections levels of immunocompromised individuals in Gauteng province. Infections increase as essential workforce size increases, effectively decreasing the fraction of the population capable of social isolation.

Utility of isolation in Kigali City province is shown as a function of essential workforce size in Figure 14. The utility of isolation is maximized when 5% of the essential workforce remains working.
Figure 14: Changes in utility of isolation with workforce size in Kigali City province.

Utility of isolation in Gauteng province is shown as a function of essential workforce size in Figure 15. The utility of isolation is maximized when 3% of the essential population remains working.
Figure 15: Changes in utility of isolation with workforce size in Gauteng province.

The fractional change in economic utility of social isolation, $U_M$, by our definition will always take on a negative value because we generate our utility by comparing to a non-epidemic outcome on GDP. However, the fractional change in epidemiological utility, $U_L$, can take on a positive value because we generate our utility by comparing to a control outcome where there is no isolation (and thus, higher final infection counts). We find that the utility of social isolation is maximized when the entire population excluding 5% and 3% of the essential workforce, respectively for Kigali City province and Gauteng province, is required to socially isolate.
Discussion

Pandemics affect economies in two main ways: 1) by contributing output losses because of deaths and 2) by contributing output losses as a result of economic slowdowns caused by policies that inhibit economic productivity, such as mass social isolation of the population. The challenge to policymakers is to minimize economic losses, while simultaneously minimizing infections. Another factor for consideration is that globally, immunocompromised individuals are found more often in developing and third world countries such as those in sub-Saharan Africa, where healthcare infrastructure is limited. Since immunocompromised individuals have a higher risk of developing severe COVID-19, this means that policymakers must balance the number of infections that will likely occur in each area with the extent of an economic slowdown that would result from social isolation policies. Our work provides a framework for analyzing the impact of a pandemic and quantifies the utility of different policies. However, it is important to note that, surprisingly, Africa may have been spared the worst of the COVID-19 pandemic.

Our results echo findings that stricter social isolation and/or lockdown policies result in lower overall infection rates within a population and short-term economic slowdown, with regions with longer and stricter lockdowns observing lower numbers of infections and higher rates of short-term economic slowdown than regions with less stringent requirements. Our model does not directly include deaths as a result of infection, and thus does not account for loss of GDP due to lives lost as a result of those infections. While this choice was made as an assumption, letting us compare the direct utility of isolation in the absence of the potential superadditive effect of overwhelming healthcare systems, it would be of critical importance to relax this assumption in direct
application to the formation of policy. Depending on the scale and severity of infection caused by a pandemic, the reduction in GDP due to loss of life may exceed short-term GDP losses as a result of social isolation.\textsuperscript{110} In addition, our model estimates for GDP losses may be artificially lowered by our assumption that all recovered individuals immediately return to work. Specifically, our model does not account for long-term lung tissue damage caused by COVID-19 that can affect the ability of individuals to return to work.\textsuperscript{114}

Our model showed that GDP losses were less severe when cost of social isolation was lower relative to income. We do not account for fluctuations in income due to a pandemic, as in the case for individuals placed on sick leave or furlough. Costs of social isolation can vary by area and infrastructure\textsuperscript{113} and our model shows that minimizing costs of social isolation is necessary to increase the utility of social isolation. To be better prepared for future pandemics, planners and policymakers should consider prioritizing the accessibility of food, medical care, and economic stimulus to marginalized groups.\textsuperscript{115,116} In addition, access to infrastructure/support that can minimize effects of displacement of consumption and stockpiling\textsuperscript{117}, and providing incentives for workspace design to facilitate social isolation should be included among prioritized policies.

We found that the extent of social isolation (i.e., the fraction of the population which socially isolates) has a greater effect on pandemic and economic outcomes than the infection threshold that triggers the need for isolation. This means that in areas with less frequent or accurate surveillance, imposing policy requiring social isolation as soon as infections are detected is the best course of action. However, we note that in our model, surveillance was assumed to be 100\% accurate and immediate, and instances where time-delays due to less accurate surveillance cause infections to be detected late would benefit
strongly from investment in surveillance systems that are more accurate. Reductions in accuracy of or delays in surveillance can amplify monetary costs for a few reasons. First, if treatment is delayed due to inaccuracy of surveillance, a higher proportion of the population will become infected, thereby increasing treatment burden. Second, if resources for treatment are limited, delays in surveillance can lead to shortages in resources to treat individuals, thereby increasing disease burden in the population. Finally, when higher proportions of infections occur, social isolation must continue for longer than in cases where fewer infections occur (as a result of imperfect isolation) because more individuals who are failing to isolate are transmitting the pathogen in the population. Other models have shown that in instances where surveillance is less accurate, coordination in pandemic-planning among neighboring policymakers helps reduce transmission rates by efficiently distributing limited resources to maximize their effect.80,118,119

Our model tracked infections of immunocompromised individuals and found that the in populations with high rates of immunocompromise, more infections overall occurred. This is likely due to the fact that the effective \( R_0 \) differs between immunocompromised and non-immunocompromised individuals as a result of immunocompromise leading to longer infection duration.82 We did not explicitly model individual decision-making in the face of risk, and instead assumed that decisions regarding risky behavior were made on the population level. However, individuals in areas where social isolation is recommended or mandated may suffer from mental health declines or social and political polarization, and may choose to engage in risky behavior to alleviate the mental health effects of lockdowns.120–124 Individual perceptions of risk combined with costs of social isolation can cause some individuals to ignore policies and mandates regarding social isolation and
partake in behaviors that increase likelihood of pathogen transmission. Our study focused on immunocompromised individuals as one such subgroup, and we found that in populations comprised of a larger fraction of immunocompromised individuals (e.g., Gauteng province), larger numbers of immunocompromised individuals became infected than in populations comprised of a smaller fraction of immunocompromised individuals (e.g., Kigali City province). It is imperative that policymakers consider their immunocompromised constituents when making decisions to encourage or discourage following social isolation mandates.

Local maxima in the utility of social isolation can be used to formulate policies. Our utilities of social isolation for Kigali City province and Gauteng province reflect that infrastructure to minimize the economic costs of social isolation is of paramount importance to successfully mitigate the economic effects of a pandemic. Although we have calculated an overall, society-wide utility of isolation, we recognize that an individual-based utility could also be calculated, and such a utility could reflect the realities of decision-making on the individual level. While our work can guide policy makers, it does not directly address the potential changes to the probability of adherence to a social isolation policy on the individual-level. Individuals are expected to make decisions regarding adherence to social isolation based on their own perceptions of the economic costs of isolation and their level of medical vulnerability. If individually perceived costs of isolation exceed perceived medical benefits of isolation, individuals are likely to fail to adhere to recommendations regarding social isolation. Individual perceptions of costs of isolation and medical benefits have widely varied in the COVID-19 pandemic and as
such represent an important factor to consider when developing pandemic management strategies.

In conclusion, we have developed a framework with which policy makers can assess the economic and epidemiological trade-offs of social isolation policies in a pandemic. The value of the utility of social isolation can be applied to a given region’s population, considering that there may be differences in epidemiological and economic severity imposed to different subgroups within that population, and used to make informed policies to mitigate the economic and epidemiological effects of a pandemic. Logical future expansions of our work include applying differing costs to the treatment of immunocompromised and non-immunocompromised individuals, relaxing assumptions regarding perfect and instantaneous surveillance, considering individual-based modeling of decision making, and expanding the modeling to other infectious diseases. This work represents a necessary step forward in planning efforts.94
GENERAL DISCUSSION AND CONCLUDING REMARKS

In this work, we have applied expected utility theory\textsuperscript{10} to characterize the trade-offs of epigenetic modulation, consensus communication regarding signals, and social isolation in a pandemic.

In chapter one, we saw that epigenetic control of gene expression evolves when timescales of environmental variation are short, and costs of epigenetic control are low. We showed that in populations with low genetic diversity, epigenetic rescue can prevent local extinction by promoting phenotypic heterogeneity. We used an expected utility framework\textsuperscript{42} to develop a model for the evolution of epigenetic mechanisms of gene regulation. We predicted that traits with high utility are expected to come under epigenetic control when environmental fluctuations are frequent and costs to epigenetic machinery are low, and that traits with low utility can only come under epigenetic control when costs to epigenetic machinery are miniscule. We found that plasticity as a result of epigenetic mechanisms evolves when relative utility of the target trait is high, windows of environmental predictability are short, and epiallelic redundancy is balanced with the cost of epigenetic modulation. We showed that developmental canalization is favored when there are a small number of genomic traits for selection to act upon, when environments are predictable for several generations, and when costs to epigenetic machinery are large.

We would like to reiterate that our model does not replace models of phenotypic plasticity or epigenetics\textsuperscript{17,39,40,126} However, even so our model captured many of the same biological phenomena as more complex models of phenotypic plasticity and epigenetics. Our model adds nuance to the ongoing discussion of costs, benefits, and trade-offs of epigenetic regulation by incorporating these concepts into a formal framework. Our model and
associated framework provide a novel and relatively simple mathematical means of addressing classic questions in evolution of phenotypic plasticity and the mechanisms that drive it.

In chapter two, we showed that variations in decision criteria for organisms that participate in consensus decisions regarding the presence or absence of stimuli can impose group-wide costs and benefits to the act of consensus decision-making itself. The perpetuation of group decision-making depended on the tradeoffs of missed detections and false alarms due to the location of the group average detection criterion. In the face of changing signals, we demonstrated that consensus rescue may prevent individuals with poorly matched criteria from dying and thereby can preserve a diversity of decision criteria among the group.

We showed that the traditional signal detection theory framework could be expanded from describing the optimal response criterion for one individual to describing the optimal response criteria for a social population. We showed that, when costs of missed detections and false alarms were not equal to benefits of correct rejections and hits, populations comprised of individuals with a diversity of response criteria detected signals more accurately than did individuals with a response criterion of maximal utility. Our application of expected utility theory framework to signal detection theory enables us to generate a novel means of extending the predictions of signal detection theory from one individual to individuals cooperating in signal detection tasks as a group.

Potential expansions for the models and framework in chapter two include time-delays in signal communication and addressing changes in the underlying signal-and-noise as well as noise-only distributions to simulate environmental fluctuations.
In chapter three, we showed that in populations comprised of non-immunocompromised and immunocompromised individuals, the utility of isolation is maximized when costs of isolation are low and costs of treatment are high, and when larger fractions of immunocompromised individuals isolate. We recommend that social isolation rates are kept as high as economically possible to limit pathogen spread, and we make this recommendation especially in cases where costs of treatment are very high.

We developed a framework based on the application of expected utility theory to susceptible-exposed-infected-recovered model simulations of pandemic spread. Policy makers can use this framework assess the economic and epidemiological trade-offs of social isolation policies in a pandemic. The value of the utility of social isolation can be applied to any given region’s population, considering that there may be differences in epidemiological and economic severity imposed to different subgroups within that population, and used to make informed policies to mitigate the economic and epidemiological effects of a pandemic.

Logical future expansions of our work in chapter three include applying different costs for the treatment of immunocompromised as opposed to non-immunocompromised individuals, making surveillance imperfect impose time-delays in surveillance, considering individual-based modeling of decision making, and expanding the modeling framework to other infectious diseases.

From this work, four key themes emerged: (1) longer timescales of environmental predictability often drive investment into more channeled and fixed phenotypes and behaviors, (2) costs have a greater effect over longer timescales, (3) redundancy can
commonly provide rescue effects (in chapter one, we saw epigenetic rescue and in chapter two, we saw consensus rescue), and (4) heterogeneity in population composition can have significant outcomes in a pandemic as well as in the broader scope of evolution. This work represents but a fraction of the potential applications of expected utility theory to ecological systems.
REFERENCES


