The Effects of Temporal Heterogeneity in Genetic Covariance

by

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Abstract

Environments are not stable, and the way they change may influence the evolutionary dynamics. Consequently, taxa may adapt to how change happens and not just to the effect of change. Here we suggest that trait covariance can change depending on how the fitness landscape fluctuates over time. So far, there is evidence for three adaptive causes for evolution in trait covariance: phenotypic plasticity, correlational selection, and antagonistic pleiotropy. This thesis shows how the synchrony of the change in selective pressures on different traits, even without a causal selective connection, can lead to covariance. We use an individual-based birth-death model to run experiments and compare the effects of correlated change in selective pressures over different traits with uncorrelated change. Our results agree with our hypothesis and show how correlated environmental change can lead to positive covariance.

Lay Summary

In a biological population, individuals have many characteristics, and some of those may covary in said population. If two characters covary, an individual with higher values for the first character will likely have higher values for the second character. When more than one gene affects multiple characteristics (pleiotropy), those characteristics will have positive covariance. There are already known factors for why pleiotropy can be evolutionarily advantageous. Here, we are suggesting an additional cause. The environment is constantly changing. What is the best combination of characteristics now may not be the same in the future. If the environment changes so that the optima of different characteristics vary in synchrony, the covariance of these characteristics will be positive. By varying in synchrony, we mean that if the most advantageous is to have more of the first character at one point, it will also be advantageous to have more of the second.

Preface

The work presented here is the original work of mine, Isabela do Ó under the supervision of Dr. Michael Whitlock. The design of the experiments and the methodology was my responsibility. Besides Dr. Whitlock's guidance, I have received suggestions and feedback by peers, lab colleagues, and by my research committee.

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Chapter 1

Introduction

The current thesis demonstrates how integrating change over time in the fitness optimum of different traits leads to covariance and how a change in covariance can reflect the evolution of the genotype to phenotype map of a population. This first chapter intends to explain the background of my hypothesis. Given that my main result is that *temporal heterogeneity* can lead to the evolution of *trait covariance*, I succinctly explain both topics. I link these two sections of my chapter with an exploration of what *evolvability* is and how a population's genetic architecture influences it.

1.1 Temporal Heterogeneity

A Changing Environment

A population's expected course of evolution is susceptible to disturbances by abiotic events and interacting species [3, 10]. Temporal heterogeneity of selection describes how the pressures posed by the environment are dependent on time. Variations to the environment are, for example, changes in the availability of resources, such as scarcity by drought or a new competitor. It may also include a new selective pressure, such as novel predators or a new physical barrier. These transformations to the habitat may occur in varying degrees of stochasticity and constancy, from an isolated random episode [55, 145] to an ever recurrent cycle [70]. Regardless, temporal heterogeneity is the norm [22].

Organisms reflect the environmental oscillations they are a part of [90], such as tides, rains, forest fires, or even just the turn of seasons or the nightfall [76, 89, 129]. The vertical migration of zooplankton is an excellent example of multiple species adapting to abiotic cycles. The organisms spend days in deeper waters and nights on the surface, with a depth variation that can go up to around 100 meters [57]. There are representatives from a wide range of clades in what we call "zooplanktons". The similarity in migratory behavior of such diverse taxa, and also diverse ecosystem since it happens in both fresh and ocean water, indicates adaptive value to the trait [52, 57].

Similarly, the reproduction of various plants and animals follows the peak availability of food in their changing environment [45, 46]. Both examples are of temporal heterogeneity within the lifespan of organisms. This type of environment fluctuation is but another characteristic of the environment. Consequently, it is clear and straightforward how individuals adapt to these changes.

Another type of temporal heterogeneity is when the present condition is different from the one the lineage was adapted to. When the change happens through generations, it impacts the demographics of a population, which may culminate in adaptation or extinction [8, 9, 85]. In the case of inter-generational environmental alterations, the way this change happens, and not just what the new environment is, affects the evolution of the lineages [15]. For instance, the speed and degree of change may dictate whether populations will persist [26, 30], which alleles are fixed [26] and the general movement towards fitness optimum of the population [27].

Experimental biology has given us great examples of how variations in the rate of change are enough to create diverse responses. For example, Morley *et al.* (2015) [96] shows how in viruses, lineages that experienced more gradual environmental change had reduced phenotypic and genotypic variation. Conversely, Collins and Meaux (2007) [27] showed how in *Chlamydomonas*, slower rates of environmental change created populations with higher genetic diversity. Both studies agree that more gradual change allows for populations to have higher fitness. Both studies exemplify how the end effect of environmental

fluctuation depends on the way these variations happen.

The predictability of change is also a parameter that can affect populations. In the absence of predictable environmental cues, a parent can produce offspring of various phenotypes to create enough diversity to survive disparate circumstances [23]. Once again, this type of adaptation is related to properties of environmental change instead of characteristics of the new selective pressures alone.

In this work, I focus on how synchrony between different aspects of the environment can affect the evolution of a population. Similar to the speed of environmental change [83] and the predictability of the variation [23], the covariance of distinct environmental aspects are all parameters of the change. I argue that despite not being direct characteristics of the environment, the dynamics of its fluctuations can create different selective pressures.

A Moving Fitness Landscape

The selective characteristics of an environment can be mathematically described as a fitness landscape. The fitness landscape is a metaphor for the optimization problem that is of the evolution of a population. The fitness function maps an individual's fitness from its trait values. Wright (1932) [155] coined the term to help solve the unpredictability of mutational impacts on fitness in the light of pleiotropy and epistasis.

Wright suggested that the genotype can be expressed as an n-dimensional

cube, n being the number of genes [155]. This hypercube is the parameter space used for a function that relates alleles to fitness. Allelic combinations with the highest reproductive success or lower mortality rates (or whichever aspect of fitness is measured) will represent local optima.

As opposed to using genes for variables, Simpson (1952) [124] focused on phenotype, which is what I also do in this thesis. We usually know more about traits and how the phenotype is related to fitness than the relation between genotype and fitness [151]. When using traits as parameters of a fitness function, the possible theoretical values of each trait fall within a section of a line in $\mathbb{R}$. Similar to the gene analogy, the phenotypic space is also represented by the geometric object confined by the lines representing each trait.

For the interests of population genetics, the object that moves across the fitness landscape is the population. This population can be represented by a single point, which could be, for example, the average phenotype. As in individual-based models, the population may also be represented as a cloud of points, a point per individual. The vector z is the set of traits of an individual and expresses the position of said individual in the landscape.

To try to predict evolutionary outcomes, natural selection can be interpreted as an optimization problem. The optimization problem that natural selection "solves" is finding the values of the vector z within the phenotypic space that maximizes the fitness function [118]. The fitness landscape is the graphical representation of this optimization problem. The population takes steps around the

landscape by genetic mutations. Because mutations and their effects are random, the search for a solution is a stochastic optimization problem.

The fitness function should represent how the interaction between traits and the environment affects the performance of individuals. Differences in how the phenotype relates to fitness affect the evolutionary dynamics and equilibrium of the biological system. In other words, alteration in the map from phenotype to fitness affects the landscape's geometry and consequently affects the population's search for the optimum. Biologically, these maps describe the selective pressures of an environment and are also capable of describing changes in these pressures [64].

Temporal heterogeneity adds another parameter to the study of fitness landscapes: Time. If the environment changes with time, the selective pressures are unlikely to be static. Consequently, the fitness landscape also changes through time. This variation can be expressed as a composition of the fitness function and time.

Considering A as the amplitude of the peak, z_{i_0} as the coordinate of i for the the center of the peak and σ_{z_i} as the spread of the peak for trait i, we can represent a single peaked fitness function as the following Gaussian:

$$f(z) = A\exp\left(-\sum_{i=1}^{N}\frac{(\bar{z_i}-z_{i_0})^2}{2\sigma_{z_i}^2}\right)$$

In this thesis, the movement of the fitness function is given by a linear Markov

chain [20]. For each trait, at each time point, the position of the optimum has a fifty percent chance of moving up or down. The exception is the boundaries, for which the optimum has a fifty percent chance of moving back or staying in the same position.

Under simple models of selection, populations evolve to follow the fitness landscape optimum [16]. Given enough time to evolve, the average phenotype of the population and most of the individuals' phenotypes will be scattered around local optima. As the environment changes, the population is forced to explore the landscape [67]. Populations will survive the environmental shifts depending on the strength of selection and the distance between the new and the previous optimum. The capacity to adapt to the new pressure also depends on characteristics of the population, such as genetic diversity and mutation rates [72].

1.2 Evolvability

Evolvability concerns the capacity of a population to adapt given an alteration in selective pressures. This adaptation may be through a change in proportions of alleles or the presence of a whole new trait. Evolvability has many definitions [28] due to its relevance in various biology fields - varying definitions that are arguably all related [102].

One of the earlier descriptions of the term creates a parallel between

evolvability and heritability. Following Fischer's theorem of natural selection, authors [41], [50] have characterized evolvability as the potential to respond to natural selection [102]. This way, the amplitude of the existing genetic variance defines the capacity of a population to persist. The equation below, known as the breeder's equation, where S is selection differential, expresses the relationship between response to selection (R) and heritability (h^2):

$$R = h^2 S$$

Other authors have, instead of heritability, linked evolvability to the genetic coefficient of variation [56], which is a mean-standardized measure of variation between quantitative traits [100]. This line of thought argues that using heritability as a measure creates difficulty generalizing and comparing evolvability between traits and taxa. One of Houle's (1991) [56] reasons is that S depends on information about the selected population instead of only being a function of the fitness landscape. They argue that the coefficient of additive variation allows for a fair comparison between traits and comparison between different populations. In my work, I use additive variance and covariance as the comparable parameter between the populations.

In this thesis, I am interested in trait covariance. Thus, I avoided environmental causes of variance. I also ignored the effects of epigenetics underlying the difference between individuals. That way, the cause of variance in the populations

I studied was additive genetic variance.

Within the genetic reasons that can contribute to diversity, there is dominance, epistasis, and additive relationship of genes. Differences in quantitative alleles with no dominance relationship and no epistasis result in additive differences between individuals. I could ignore the effects of dominance in the model because I worked with haploid populations. For the asexual populations in this thesis, the effect of epistasis should not affect our results. In the cases with recombination, I point out the differences of variances and covariances with and without epistasis.

A third group of authors concerned with defining evolvability discussed the necessity of a distinction between variation and variability [142]. Wagner and Altenberg explain that variation is the diversity present among individuals in a sample. On the other hand, variability is the potential of change, like solubility is the potential for a substance to dissolve in another. They describe evolvability as the ability to produce adaptive variants, thus, depending on the variability instead of variance. Thus, the steadiness, or robustness, of the population's genetics will impact evolvability.

Generally, robustness refers to how a characteristic of a biological system may persist despite perturbations or uncertainty [73]. This way, robustness may seem like the opposite effect to evolvability. However, it is arguable that robustness is an essential attribute for evolvable systems [73]. Wagner used the RNA secondary structure to illustrate the intimate relationship between robustness and evolvability [140].

According to Wagner, using separate definitions for robustness and evolvability in different contexts, specifically, sequence space or structure, relaxes the apparent tension between the terms. Sequence robustness is the number of other genotypes with the same structure separated by nucleotide substitutions from a given genotype. The average of this number for all genotypes is the value for structure robustness. Sequence evolvability is the number of different structures separated by nucleotide substitutions. Similarly, structure evolvability is the number of different structures found in the neighborhood of a given structure.

With sequence working as an abstraction for genotype and structure for phenotype, Wagner's propositions are expandable to different levels of biology. Wagner [140] explains that although highly robust RNA genotypes are less evolvable, the opposite can be true for phenotypes: High robustness at the phenotype level leads to high evolvability because of the greater genetic flexibility. Populations with more robust phenotypes can explore more of the sequence space, creating increased diversity of possible mutational steps to take at a population level. However, some researchers do not fully agree with Wagner's suggestions. Mayer and Hansen's experiments went against Wagner's suggestion. According to Mayer and Hansen's experiments work, Wagner's explanation is too theoretical and does not work for general biological systems [91].

Another central topic on evolvability is modularity. Modularity is the degree to which characteristics cluster [102], creating subsystems. It is commonly

argued that modular organization supports evolvability [106, 143]. Lewontin [82] suggested that adaptive evolution depends on a degree of the evolutionary grouping of traits, or what he called quasi-independence of sections of the phenotype. A simple explanation for this proposition is that modularity allows for significant changes in a group of related traits without affecting the entire phenotype. The extent to which modularity is necessary for evolvability is still in debate [102].

Modular phenotypes are a specific case of gene-to-trait maps. The connection between different traits is reflective of their function and relation to the environment. It can also be solely dependent on underlying genetics [1, 58]. Discussions on modularity fall into the theme of genetic architectures. Therefore, we should understand the causes of traits' interdependence to understand the effect of interdependence on adaptability.

1.3 Trait Covariance

Traits do not interact with the environment separate from other traits. Consequently, their evolution will not be independent. Such dependence between characters is observable through their covariance within a population [56]. Joint variation between two or more traits happens as a result of different processes. Linkage disequilibrium [24] and pleiotropy [99] are the two causes of genetic covariance of traits.

Pleiotropy causes the entanglement of molecular networks. A unique mutation may affect more than one trait because of interactions between genes and genetic products related to these supposedly distinct traits [74],[101]. A single protein that performs multiple molecular functions for different aspects of the phenotype would cause multiple traits to have some level of connection. Glyceraldehyde-3-phosphate dehydrogenase is an example of a protein that acts on many different processes: It is more known for its importance for the Calvin Cycle and glycolysis, but it also has nonenzymatic functions as a transcription activator and as an initiator of apoptosis [37]. Even a protein with a single function may generate pleiotropy. The deactivation of phenylalanine hydroxylase triggers a multi-trait condition – phenylketonuria [37].

Pleiotropy is the source of a more lasting type of covariance when compared to linkage disequilibrium [88]. Linkage disequilibrium is the nonrandom association of alleles in a population. Linkage disequilibrium can result from natural or sexual selection, population structure, mutation on specific backgrounds, and drift. [39]. Linkage disequilibrium should dissolve after enough recombination and segregation [125].

Measuring Trait Covariance

Existing variation within a population is a reflection of the environment and genetics. The environment can influence variation because the same set of alleles may create different phenotypes depending on environmental cues [128]. More

exposure to sunlight darkens skin in humans without necessarily changing the genome of individuals. Genetic diversity refers to differences within heritable aspects of individuals [88].

The evolution of a population depends on the existence of diversity and the genetic constraints of the taxon. While genetic variance is a measurement of diversity, additive genetic covariance describes the joint variability of traits. The additive genetic variance and covariance refer to the genetic variation among individuals due to the presence of different alleles. The additive genetic covariance is a measurable unit for expressing the effects of pleiotropy (and linkage disequilibrium).

The Variance-Covariance or **G** Matrix is a classical tool of quantitative genetics for describing a summary of all associations between phenotypic characters. The Variance-Covariance Matrix's diagonal describes the variances of traits in a population, and the off-diagonal contains the covariances. This matrix represents specifically the additive genetic variances and covariances, which are values that describe inheritance and derive from the frequency and effects of alleles. The additive genetic covariance describes how genetically co-dependent are pairs of traits [77, 79, 80].

The co-dependence of trait variation alters the rates of evolution based on univariate predictions. In other words, the pace of change of a lineage is different depending on whether traits are dependent or independent. This is because genetic correlation allows for selection on one trait to affect another trait.

According to Lande and Arnold [80], the change in mean phenotype at a given time point follows the equation below where z_i refers to the mean of trait i in a population and β to the selection gradient on each trait:

$$\Delta z = \mathbf{G}\beta$$

$$\Delta z_1 = \mathbf{G}_{11}\beta_1 + \mathbf{G}_{12}\beta_2$$

$$\Delta z_2 = \mathbf{G}_{22}\beta_2 + \mathbf{G}_{21}\beta_1$$

There is a direct connection between this equation and the breeder's equation presented earlier [19]. The response to selection is how much the average of the trait changed, so $R = \Delta z$. Heritability can also be rewritten as a relationship between phenotypic variance and additive genetic variance:

$$h^2 = \frac{V_A}{V_P}$$

β, the selection gradients, is the effect of a trait on fitness when other traits are constant. We can calculate β from the slope of the regression of fitness on the trait. Selection gradient is the strength of direct selection on the trait. In contrast, a selection differential calculates the total strength of selection. The selection differential does not remain constant in nature.

For example, consider a single trait. For that case we have the following:

$$\mathbf{G} = V_A \text{ and } \beta = \frac{S}{V_P} \Longrightarrow \mathbf{G}\beta = h^2 S$$

Evolution of Trait Covariance

When selection is strong enough to significantly alter the gene frequencies of the traits subject to it, there will potentially be a change in that portion of the **G** matrix in which these genes have influence. When selection changes allele frequencies, it is therefore also changing the variances and covariances. The additive genetic variance of the target trait plus the additive genetic covariances between the target trait and other non-target traits will change. In general, the change in the **G** matrix will show no overall general pattern. Still, it will depend upon the selection regime and the traits included in the matrix.

The genotype-to-phenotype map describes which genes affect which traits and to what extent [49, 95]. Since the **G** matrix expresses the additive genetic covariance of traits in a population, it expresses how additive genetic effects may influence different traits. That way, it gives us an idea of pleiotropic effects existing in the population. Note that pleiotropy can exist even if it is not observable through covariance, for example, when there is little diversity in the population.

The G-P map creates a bridge between genes and the environment. Because

traits are the aspects of the individuals which interact with the environment, they are visible to natural selection. From what both empirical data and theoretical predictions show, environment change is one of the causes of change in the G-P map [2], thus changes in **G**.

Genetic correlations between traits can switch from negative to positive depending on the environmental conditions [120]. An example of this change in correlation comes from sawflies from northern Finland. Experiments on these insects [68] show that genetic correlation between body size and development time went from significantly positively correlated in high-quality diet to significantly negatively correlated in the low-quality diet. In plants, field experiments provide another example. Donohue et al. (2000) showed that density of neighbors was crucial for determining whether meristem traits were positively or negatively correlated [34].

Traits can also shift from uncorrelated to correlated according to environmental conditions. Hausmann et al. (2005) observed that fruit number in the dry environments was not correlated with the number of branches [54]. However, in wet environments, fruit number was positively correlated with the number of branches. Czesak and Fox (2003) showed a similar result for correlation between body mass and egg size in beetles [29]. Depending on where the females laid their eggs, there was a positive correlation between egg size and the parent body mass. The phenomenon of changing the correlation between traits in distinct environments can be due to environment-dependent pleiotropy [113].

It is still unclear how much of the instability of **G** is due to evolution (selection and drift) [147] or ecology (environment-specific allelic effects) [154]. Here I aim to show how correlated environmental fluctuations have the potential to change genetic covariance. I suggest that the covariance observed between traits may not reflect selection for correlated traits. Synchrony of the selective pressures on different traits should result in the covariance of traits within a population.

Adaptive Causes of Covariance

There are three selective causes for trait covariance recorded in the literature: correlational selection, plasticity, and antagonistic pleiotropy. In this last section of my introductory chapter, I will succinctly explain these three processes. Then, I explain how this thesis aims to suggest another form in which covariance can emerge due to changes in selective pressures.

Correlational selection occurs when more than one trait affects fitness in an interactive (correlated) way. This type of selection creates a ridge in the fitness landscape. Correlational selection can be a result of fitness epistasis, which is when fitness is a result of interactions between traits besides just the independent [125, 151].

Correlational selection can reshape the G-P map, and consequently alter trait covariances (eg:[132]). As opposed to a single-peaked landscape, a ridge promotes diversity since multiple trait combinations confer fitness optimum.

However, the polymorphism is restricted to an area of the phenotype space. There is a fitness difference between the phenotypes in the ridge and the rest of the phenotype space.

Plasticity is the term given to a single genotype producing different phenotypes depending on inputs from the environment [127]. This response may or may not result from selection. There is theoretical evidence for plasticity to accelerate evolution and increase evolvability [35, 38, 40]. With individuals' phenotypes changing within their lifespan, it increases the probability of lineages to survive adverse conditions [149].

Plasticity affects the variance-covariance patterns in a population. Draghi and Whitlock (2012) suggest that flexible phenotypes promote greater genetic diversity [35]. Their simulation experiments show that populations whose phenotypes' changed based on environmental cues evolved **G** matrices with greater values in the dimension of plasticity. Genetic covariance can increase for traits whose optima covary over time.

Correlational selection and phenotypic plasticity are adaptive causes that may increase covariance. On the other hand, antagonistic pleiotropy is a maladaptive cause of covariance. Antagonistic pleiotropy occurs when an allele is responsible for increasing one components' fitness and decreasing another when a finite resource must be divided between components. For example, the same allele can affect fecundity positively but negatively affect life expectancy [109]. Alternatively, an allele can be advantageous for females and disadvantageous for

males. Antagonistic pleiotropy creates a negative correlation between traits.

Antagonistic pleiotropy decreases fitness differences between types, extending the time of polymorphism in the population [17, 43, 110, 134].Consider a population with two alleles: One which confers higher fitness for circumstance A (*e.g.* beginning of life, or females) but lower fitness for circumstance B (*e.g.*. life expectancy, or males), and a second allele that has the opposite fitness relationship. These circumstances can be comparable in terms of how much they affect total fitness. There is a similar probability of individuals with either allele passing on their genes in this scenario. Therefore, polymorphism persists longer, and the negative correlation between traits creates a negative covariance in the population.

Jones *et al.* (2004) [62] show through simulation experiments how in a finite population a moving optimum provoking directional selection increases stability of **G**. They explain that stability is promoted when the optimum changes in the same direction as to the one with the highest genetic variance in the population, the genetic line of least resistance [117]. Their results show that continuous unidirectional movement of the optimum promotes higher absolute values of covariance. Our goal here is to extend Jones *et al.*'s results by focusing on the cause of increased genetic covariance of traits instead of on stability. Beyond that, we expand our analysis to discuss how heterogeneity of the fitness landscape over time can explain complex configurations of the genotype-to-phenotype map.

Here I show how the synchrony of selective pressures of different traits can

cause covariance. Given that the fitness landscape changes, the pressures of different traits may vary in a dependent or independent way. If the change of the pressures on different traits is dependent, I call it correlated change. I refer to an uncorrelated changing environment when the selective pressures of different traits vary independently. I suggest that the correlated change of selective pressures on different traits increases the magnitude of additive genetic covariance.

To check my hypothesis, I ran a series of simulations. I used an individual-based birth-death model to describe the evolution of the populations. Three general types of populations differed in the level of connectivity of their genetic architecture. I compared populations evolving in a correlated changing environment with a population under the same parameters, but that evolved in an uncorrelated changing environment for each of my experiments. The uncorrelated changing environment condition served as a control.

Indeed, covariance develops as a result of how an environment changes. When selective pressures on different traits vary in a correlated way, there is significantly more additive genetic covariance of traits than when pressures vary uncorrelated way. Further, according to my model, modularity also develops as a result of how changes happen.

Chapter 2

The Evolution of Trait Covariance in Temporally Heterogeneous Environments

2.1 Introduction

Environments are unstable and heterogeneous both due to predictable daily, seasonal, or geological thermal cycles, as well as to stochastic changes, like natural catastrophes, sea surface temperature anomalies, or human interference [92–94, 156]. Changes in the environment affect biological systems on many levels, from individuals to communities [21, 42, 153]. For example, trivial fluctuations as a result of sunrise or nightfall affect food availability or presence

of predators and consequently affects the physiology [12], and behavior [76] of organisms.

It is also typical for the same geographical region to be affected by extreme variations of opposite effects on biological systems [36], such as heatwaves and hurricanes, droughts and floods, and exceptional rainfall and fires[60, 135, 150]. These events force organisms living in these areas to balance between such extremes. When perturbations are more significant, they can lead to more severe changes in populations' demographics, leading to extinction or adaptation.

A single erratic disturbance in the environment may provoke coupled variations in selective pressures because a single change may impact two completely distinct traits. For example, aridity hampers the movement of nutrients through the roots of plants [25] and also causes stomatal stress [103]. Additionally, a change in one aspect of the environment may also be associated with another. For instance, rises in ocean temperatures commonly co-occur with water acidification [33, 81]. The literature suggests that such co-occurring disturbances have interacting effects on the selective pressure of different traits [32, 75, 105], where a change in one parameter (e.g., water temperature) can intensify the sensitivity to selection in another parameter (e.g., pH) [75].

There is a broad list of examples of environmental shifts causing changes in a population's gene pool (e.g. [5, 9, 14, 18, 44, 48, 111, 122, 126, 136]). One of those examples is the change in plant populations as a result of loss of animal species [13]. Hunting large herbivores in tropical forests reduce their populations,

forcing plants that depend on seed dispersal by these animals to adapt. A specific case is how the functional extinction of large-gape birds in the Brazilian Atlantic Forest was the most likely agent for seed size decrease in palm trees. Without these larger birds to disperse the larger palm seed trees, smaller fruits and seeds had the competitive advantage [44].

There is evidence showing populations experiencing fast adaptation due to the progression of temperature change [11, 97], increases in CO_2 concentrations [114], and city expansions [59]. These populations persevere despite strong selective pressures due to sufficient genetic variance [7, 47, 65, 87]. Variance allows for evolution, and in turn when populations follow optimum shifts the evolutionary response impacts variance.

Similarly, trait covariance affects and is affected by evolution [2, 137, 154]. While genetic variance for a trait expresses the diversity of a population and enables adaptation, covariance expresses the level of concerted change of two or more characters in a population. Evidence shows that phenotypic covariance can both constrain and accelerate adaptation [146].

If individuals in a population have associated traits and the environment poses similar pressures on both traits, this will speed up adaptation. For example, suppose height and width positively covary in a population and the fitness optimum favors larger individuals in general. In that case, the individual selected will be better adapted than the others in both traits. However, if the most advantageous phenotype is short and wide individuals, the adaptation of our

hypothetical population is hampered.

Traits may be genetically correlated due to two phenomena: linkage disequilibrium and pleiotropy[2, 157]. As opposed to linkage disequilibrium, which can be ephemeral to a few generations [31, 125] given enough recombination, when pleiotropy is the cause, correlation is more resilient [108, 133]. Pleiotropy occurs when mutations on a single gene affect more than one trait. The covariance for a pair of traits combines the mixture of positive and negative effects of alleles at different loci and thus can evolve.

The additive genetic variance-covariance (also called **G**) matrix is a classical tool that can describe the evolution of trait variances and covariances of a population [78]. These matrices carry a summary of the genetic variation of a population. The diagonal of the **G** matrix represents the additive genetic variances, and the off-diagonal the additive genetic covariances.

The genetic architecture, or in other words, the relationship between genes and traits, evolves [2, 154]. Consequently, **G** matrices should change through time as well [130, 157]. Experimental [121, 152] and observational data [98] agree on the volatility of **G**. Roff and Mousseau (1999) performed a survey comparing **G** matrices at different taxonomic levels. They found that at least at the species level, there were commonly significant differences between **G** matrices [107].

G can change due to stochastic processes such as genetic drift and mutations. Mutations can alter the vector shape and the orientation of **G**, depending on

whether the mutation is pleiotropic or not. Higher correlation between mutational effect grants more stability to **G** [2, 61, 104]. Drift tends to always decrease variance, which affects the shape of **G**. Jones **et al.** suggest results suggest that almost all variations in the genetic variance are a result of genetic drift [61].

Intuitively, the direction of selection impacts the stability of the variance-covariance matrix, with directional selection in the same direction of the covariances creating more stability. Data and simulations shows that the **G** matrix evolves following the pressures of correlational selection [108] and phenotypic plasticity [35]. To our knowledge, there is evidence for only these two causes for adaptive evolution of genetic covariances: Phenotypic plasticity and Correlational Selection.

Draghi and Whitlock (2012) showed how populations able to react to a changing environment within an individual's lifespan had, with time, the greater values of their **G** matrix being related to the traits with plasticity [35]. Correlational selection, the other known adaptive cause of covariance, occurs when the fitness landscape has a ridge instead of a peak. This type of selection happens when the environment benefits individuals with correlated characters, consequently creating nonzero covariance in the population [108].

Here we show another cause of covariance, which does not involve plastic phenotypes or a ridged fitness landscape. We suggest that the synchrony of selective pressures on different traits leads to genetic covariance. Environmental pressures changing in a correlated way should increase trait covariance compared

to environmental pressures changing independently.

Jones *et al* (2004) [62] through a study that focused on stability of **G** matrix found that continuous unidirectional movement of the optimum promotes higher absolute values of covariance. Our goal here is to extend Jones *et al.*'s results by focusing on the cause of increased genetic covariance of traits instead of on stability. Beyond that, we expand our analysis to discuss how movement of the fitness landscape can explain complex configurations of the genotype-to-phenotype map.

The pressures that the environment poses on individuals can be separated into the pressures it poses on each trait. Given that environmental pressures change, the pressures of each trait may vary in a dependent or independent fashion. Here we will refer to environments that all selective pressures change in a dependent way as a "correlated changing environment" Similarly, when the pressures on different traits vary independently, we refer to it as an "uncorrelated changing environment".

To check our hypothesis, we ran a series of simulations. We use an individual-based birth-death model to describe the evolution of our populations. There were three main types of populations, which differ in the connectivity of their gene-to-trait map. We compared populations evolving in a correlated changing environment with a population under the same parameters, but that evolved in an uncorrelated changing environment for each of our experiments. The uncorrelated changing environment condition served as a control.

2.2 Methods

General Parameters

In our model, we consider a haploid population with a constant number of individuals, N. Our populations may be asexual or sexual with free recombination. We characterize individuals by their genotype, which has two types of heritable components. One type defines which gene contributes to which trait. We represent this portion of the genotype as a matrix, which we call the contribution matrix, and the entries we refer to as c_{ij}. The other part of the genotype is represented by a vector that expresses each gene's weight on each trait. We call this vector the weight vector and refer to its components as the weight genes, and the entries we refer to as a_j. Each entry of the vector and each entry of the gene represents an independent gene for a total of twenty genes in the genome that may potentially affect these four traits.

Individuals' phenotypes depend on their genotypes. To calculate the phenotype, consider c_{ij} to be the contribution of the gene j on the trait i, a_j to be the weight value of allele j, and g to be the total number of genes. We follow the equation below in which $\vec{z}$ is a vector that represents the phenotype, and its component z_i is the trait i given by

$$z_i = \sum_{j=1}^{n} c_{ij} a_j$$

The fitness of an individual depends only on its phenotype. We focus on stabilizing selection with temporally variable optima; consequently, we use a Gaussian fitness landscape with varying centers and variance of one. The equation below shows how our fitness landscape can be expressed mathematically:

$$f(z) = \exp\left[-\sum_{i=1}^{n} \frac{(\bar{z}_i - z_{i_0})^2}{2\sigma_{z_i}^2}\right]$$

Our model was implemented in Python [71], version 3.6.2 using module Numpy [138]. We used a separate script also in Python for the statistical tests. The source code and the entire data related to this thesis is available at the github repository [github.com/isadoo/evolution_of_covariance].

Birth-Death Process

We use a Moran birth-death model, holding the population size constant over time. Specifically, at each time point, two main events happen, the birth of a new individual and the death of another. The choice of which individual gives birth is random but proportional to its fitness. The new offspring will replace another individual, which is chosen randomly with equal probability for each individual. [Figure 2.1].

Once a birth happens, mutations may happen on either the weight vector or the contribution matrix. A mutation happens in a component of the weight vector with a rate of μ_a. There is a probability of μ_c for each of the contribution entries to

suffer a mutation. The effect of the mutation is chosen from a normal distribution centered at 0 with a variance of 0.5. The mutated alleles value is the sum of the original value and the change due to the new mutation [Figure 2.1].

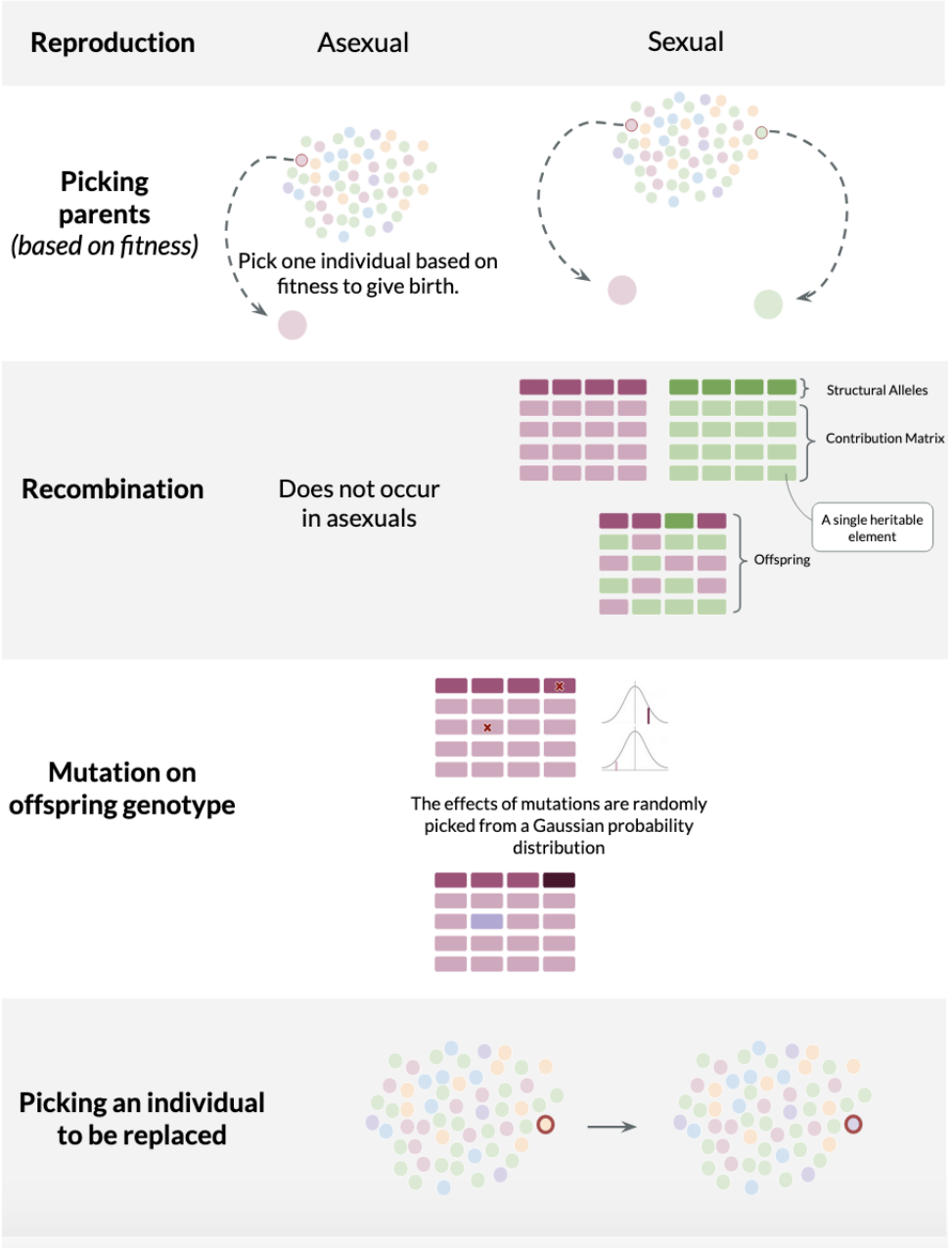

Figure 2.1: The entire Birth-Death process of our model. The first step is the choice of an individual to give birth. When there is no recombination, a single individual gives birth, while two individuals are picked for the process with recombination. Subsequently, for simulations with recombination, there is the process of combining the genome of both parents. Each gene has the same probability of being from one or the other parent. After, mutation may happen at any gene, which means both the weight vector and the contribution matrix are subject to change. Finally, this new individual will substitute one other in the population. Death happens at random, meaning that all individuals have the same probability of dying and being substituted.

Our populations can be either asexual or sexual. With sexual reproduction, two individuals are chosen based on fitness instead of a single individual to give birth. The offspring have a combination of the chosen individuals' genomes. Each heritable element, either from the weight vector or the contribution matrix, has an equal probability of coming from either parent. In other words, there is free recombination [Figure 2.1].

Simulation Experiments

We always compared the results of a correlated changing environment with an uncorrelated changing environment for all our simulation experiments. We had two main types of experiments, one type without mutation in the contribution matrix, which means no evolution in the genotype-to-phenotype map, and another type of experiments with mutations in the contribution matrix. Within those experiments that the contribution matrix was allowed to evolve, we had three kinds of experiments. One in which we were just observing the evolution of **G** given different starting parameters without recombination. There was a second set of experiments in which we added recombination. Finally, we had a third type of experiments involving the evolution of **G** in a changing environment in which we separated the selective pressures into pairs. Each pair of selective pressures varied independently from other pairs.

There were three types of starting genetic architecture "One-to-One", "Modular", and "All connected". The first referred to a diagonal contribution

matrix, which means each weight gene only contributes to a single trait, and each trait is only affected by a single weight gene. In our model, this means that the contribution matrix will look like the identity matrix. For the "Modular" type, half of the genes were connected to the same half of the traits and unconnected to the rest. Conversely, "All connected" is a starting condition in which all the weight genes are connected (through contribution genes) to all traits [2.2].

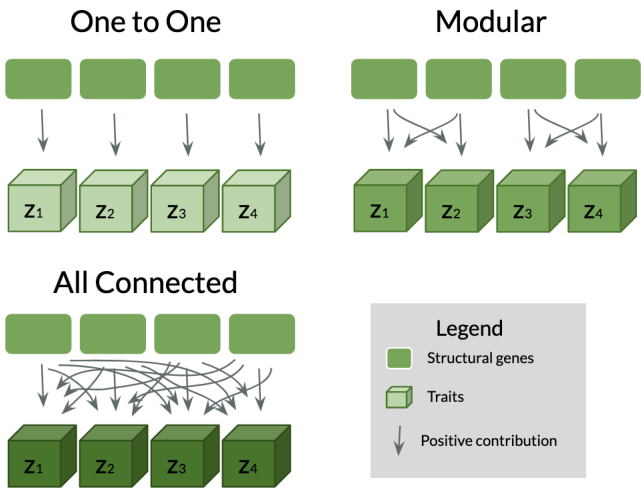

Figure 2.2: We had three types of starting genotype-to-phenotype maps. This figure explains the relationship between genes and traits of each one of the three types. The squares symbolize weight genes, the arrows are nonzero contribution genes, and the cubes are traits. The "One-to-One" type has, as the name implies, a one-to-one relationship between genes and traits. The "Modular" type has two modules, each with two genes that impact both the same two traits. Finally, the "Al Connected" type is the one in which all weight genes affect all traits.

Our general goal was to understand the effects of environmental change on evolution. Thus, we had different scenarios of imposed periodic changes in our populations. For most of our simulation experiments, we compared two types of changing environments for all cases during our analysis: the ones in which the optimum of traits varied in a correlated fashion and the ones in which they moved

independently [Figure 2.3]. Of course, varying in a correlated manner restricts the optimum movement to the points in which all traits have the same values, the diagonal between all axes. In contrast, uncorrelated movement allows for a broader exploration of the trait space.

We also had a third type of environmental change, which we called the "paired" environmental change. For this type of change, the four traits were divided into two pairs, and the optima of each pair changed in a correlated way. We used the "paired" environmental change only for one group of experiments, which were specifically focused on understanding how environmental change can cause modularity.

Our experiments varied in the existence of recombination, mutation rates, and environmental steps. In Table 1, we show all types of experiments with evolution in the contribution matrix. We ran 50 replicates of each experiment with independent populations of 10^3 individuals. For simplicity, individuals have a constant number of traits (4) and genes (20). We calculate phenotypes as the product of the weight vector and contribution matrix.

Experiment Types

Genotype-to-phenotype Map	μ_c	μ_a	Env. C. Step	Recombination
One-to-One	3.215×10^{-4}	1.25×10^{-3}	0.2	FALSE
One-to-One	$\mathbf{3.215 \times 10^{-3}}$	$\mathbf{1.25 \times 10^{-2}}$	0.2	FALSE
One-to-One	3.215×10^{-4}	1.25×10^{-3}	**1**	FALSE
One-to-One	3.215×10^{-4}	1.25×10^{-3}	0.2	**TRUE**
One-to-One	**0**	1.25×10^{-3}	0.2	FALSE
All connected	3.215×10^{-4}	1.25×10^{-3}	0.2	FALSE
All connected	$\mathbf{3.215 \times 10^{-3}}$	$\mathbf{1.25 \times 10^{-2}}$	0.2	FALSE
All connected	3.215×10^{-4}	1.25×10^{-3}	**1**	FALSE
All connected	3.215×10^{-4}	1.25×10^{-3}	0.2	**TRUE**
All connected	**0**	1.25×10^{-3}	0.2	FALSE
Modular	3.215×10^{-4}	1.25×10^{-3}	FALSE	

Table 2.1: In bold face are the changes of each experiment compared to the experiment shown in the first line

The probability of mutation in the weight vector is $\mu_a = 1.25 \times 10^{-3}$ per individual birth, or $\mu_a = 1.25 \times 10^{-2}$ in specific experiments with a higher mutation rate. The probability of mutation in the contribution matrix is $\mu_c = 3.215 \times 10^{-4}$, or $\mu_c = 3.215 \times 10^{-3}$ in specific experiments with higher mutation rates. There were also experiments with the mutation rate of the contribution matrix set to zero.

These mutation rates account for 5 or 50 mutations in the entire population per

generation. One generation is the same as one thousand births since there are one thousand individuals. The mutation rate could be these two values (5 or 50 per generation) or no mutation at all for the contribution matrix.

Changes to the environment potentially happen every 10 generations (every 10^4 births). The magnitude of the change in the environment was either 0.02 or 1. Changes to the optima either increased or decreased with a probability of fifty percent for either movement. The position of the optima was restricted to the interval $[1,-1]$ in any of the cases. When the optima reached a boundary, the optima had a fifty percent chance of staying at the same position or of moving. The optimum is thus expected to spend the same amount of time at any given point of the set of possible points.

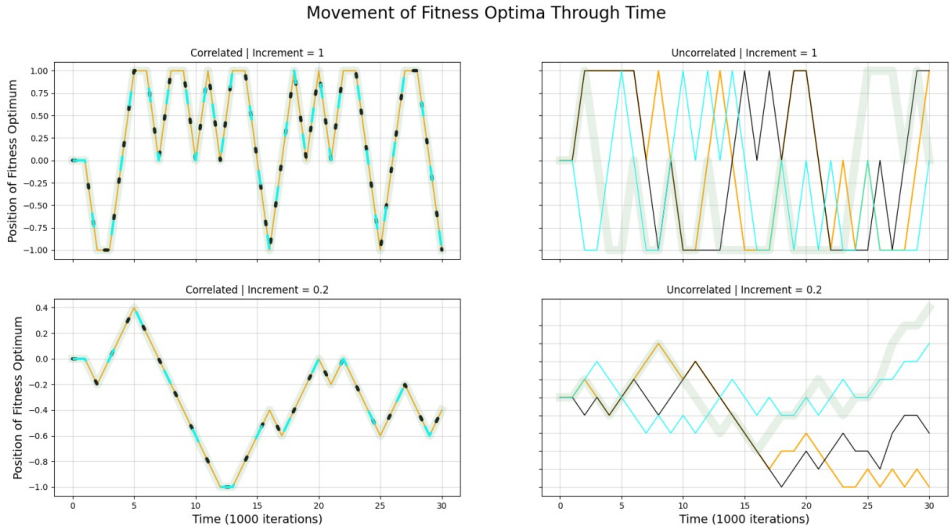

Figure 2.3: The graphs show how the optima of traits change through time. The two graphs on the left show correlated environmental change. In this condition, at all times, all optima are in the same position. The graphs on the right show how the position of the optima moves independently in the uncorrelated environmental change condition. The two graphs on the top row show a change of increment 1, while the graphs on the bottom show for increment of 0.2.

Effects of Environmental Change on different Genotype-to-Phenotype Maps

We observed how environmental change influenced the population's fitness for the first set of experiments. For experiments with no mutations in the contribution matrix, we used the three types of starting maps. We ran these simulations because we were interested in seeing how restrictive evolution was for each of the starting architectures. Thus, we merely compared the fitness variation through time.

Evolution of the Genotype-to-Phenotype Map

For experiments with mutation acting on the contribution matrix, we had a few different conditions [Table 1]. We varied the rate of mutation, the size of environmental change, and whether there was recombination or not. For all our experiments, our main focus was a comparison of variances and covariances of correlated and uncorrelated environmental change. The one exception was a single set of experiments in which we were interested in seeing the effects of paired environmental change in the modularity of the genotype-to-phenotype map. For this last group of experiments, we used the paired environmental change in populations starting with the "one-to-one" type of genotype-to-phenotype map.

Measuring Variances and Covariances

For all experiments, we have 50 independent replicate populations. After the population has evolved for a given time, specifically on the last tenth of

the simulation, we start annotating the trait values for all individuals. For the experiments without mutations on the contribution matrix, we measured the fitness through time for our replicates.

For every given time point measured in a population, we have $4x10^3$ trait values. For the experiments related to genotype-to-phenotype map evolution, we calculate the trait variance and covariance per time point, so using these $4x10^3$ values. For every replicate population, we average the resulting variances and covariances of all time points together so that for each replicate, there are only four values for variances and 6 for covariances [figure 2.4] after an entire run. For all our experiments, we compared two sets of variances and covariances through a Student's t-test [figure 2.5]. The p-value obtained tested whether correlated and uncorrelated treatments lead to significantly different values for variances and covariances.

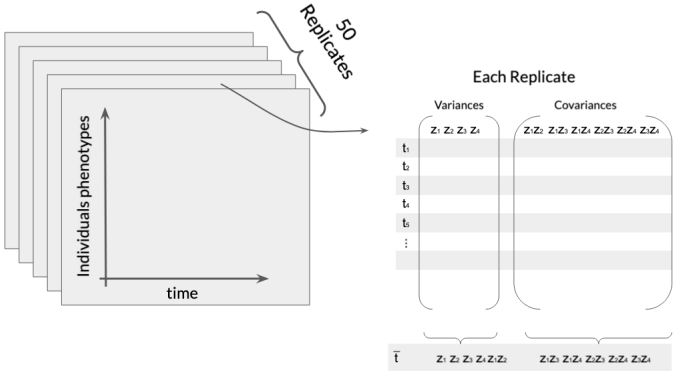

Figure 2.4: For each experiment, we ran 50 replicate populations. For each replicate, we record the trait values of all individuals. For each time step after a given time has passed in the evolution of the population. We calculate the trait variances and covariances per time step.

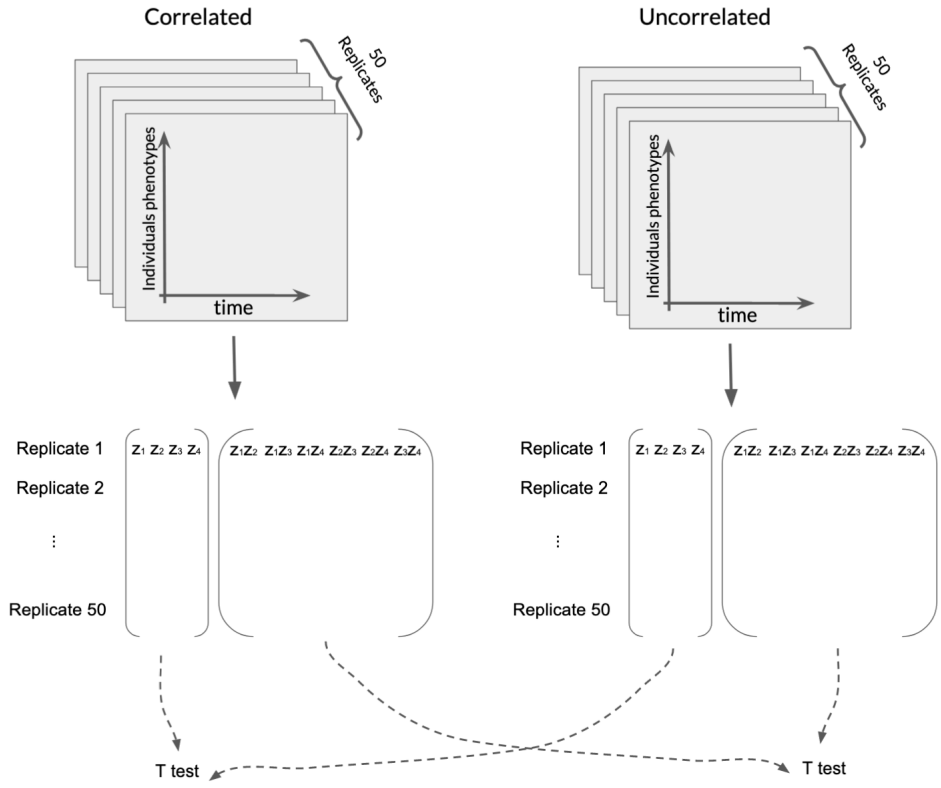

Figure 2.5: For each experiment with mutations in the contribution matrix, we compared correlated replicates with uncorrelated replicates. For each replicate, we had four values for variances and six values for covariances. The tables of variances for correlated were compared with the table of variances for uncorrelated. The same was done for covariances.

2.3 Results

Effects of Environmental Change on Different Genotype-to-phenotype Maps

Different types of genotype-to-phenotype maps impact the movement towards fitness optima differently [Figure 2.6]. As mentioned in our methods, we had three types of genotype-to-phenotype maps: “All Connected”, “One-to-One”, and “Modular”. Whether the change is correlated or uncorrelated has less difference for the least interconnected map (One-to-One) than the most interconnected one (All Connected). The set of populations with the highest fitness were those with the All Connected map evolving in the correlated changing environment. On the other hand, the set with the lowest fitness was with the All Connected map evolving in the uncorrelated changing environment.

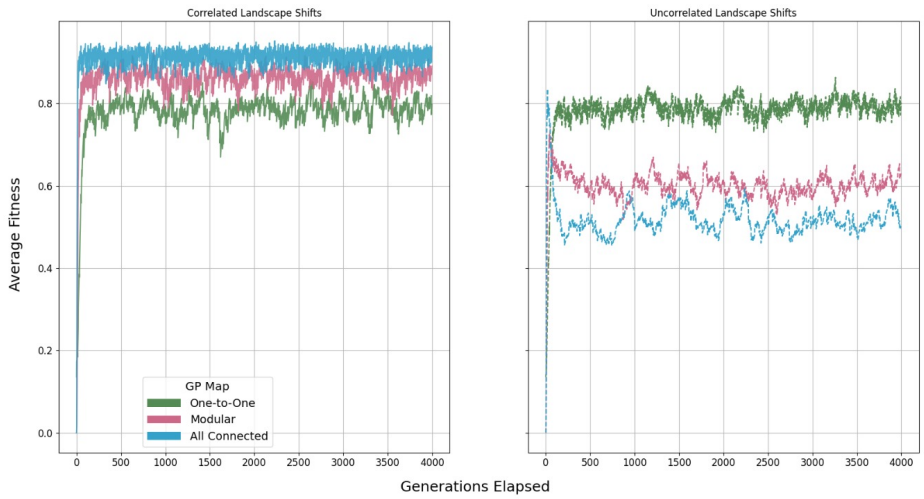

Figure 2.6: Average fitness of 1000 populations per experiment through time. Populations evolved without mutations to the map itself. Fitness on the Y-axis and time represented by generations on the X-axis. The one-to-one uncorrelated results are obscured by the correlated results.

These results show that genetic fitness is higher when genetic correlations match the change in fitness. The follow-up question is understanding whether the genetic architecture of a population evolves to match the nature of environmental change. Whether the population does evolve is not obvious because population quantities are not constrained to increase individuals' fitness.

Evolution of the Genotype-to-Phenotype Map

Populations evolving in an environment in which the optima for all traits change in a correlated fashion evolves traits that are on average more genetically correlated than populations evolving in environments in which the optima change in an uncorrelated way. In equation (2.1), we show the average **G** matrices for

one of our experiments as well as the p-value related to the difference between the entries in the matrices. This particular experiment was using populations with One-to-one starting architecture, $\mu_c = 3.215 \times 10^{-4}$ and $\mu_a = 1.25 \times 10^{-3}$, environment change every 10 generations with a variation of trait optimum of 0.2 and no recombination.

Correlated | Uncorrelated | p-value, Correlated versus Uncorrelated

$$\begin{bmatrix} 0.086 & 0.033 & 0.034 & 0.031 \\ – & 0.089 & 0.033 & 0.037 \\ – & – & 0.086 & 0.036 \\ – & – & – & 0.077 \end{bmatrix} \quad \begin{bmatrix} 0.119 & 0.012 & 0.015 & -0.005 \\ – & 0.093 & 0.013 & 0.003 \\ – & – & 0.114 & 0.008 \\ – & – & – & 0.101 \end{bmatrix} \quad \begin{bmatrix} 6.217 \times 10^{-3} & 2.197 \times 10^{-3} & 3.312 \times 10^{-2} & 1.190 \times 10^{-5} \\ – & 6.695 \times 10^{-1} & 4.50 \times 10^{-3} & 9.655 \times 10^{-8} \\ – & – & 1.227 \times 10^{-2} & 5.726 \times 10^{-4} \\ – & – & – & 1.33 \times 10^{-2} \end{bmatrix} \tag{2.1}$$

Our results were consistent throughout all experiments (Table 2.2). There was a large (one order of magnitude) and significant difference between the correlated environmental change and the uncorrelated environmental change for all experiments. When the trait optima change in a correlated way, the covariances have higher and more positive values than the cases with uncorrelated change.

Our model has no difference in evolutionary forces acting among traits, especially given that the architectures that we chose for our starting conditions create complete symmetry among traits. Given that all pairs of traits replicate the same process, we can average our results in six values for covariance and four for variance per experiment. In Table 2.2, we show the summary of our results.

Starting genotype-to-phenotype Map	Mutation Rate	Landscape Shifts	Correlated		Uncorrelated		p value	
			Variance	Covariance	Variance	Covariance	Variance	Covariance
One-to-One	Low	0.2	0.0167	0.0040	0.0194	-1.190×10^{-05}	0.00017	3.4×10^{-13}
All Connected	Low	0.2	0.016	0.009	0.020	0.002	1.9×10^{-10}	3.9×10^{-33}
One-to-One	Low	1	0.048	0.023	0.055	-0.0004	0.0004	1.08×10^{-28}
All Connected	Low	1	0.054	0.031	0.054	0.006	0.73	3.7×10^{-34}
One-to-One	High	0.2	0.0813	0.022	0.101	-0.0002	6.8×10^{-05}	1.8×10^{-11}
All Connected	High	0.2	0.0847	0.0341	0.107	0.008	0.0001	4.6×10^{-10}

Table 2.2: Low mutation rates are equal to $\mathbf{3.215 \times 10^{-4}}$ for the contribution matrix and $\mathbf{1.25 \times 10^{-3}}$ for the weight vector. High mutation rates are equal to $\mathbf{3.215 \times 10^{-3}}$ for the contribution matrix and $\mathbf{1.25 \times 10^{-2}}$ For each replicate we calculated the average of variances and covariances. That way, for the statistic test (t-test), we used a single variance and covariance value per replication. For each set of parameters, we ran experiments for correlated and uncorrelated. For every set of parameters, we compared fifty replicates of correlated with fifty replicates of uncorrelated experiments.

Starting genotype-to-phenotype Map	Recombination	Correlated		Uncorrelated		p value	
		Variance	Covariance	Variance	Covariance	Variance	Covariance
One-to-One	No	0.0167	0.004	0.0195	-1.190×10^{-05}	0.0002	3.5×10^{-13}
One-to-One	Yes	0.0028	0.00147	0.0026	0.000289	0.74	0.009

Table 2.3: For sexual populations, we calculated additive genetic variance and total genetic variance for asexual populations.

Evolution of the Genotype-to-Phenotype Map in Sexual Populations

Results for populations that underwent recombination were similar to the asexual ones; covariance emerged spontaneously through the correlated environmental change (2.3). For the simulations without recombination, the relevant value was the total genetic variance. For sexual populations, we specifically calculated both the total genetic variance/covariance and the additive genetic variance because that is the appropriate quantity to predict evolvability in sexual populations. For sexual populations results differ from total genetic covariance and additive genetic covariance (tables (2.3) and (2.4)).

Trait variance in asexual populations was significantly larger than in sexual populations, similarly with covariances (2.4). Nevertheless, when comparing correlated and uncorrelated changing environments, populations in the first had positive covariances (2.3).

	Variance	Covariance
Asexual	0.0167	0.004
Sexual	0.0028	0.0028
p-value	5.7×10^{-40}	3.84×10^{-6}

Table 2.4: Comparison of genetic variance between asexual and sexual populations. For sexual populations, we calculated additive genetic variance, and total genetic variance for asexual populations.

Paired Environmental Change effect on Genetic Architecture

The selective pressures of part of the set of traits can change in synchrony. See matrices on equations (2.2) and (2.3). In (2.2) and (2.3) values in bold represent the two entries that differed the most between paired environmental change and uncorrelated environmental change. These two entries represent the covariance for the traits which selective pressures changed together in the paired changing environment. When selective pressures of traits vary paired, positive additive genetic covariance of the paired traits emerges. The positive additive genetic covariance between sections of the phenotype and lack of additive genetic covariance between other combinations of traits result from the evolution of modularity of the genome. As suggested by previous authors [66, 86, 139], we found that modularity emerges as a reaction to a modularly changing environment.

Paired

$$\begin{bmatrix} 0.0195 & \mathbf{0.003} & 0.0003 & 0.001 \\ - & 0.021 & 0.0009 & -0.001 \\ - & - & 0.019 & \mathbf{0.003} \\ - & - & - & 0.020 \end{bmatrix}$$

Uncorrelated

$$\begin{bmatrix} 0.020 & \mathbf{-0.0006} & 0.0005 & -0.0009 \\ - & 0.019 & 0.0002 & 0.0002 \\ - & - & 0.019 & \mathbf{0.0005} \\ - & - & - & 0.019 \end{bmatrix} \quad (2.2)$$

p-value

$$\begin{bmatrix} 0.619 & \mathbf{0.002} & 0.890 & 0.030 \\ - & 0.288 & 0.378 & 0.204 \\ - & - & 0.725 & \mathbf{0.017} \\ - & - & - & 0.319 \end{bmatrix}$$

G-Matrix

$$\begin{bmatrix} \mathrm{Var}(z_1) & \mathbf{Covar}(z_1z_2) & \mathrm{Covar}(z_1z_3) & \mathrm{Covar}(z_1z_4) \\ - & \mathrm{Var}(z_2) & \mathrm{Covar}(z_2z_3) & \mathrm{Covar}(z_2z_4) \\ - & - & \mathrm{Var}(z_3) & \mathbf{Covar}(z_3z_4) \\ - & - & - & \mathrm{Var}(z_4) \end{bmatrix} \quad (2.3)$$

2.4 Discussion

In this chapter, we analyzed the effects of environmental change on the evolution and genetic architecture of a population. Specifically, we looked into the evolution of average fitness or additive genetic covariance of a population in fluctuating environments. We studied how the change in the fitness landscape influences population-level quantities. We focused on the correlation between the

change in the selective pressures of different traits.

The first question we tried to answer was: What is the relationship between connectivity of the genotype-to-phenotype map and the evolution of average fitness for populations evolving on correlated versus uncorrelated environments? We compared three different types of populations with different levels of static connectivity evolving in correlated and uncorrelated environments.

Our first set of results (Figure 2.2) shows that population mean fitness is higher when genetic correlations match the change in the fitness landscape. The naturally following question is whether the genetic architecture of a population evolves to match the nature of environmental change, which was the second question we answered. Since selection acts at an individual level, while variance and covariance are population-level quantities, there is no direct force pushing the population to have an "optimal" **G** matrix. However, despite the lack of direct selective action at a population level, our results show positive covariance evolving.

Positive trait covariance emerges as a result of pressures posed on different traits changing in a correlated form. When the environment changes, the new circumstance may change the fitness optimum of only one trait or many traits. If the alteration in the environment affects multiple traits, the variation in selective pressure of one trait might move the optimum up, while for another, it might move down. That way, the vector of change is different for different traits. In other cases, the environment continuously varies so that all optima follow the

same change vector; in these cases, positive covariance emerges.

In the correlated changing environment, the possible positions of the optimum are limited to part of the fitness landscape. The optimum will always be positioned at some point on the principal diagonal formed by the traits' axes. Trait combinations outside the diagonal will never be optimal, and the farther phenotypes are from this diagonal, the lower their fitness. Consequently, given enough time, all lineages will be adapted to some point within the diagonal.

The population diversity usually reflects the fitness landscape. This is also true for a fluctuating environment with the movement of optima restricted to a specific subsection of the landscape. For the correlated changing environment, because the optimum is always along a diagonal when the population spends enough generations in this changing environment, the diversity becomes confined to the trait combinations along the diagonal. In other words, given enough time for the population to evolve, the probability of finding an individual in the population with a trait combination within the diagonal is higher than any other trait combination.

In summary, the movement of the fitness optimum over time results in polymorphism. The movement's confinement creates a fitness differential. The fact that it is confined to the diagonal between the trait axes allows for pleiotropy to evolve. Polymorphism in the population and pleiotropy between traits results in covariance.

Our results were consistent with different mutation rates, different degrees of change in the environment, and different starting genotype-to-phenotype maps. We also obtained similar qualitative results for our experiments on sexual populations. The t-test indicates a smaller difference between correlated and uncorrelated treatments for our sexual populations when compared to the difference between correlated and uncorrelated treatments for asexual populations. Also, for sexual populations evolving in a correlated changing environment, the variance and covariance were lower than for asexual populations evolving in the same type of environment.

Further, for the third and last question, we explored how our results (covariance emerging from correlated environmental change) could be used to show how modularity emerges spontaneously given a correlated change of a subset of selective pressures over traits. In our primary set of experiments related to the evolution of the genotype-to-phenotype map, we compare two types of fluctuating environments: one with the selective pressures of all traits suffering correlated change and another with all selective pressures varying independently. We expand our model to show how modularity develops simply by having only part of the selective pressures over traits change in a correlated way instead of having all of them changing that way. Our results agree with previous experiments and theoretical work showing modularity evolving from environmental change [66, 86, 139, 144]. However, we show how fitness calculation does not need to be modular in relation to traits for genetic modularity to evolve.

In Kashtan and Alon's (2005) [66] experiments, fitness is calculated through a strong nonlinear interaction between traits within each generation. At each time step, and for the choice of each birth, selection was correlated. In our experiments, the modularity in fitness was given because of how the optimum for each trait changed in relation to each other through time. At any given time point, each trait affected fitness independently. At a given time point Kashtan and Alon's fitness landscape has ridges, while our fitness landscape is always represented by a single peak. Additionally, Kashtan and Alon's (2005) [66] work describes the development of an individual while we are interested in a population-level phenomenon. They do not analyze patterns of variation at a population level. Nevertheless, we also saw the spontaneous emergence of modularity.

Our results show how the way environment changes can create polymorphism in the contribution of genes to traits of a population. What we call the contribution matrix is a simplification of the genotype-to-phenotype map of an individual. We observed the evolution of the contribution matrix through changes in the **G** matrix. Correlation between the change in selective pressures of different traits is an adaptive cause for the emergence of positive covariance between traits, which can also explain the modularity of the genotype-to-phenotype map.

Chapter 3

Conclusions

The Evolution of Covariance

Temporal heterogeneity refers to how environments change over time. Characteristics of habitat can go through daily, seasonal, or multi-year fluctuations. The variability of the environment can be separated into two categories: Within generation and between generations [119]. Changes within generations are simply another characteristic of the environment to which lineages adapt. For example, the migratory behavior of birds is an adaptation to yearly changes in temperatures, and food availability [51].

Between-generation environmental change occurs when individuals are exposed to circumstances different from those their lineages adapted to. If the

selective pressures change, the population will adapt to the new pressures or go extinct [6, 15, 69]. The instability of the environment can transpire through characteristics of the taxa present in that space. For example, organisms may adapt to between-generation unstable and unpredictable environments by parents having a diverse set of offspring [4]. Adaptive phenotypic plasticity is another observable characteristic of lineages that evolved in fluctuating environments [84].

The fitness function describes the selective pressures over phenotypes. When the environment changes, selective pressures change, and the fitness function suffers a transformation. Similar to how unpredictable fluctuations can result in changes to heritability within a lineage, the speed of the environmental variation also affects populations. For example, the more gradual change allows for populations to have higher fitness. Unpredictability and speed of change are potentially important properties of environmental change [27]. In this thesis, we analyzed another property of environmental change. We studied the effects of correlation of the change in selective pressures of different traits in the evolution of genetic covariance.

First, we tried to understand the relation between the evolution of fitness and different genotype-to-phenotype maps in a changing environment. We wanted to know the relationship between the average fitness of populations with specific GP maps and the correlatedness of change between different traits' selective pressures. We found that genetic fitness is higher when genetic correlations match the change in fitness. In other words, populations whose individuals have

less interconnected maps can achieve higher fitness in uncorrelated changing environments when compared to more interconnected maps. On the other hand, more interconnected maps do better in correlated changing environments.

Then, it led us to our following question: whether the genetic architecture of a population evolves to match the nature of environmental change. To answer that, we ran experiments that allowed for the evolution of the genotype-to-phenotype map. We compared the results of populations evolving in a correlated changing environment with those evolving in an uncorrelated changing environment, but otherwise under identical parameters. Regardless of mutation rate, size of environmental change, initial GP map, or presence of recombination, we found that positive covariance emerges spontaneously in correlated changing environments.

One of the future steps will be to describe how much the covariance arose due to Linkage disequilibrium versus pleiotropy due to mutational alignment. We will do that by comparing our present results for covariance values with covariance after taking out all possible effects of linkage disequilibrium. To eradicate the effects of linkage disequilibrium, we will randomly redistribute the genes of all individuals in the population and calculate the covariance of this new grouping of genes.

We are also interested in studying the change in the mutational variance-covariance matrix, **M**. The **M** matrix expresses the effect of mutations on variances and covariances. Our goal would be to understand how **M** evolve in the

uncorrelated and correlated changing environment, hopefully expanding Jones *et al.* (2007) [63] results.

Despite our attempt to cover a diverse set of parameters, there is still a lot to be explored using our model. The complexity of the environment can be extended by allowing spatial heterogeneity and also asymmetrical fitness functions. In terms of the lineages, it would be interesting to see the effects of different levels of dominance in the evolution of covariance. Also, a few changes in the existing model could allow for fluctuating population size, which would be necessary to study extinction rates.

The Evolution of Modularity

In biology, modularity can refer to the organization at different levels of the biological system [112]; here, we focus on the modularity of the Genotype-to-Phenotype map. In that sense, modularity refers to heterogeneity of connectivity between traits given by almost independent groups of genes affecting different sets of traits. Modular GP maps have highly genetically connected sets of traits that have little to no genetic connection with other traits [115, 116, 144, 148].

There are mainly two discussed advantages of modularity, and both are related to evolvability. When a modular system suffers mutations, the perturbations are commonly contained within a module, with little effect on the rest of the organism [123]. The other advantage is the possibility of combining and reusing modules

to new biological functions [142].

Because the genetic modularity of traits does not directly interact with the environment, it does not directly influence fitness, which makes understanding the evolutionary cause of modularity difficult. Many evolutionary causes for the emergence of modularity have been suggested [144], one example is modularity evolving as an effect of a changing environment [141]. Kashtan and Alon's (2005) simulations showed the spontaneous evolution of modularity from a changing modular environment [66], confirming previous suggestions.

Here we showed at a population level the evolution of modularity through a changing environment without correlated selection. In Kashtan and Alon's work [66], their fitness function varied between two states. In both states, the fitness function had subgrouping (modules) of the effects of traits in the total fitness. The difference between the two states was how these subgroups change in relation to each other. That way, the traits did not independently add to the total fitness. Instead, fitness was always determined by a nonlinear interaction between the two modular subgroups. total fitness.

In Kashtan and Alon's work [66], the fitness is determined from a strong nonlinear interaction between traits within each generation (selection was correlated at each time step). In our case, each trait affected fitness independently. The grouping of the traits was not given by the fitness function at a given time point but by the form in which the optimum for each trait changed through time. Thus, a main difference between the two methods is that in Kashtan and Alon's

work, the modularity of the fitness function affects a given generation, while in our work, the fitness function is modular when analyzing the change in the function through generations.

What drove modularity in our results was how the selective pressures of different traits changed through time in relation to each other. We showed that modularity emerges when the selective pressures of some traits change in synchrony with each other but not with the ones of other traits. It does not require correlated selection or fitness interactions among the traits for modularity to evolve.

Another difference between our work and Kashatan and Alon's results is the fact that we refer to population-level quantities while they focused on the development of an individual. Additionally, here we are dealing with quantitative traits, while Kashatan and Alon focused on binary states. Finally, we believe that both the quantitative aspect and the stochasticity of our methodology result in a closer description of what is found in biological populations.

Sun and Deem (2009) [53, 131] have shown the spontaneous emergence of modularity in a changing environment, but with the necessity of horizontal gene transfer. The results we obtained for the emergence of modularity were on populations with no recombination. In a future step, we could expand our experiments to add populations with recombination in the paired environmental shifts. Their results are also bound to a rugged fitness landscape, while at any given time point, we had a smooth single peaked landscape.

Lipson *et al.* (2002) [86], characterized individuals in a similar way to our methodology, with a caveat that their results, like Kashatan and Alon, are not for quantitative traits. They defined individuals through matrices with entries that are either $1, 0$ or -1. Both our work and theirs used a matrix that could measure the connection between traits. However, their work focused on comparing the environment's rate of change with the average modularity of a population. They show that higher rates of change lead to more modular systems. Here we focused on how the type of change is possibly more relevant than the rate of change.

We argue that different rates of change should give the same qualitative results in terms of modularity. The relevance should be on the type of change, in terms of whether there is correlated evolution, as shown by Kashtan and Alon, or correlation between varying selective pressures, as we have shown here. It is possible that the quantitative difference observed by Lipson *et al.* would disappear if each condition was given accordingly enough time to evolve. A deeper investigation of the relationship between type and rate of change over the evolution of modularity is warranted to understand if there is a qualitative difference between the evolved modular systems.

Expanding our results to discuss modularity was the first step of possibly many in understanding how changes in selective pressures can lead to the evolution of the GP map. A relevant update to our existing model for studying the evolution of the GP map would be to include more complex mutations. One example is allowing whole gene or whole gene duplication.

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