Fitness-valley crossing with generalized parent–offspring transmission

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HIGHLIGHTS

- Epistasis creates peaks of high fitness separated by "fitness valleys".
- Crossing fitness valleys allows populations to become better adapted.
- We extend fitness valley crossing by relaxing the assumption of Mendelian inheritance.
- We investigate meiotic drive, cytonuclear interactions, and cultural inheritance.
- Fitness valley crossing can be much more likely with non-Mendelian inheritance.

ARTICLE INFO

ABSTRACT

Simple and ubiquitous gene interactions create rugged fitness landscapes composed of coadapted gene complexes separated by "valleys" of low fitness. Crossing such fitness valleys allows a population to escape suboptimal local fitness peaks to become better adapted. This is the premise of Sewall Wright's shifting balance process. Here we generalize the theory of fitness-valley crossing in the two-locus, bi-allelic case by allowing bias in parent–offspring transmission. This generalization extends the existing mathematical framework to genetic systems with segregation distortion and uniparental inheritance. Our results are also flexible enough to provide insight into shifts between alternate stable states in cultural systems with "transmission valleys". Using a semi-deterministic analysis and a stochastic diffusion approximation, we focus on the limiting step in valley crossing: the first appearance of the genotype on the new fitness peak whose lineage will eventually fix. We then apply our results to specific cases of segregation distortion, uniparental inheritance, and cultural transmission. Segregation distortion favouring mutant alleles facilitates crossing most when recombination and mutation are rare, i.e., scenarios where crossing is otherwise unlikely. Interactions with more mutable genes (e.g., uniparental inherited cytoplasmic elements) substantially reduce crossing times. Despite component traits being passed on poorly in the previous cultural background, small advantages in the transmission of a new combination of cultural traits can greatly facilitate a cultural transition. While peak shifts are unlikely under many of the common assumptions of population genetic theory, relaxing some of these assumptions can promote fitness-valley crossing.

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1. Introduction

Epistasis and underdominance create rugged fitness landscapes on which adaptation may require a population to acquire multiple, individually-deleterious mutations that are collectively advantageous. Using the adaptive landscape metaphor, we say the population faces a fitness "valley" (Wright, 1932). Such valleys appear to be common in nature (Weinreich et al., 2005; Szendro et al., 2013, but see Carneiro and Hartl, 2010) and affect, among other things, speciation by reproductive isolation, the evolution of sex, the evolvability of populations, and the predictability of evolution (Szendro et al., 2013). Here we are interested in the speed and likelihood of fitness-valley crossing, which we determine by examining the first appearance of an individual with the collectively advantageous set of mutations whose lineage will eventually spread to fixation.

Believing epistasis to be ubiquitous, Wright (1931, 1932) formulated his "shifting balance theory", which describes evolution

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as a series of fitness-valley crossings. In phase one of the shifting balance process, small, partially-isolated subpopulations (demes) descend into fitness valleys by genetic drift. The new mutations are selected against when rare, as they will tend to occur alone as single deleterious alleles. Eventually drift may allow the deleterious mutations to reach appreciable frequencies in at least one deme. Once multiple synergistically-acting mutations arise together, they begin to be locally favoured by selection. In phase two, these favoured combinations of mutations sweep to fixation, and those demes ascend the new "fitness peak". Finally, in phase three, the demes that reach the new fitness peak send out migrants whose genes invade and fix in the remaining demes, eventually "pulling" the entire population up to the new fitness peak. Our focus here is in the first appearance of a genotype on the new fitness peak whose lineage will eventually fix, considering a single isolated deme. This is typically the longest stage of phases one and two (Stephan, 1996) and hence is likely the limiting step in fitness-valley crossing.

Fitness-valley crossing has been investigated in a large number of theoretical studies. In the context of multiple loci with reciprocal sign epistasis, the first appearance of the genotype with the best combination of alleles has been the focus of a few studies (Phillips, 1996; Christiansen et al., 1998; Hadany, 2003; Hadany et al., 2004; Weissman et al., 2009, 2010). Many authors have gone on to examine the remainder of phases one and two (Crow and Kimura, 1965; Eshel and Feldman, 1970; Karlin and McGregor, 1971; Kimura, 1985; Barton and Rouhani, 1987; Kimura, 1990; Phillips, 1996; Michalakis and Slatkin, 1996; Stephan, 1996; Weinreich and Chao, 2005; Weissman et al., 2009, 2010), as well as phase three (Kimura, 1990; Crow et al., 1990; Barton, 1992; Kondrashov, 1992; Phillips, 1993; Gavrilets, 1996; Hadany, 2003; Hadany et al., 2004). Similar attention has been given to situations with a single underdominant locus (Slatkin, 1981; Gillespie, 1984; Barton and Rouhani, 1993; Peck et al., 1998) or a quantitative trait (Lande, 1985a; Barton and Rouhani, 1987; Rouhani and Barton, 1987a,b; Charlesworth and Rouhani, 1988; Barton and Rouhani, 1993). The theoretical and empirical support for Wright's shifting balance process has been summarized and debated (Coyne et al., 1997; Wade and Goodnight, 1998; Coyne et al., 2000; Whitlock and Phillips, 2000; Coyne et al., 2000; Goodnight and Wade, 2000; Goodnight, 2013), and the general consensus appears to be that, unless the valley is shallow (weakly deleterious intermediates), crossing a fitness valley is unlikely.

Despite the abundance of literature on fitness-valley crossing, the above studies all assume perfect Mendelian inheritance. The question therefore remains: how robust are our ideas of fitness-valley crossing to deviations from Mendelian inheritance? Specifically, how does transmission bias (e.g., meiotic drive or uniparental inheritance) affect the speed and likelihood of valley crossing? Departing from strict Mendelian inheritance also allows us to consider the idea of valley crossing in cultures, considering the spread of memes (Dawkins, 1976) rather than genes. This simultaneously adds a level of complexity to current mathematical models of cultural transmission, which typically consider only one cultural trait at a time (e.g., Cavalli-Sforza and Feldman, 1981; but see, e.g., Ihara and Feldman, 2004; Creanza et al., 2012).

Transmission bias in the form of segregation distortion is likely to have a large effect on valley crossing, as distortion represents a second level of selection (Sandler and Novitski, 1957; Hartl, 1970). Insight into how segregation distortion affects valley crossing comes from models of underdominant chromosomal rearrangements (mathematically equivalent to models with one diploid biallelic locus), which often find meiotic drive to be a mechanism allowing fixation of a new mutant homokaryotype (Bengtsson and Bodmer, 1976; Hedrick, 1981; Walsh, 1982). Populations that have fixed alternate homokaryotypes produce heterokaryotype hybrids, which have low viability and/or fertility; thus gene flow between

these populations is reduced. Segregation distortion is therefore thought to be a mechanism that promotes rapid speciation (stasipatric speciation; White, 1978). Although the role of underdominance in chromosomal speciation has recently been questioned (reviewed in Rieseberg, 2001; Hoffmann and Rieseberg, 2008; Faria and Navarro, 2010; Kirkpatrick, 2010), it is hypothesized to be relevant in annual plants (Hoffmann and Rieseberg, 2008) and appears to play a dominant role in maintaining reproductive isolation in sunflowers (Lai et al., 2005) and monkey flowers (Stathos and Fishman, 2014).

Another common form of transmission bias is sex specific, with the extreme case being uniparental inheritance. In genetic transmission, strict uniparental inheritance is common for organelle genomes, such as the mitochondria, which is typically inherited from the mother. Uniparental inheritance will tend to imply further asymmetries. For instance, the mutation rate of mitochondrial genes is estimated to be two orders of magnitude larger than the mutation rate of nuclear genes in many animals (e.g., Linnane et al., 1989). Higher mutation rates will likely facilitate crossing. That said, higher mutation rates in only one gene may have limited effect because the production of double mutants by recombination will be constrained by the availability of the rarer single mutant. Previous models of fitness-valley crossing have tended to ignore asymmetries (but see Appendix C of Weissman et al., 2010).

Transmission bias is an integral characteristic of cultural transmission, where it is referred to as "cultural selection" (Cavalli-Sforza and Feldman, 1981; Boyd and Richerson, 1985). However, to the best of our knowledge, no attempts have been made to examine the evolution of cultural traits (memes) in the presence of a "fitness" valley. Boyd (2001) reviews the genetic theory of the shifting balance, and notes that it could be applied to culture, but no explicit cultural models were presented. Meanwhile, instances such as the so-called "demographic transition" in 19th century western Europe, where societies transitioned from less educated, large families to more educated, small families (Borgerhoff Mulder, 1998), suggest that alternate combinations of cultural traits (e.g., 'value of education' and 'family-size preference') can be stable and that peak shifts may occur in cultural evolution. In fact, alternate stable cultural states may be pervasive (Boyd and Richerson, 2010), as alluded to by the common saying that people are "stuck in their ways". Paradigm shifts in the history of science (Kuhn, 1962) may provide further examples (Fog, 1999). Cultural peak shifts can also be relatively trivial; for instance, changing the unit of time from seconds, minutes, and hours to a decimal system is only advantageous if we also change units that are based on seconds, such as the joule and volt (Fog, 1999).

Here we focus on a population genetic model with two bi-allelic loci under haploid selection in a randomly-mating, finite population. This model can easily be reduced to a single-locus model with two alleles and diploid selection, which is formally equivalent to a model of chromosomal rearrangements (e.g., a chromosome has an inversion or not). Interpreting genes as memes produces a model of vertically-transmitted cultural evolution. Our model incorporates both transmission bias and asymmetries in mutation and initial numbers of single mutants. We first give a rough semi-deterministic sketch to develop some intuition, then follow with a stochastic analysis using a diffusion approximation. Our analysis corresponds to the stochastic simultaneous fixation regime of Weinreich and Chao (2005), and the neutral stochastic tunnelling and deleterious tunnelling regimes of Weissman et al. (2010), where the appearance of the new, favourable, and eventually successful "double mutant" occurs before the fixation of the neutral or deleterious "single mutants". Finally, we apply our results to the specific cases of segregation distortion, uniparental inheritance, and cultural transmission.

We derive the expected time until the appearance of a double mutant whose lineage will fix when single mutants are