Anxiety-causing alleles may confer evolutionary advantages not in very dangerous but in moderately stressful environments

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Abstract

Evolutionary biologists have hypothesized that humans have evolved to experience excessive emotional pain, leading to anxiety and depression, for certain adaptive reasons. This hypothesis is supported by the observation that several stress-sensitive alleles coexist with relatively stress-insensitive wild-type alleles at higher frequencies in Eurasia than in Africa. However, the selection pressure that has shaped this geographic gradient remains a subject of debate. Additionally, the relationships between stress sensitivity, anxiety, and depression remain ambiguous. In this study, we developed three models (anxiety, depression, and combined models) capturing the dynamics of a stress-sensitive allele frequency in a prehistoric human population to examine the mechanisms maintaining polymorphism. The outcomes of the three evolutionary models suggest that stress-sensitive alleles are favored and that a stable polymorphism is possible in a moderate environment, not in a very dangerous environment. These findings further substantiate the notion that anxiety and depression share genetic factors.

Keywords: 5-HTTLPR, Depression, Anxiety, Evolutionary medicine, Mathematical biology, VMAT1

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Highlights:

- The question of why stress-sensitive alleles are observed at higher frequency in human diffusion frontiers was addressed using three models that describe prehistoric environment.
- The models demonstrated that an allele inducing an escape from a site with bad condition to another site can be maintained or even fixed if the frequency of the bad sites takes an intermediate value.
- The model outcomes posit a novel and counterintuitive hypothesis that a human frontier was on average less stressful than the original place of Africa.
- The models also shed light on the relationship between anxiety and depression, which has previously been ambiguous.

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1. Introduction

It is argued that seemingly maladaptive traits, some of which are currently classified as diseases or traits found in otherwise healthy individuals, may have been adaptive at some stage of human evolution. For example, “normal” people feel excessive pain against uncertain external stimuli, which is apparently maladaptive compared to an acute response to it (Nesse, 2005). However, researchers in evolutionary medicine have proposed that this excessive sensitivity to pain may have served an adaptive function by promoting caution and avoidance of potential harm in ancestral environments.

Excessive emotional pains such as anxiety and depression, which often provoke a motivation to suicide, may also have played some adaptive roles (Nesse & Schulkin, 2019). Several studies have suggested that low mood, or mild depressive symptoms, can lead to escape from the situations in which any effort is useless or even harmful. Specifically, low mood is known to motivate waiting, changing strategies or disengaging from the goal (Nesse & Schulkin, 2019). Given that those emotional pains are products of evolution, there would be a biological or genetic, though there are several negative chronical data not supporting this view (Border et al., 2019; Eisenberg & Hayes, 2011; see Discussion).

The serotonin transporter (5-HTT) gene has attracted considerable research interest because of its polymorphic region, 5-HTTLPR, which has been

implicated in the regulation of mood and emotional response (Lesch et al., 1996). This polymorphism consists primarily of two alleles, the short (S) and long (L) alleles. The S allele is associated with increased sensitivity to environmental stressors, which increase susceptibility to anxiety and depression (Gerretsen et al., 2009; Miño et al., 2023). Further research indicates an intermediate stress response in individuals with the heterozygous L/S genotype, demonstrating a graded sensitivity to stressful events (Caspi et al., 2003). The S allele is associated with increased hypothalamic-pituitary-adrenal (HPA) axis reactivity to stress, leading to heightened stress responses (Gotlib et al., 2008). Neuroimaging studies found that activity of amygdala, a brain structure critical for emotional behavior, was greater in individuals carrying the S allele than that in L/L homozygotes (Hariri et al., 2002).

The global pattern of 5-HTTLPR allele distribution indicates several important trends. First, the remarkable conservation of this polymorphism across populations suggests evolutionary stability and indicates that this genetic variation has been maintained across diverse ecological and cultural environments (Gelernter et al., 1999). Second, a geographic gradient in the frequency of the S allele is evident, with a significant increase from African to East Asian populations (Gureyev et al., 2016). In Eurasia (especially in East Asia), the frequencies of the S allele are significantly higher than those in Africa, raising questions about the environmental and social factors that may have

influenced this distribution (Goldman et al., 2010). This geographic variation suggests the potential for evolutionary selective pressures in which traits related to stress response may have conferred survival advantages in certain environments (Way & Lieberman, 2010). We should note that similar patterns of frequency gradients have been observed for other loci such as SLC18A1, which is also associated with anxiety (Sato & Kawata, 2018), indicating some generality of this trend.

The question then arises as to what kind of selective pressure shaped and has maintained the worldwide allelic polymorphism and the prominent gradient. Some researchers have hypothesized that the prevalence of the S allele in East Asia reflects adaptation to severe environmental conditions there; Heightened sensitivity to stress may have provided a survival advantage in environments characterized by unpredictability, food scarcity, and natural disasters, thereby promoting risk-averse behavior (Way & Lieberman, 2010). To our knowledge, however, the above verbal argument has not yet been tested by mathematical models. In particular, it is worth examining quantitatively why the stress-sensitive S allele is not fixed and the polymorphism is maintained in each population.

Another important topic to be addressed is a relationship between anxiety and depression. Depression and anxiety share the same risk genes. Anxiety disorders often precede the development of depression, leading to the

hypothesis that these two conditions represent a continuum rather than distinct clinical entities (Lesch et al., 1996). Both disorders also share neurobiological mechanisms, suggesting that they are different manifestations of the same underlying vulnerability (Price, 2013). Experiments in humans and mice indicated impact of the 5-HTTLPR genotype and stress on both disorders (Carola et al., 2008; Hammen, 2005; Homberg & Lesch, 2011; Santarelli et al., 2016). A recent study highlighting glucocorticoid receptor balance in stress-induced behavior strengthened the link between anxiety and depression (Otto & Day, 2011).

In this modeling study we test the hypothesis that anxiety- or depression-related traits offer an evolutionary advantage in certain environments, with a particular focus on polymorphisms in stress-sensitive alleles and the causes of geographic gradients. Specifically, we developed mathematical models capturing the frequency dynamics of alleles that govern the degree of individual tendency to be anxious and/or depressed. Using the model, we specify the environmental factors affecting allele frequencies.

2. Methods

2.1 Shared assumptions

The present models describe allele frequency dynamics of an infinitely large diploid population. Consider a locus that has two types of alleles, L and S, and thus there are three genotypes, L/L, L/S, and S/S. Individuals with different genotypes exhibit different behaviors, yielding different mean fitness. Denote expected fitness of individuals of genotype L/L, L/S, and S/S by F_0, F_1, and F_2, respectively. Further assuming a discrete-generation, bisexually reproducing, and randomly mating population, we obtain the results that (i) there are always two monomorphic equilibrium states (L-only state and S-only state), (ii) no other equilibrium states are found if $F_0 < F_1 < F_2$ or $F_2 < F_1 < F_0$, otherwise there is one dimorphic equilibrium state, and (iii) the dimorphic internal equilibrium is evolutionarily stable if $F_1 > \max\{F_0, F_2\}$ and unstable if $F_1 < \min\{F_0, F_2\}$ (Otto & Day, 2011). Note that the above results are robust within a broader range of assumptions on the population. For example, we have exactly the same results by assuming a two-sex population in place of the bisexual population if the expected fitness F_0, F_1, and F_2 are independent from sexes.

The three models in this study share the assumption below. Every individual performs N rounds of trials to accumulate resources and energy for reproduction, where N is a positive integer. Each trial is held at a site assigned to the individual, which could be a hunting or working ground. There are no interindividual interactions. Result of the trial is twofold, success or failure, and is determined probabilistically at the beginning of the round. The probability

depends not on individual properties but on condition of the site, good or bad. Failure rates in good and bad sites are w_{G} and w_{B}, respectively ($0 < w_{\mathrm{G}} < w_{\mathrm{B}} < 1$). Every individual gets to know the result of the round at a certain time point during the same round without perception errors, whereas they cannot perceive the site condition.

Success yields an increase of one unit in an individual's cumulative gain. The maximum value for cumulative gain after N rounds is the same as the number of rounds, i.e., N. On the other hand, failure can increase the gain by at most a ($a < 1$). Note that the cumulative gain can decrease when $a < 0$. Here, L/L-, L/S-, and S/S-individuals that have failed in a trial are assumed to withdraw from the failed trial in the middle of that round with probabilities x_0, x_1, and x_2, respectively. As a result of this interruption, gain accumulation (or reduction) a is suppressed by a factor of $1 - s$ ($0 < s < 1$). In other words, they lose gain as by quitting the trial. The fitness of an individual is assumed to be positively correlated with their accumulated gain.

2.2 Anxiety model

The anxiety model investigates whether intermediately anxious individuals can get the highest benefit by escaping from a site (or changing their behavior) due to mild depressive mood. The model assumes that an individual that has failed

in a trial probabilistically quit the trial in order to escape from the current site and search for a new one (figure 1A). However, this move yields a cost of as, and thus too frequent moving may yield a lower total fitness.

We assume that individuals are initially assigned to good sites and bad sites with probability $1 - q_1$ and q_1, respectively ($q_1 > 0$). Denote probabilities that the move from good and bad sites actually change the situation (i.e., probabilities that an individual at a good site moves to a bad site and one at a bad site moves to a good site, respectively) as v_{GB} and v_{BG}, respectively. We additionally assume that each individual can only move to a neighboring site among infinitely many sites. When the good and bad sites are well-mixed (hereafter called the random distribution case), $q_1 = v_{\mathrm{GB}} = q$ and $v_{\mathrm{BG}} = 1 - q$ hold, where q represents proportion of the bad sites among all. When the same type of sites form a cluster, v_{GB} and v_{BG} take values less than one-half.

2.3 Depression model

The depression model tests another hypothesis that the complete immobility of major depression is adaptive because it serves as a type of dormancy, passing through a bad situation. This model, unlike the anxiety model, assumes that individuals never change sites, while condition of sites change probabilistically (figure 1B).

As in the anxiety model, each site is initially in good and bad conditions with probability $1 - q_1$ and q_1, respectively. Then we consider a type of Markov process: at the beginning of each round, sites in good and bad conditions shift to the opposite condition (i.e., bad and good conditions, respectively) with probabilities u_{GB} and u_{BG}, respectively, and otherwise maintain the condition.

2.4 Combined model

It is possible that major depression is an inevitable side effect of anxiety, which can be maintained in the population. Here we combine the above two models. Specifically, an individual that has failed in a trial probabilistically quits the trial and either move to a new site or do nothing (Figure 1C).

The combined model is based on the anxiety model, and thus probability of moving to a new site is denoted as x. In addition, denote the probability of doing nothing as $y = h(x) = \rho\left(\frac{x}{x_2}\right)^{\kappa}$. Here, ρ and κ are the parameters to determine the shape of $h(x)$.

3. Results

3.1 Dimorphism is maintained under limited parameter region in the anxiety model

Figure 2 shows examples of change in frequency of individuals in bad sites (Figure 2A–C) and cumulative gain (divided by the number of rounds; Figure 2D–F) of the three genotypes as the round number advances in the random distribution case. We define $q_{\mathrm{A}}(x,n)$ as the probability that the player with quitting rate x is in a bad site at round n. This value dynamically changes and approaches an equilibrium state q_{A}^{*}. The genotype with greatest cumulative gain, $f_{\mathrm{A}}(x)$, is L/L (the lowest x) at the beginning, S/S or L/S in the middle, and L/L in the end. Genotypes S/S and L/S can approach the equilibrium point q_{A}^{*} more quickly than L/L and thus have a higher probability of success. However, as rounds progress, these genotypes reach near note that (i) q_{A}^{*} is a dynamic equilibrium at which the number of individuals moving from good to bad is equal to that of individuals moving from bad to good, (ii) the above number is greater for greater x, and (iii) each moving yields a cost. Therefore, after genotype L/L also reaches near q_{A}^{*}, they eventually acquire the greater gain $f_{\mathrm{A}}(x)$ (Figure 3E). Indeed, when the number of rounds is infinitely large, can be calculated as:

$$\lim_{N\to\infty}\frac{f_{\mathrm{A}}(x)}{N}=\begin{cases}\{1-(asx+1-a)[w_{\mathrm{G}}(1-q_{\mathrm{A}}^{*})+w_{\mathrm{B}}q_{\mathrm{A}}^{*}]\} & \text{for } x>0\\ 1-(1-a)[w_{G}(1-q_{1})+w_{B}q_{1}] & \text{for } x=0\end{cases}.$$

Smaller but positive x is favored most.

The gain $f_{\mathrm{A}}(x)$ is an N-th polynomial of x, this has at most $N-1$ extreme values. If $f_{\mathrm{A}}(x)$ has at least one maximal point within the range $0<x<1$,

adequate choice of the values of x_0 , x_1 , and x_2 yield heterozygote overdominance, in which case the population maintains allelic dimorphism. When $N = 1$, $A_A(x)$ does not depend on x. In this case, equation 6 indicates that smaller x is always favored as long as $a > 0$ (Figure 3A). That makes sense because costly moving is totally for the following rounds in this model, whereas $N = 1$ means that there are no following rounds. When $N = 2$, it is analytically shown that there are no stable dimorphic states and either or both of monomorphic states are stable (see Appendix). When $N \geq 3$, a parameter region in which dimorphism can be maintained is numerically found (Figures 3 and 4). In general, S allele is more likely to be fixed for smaller s (cost of moving) or a (gain under failure), and stable dimorphism can be observed in the marginal region between the regions in which a monomorphic state is stable (Figures 3). In addition, an intermediate value of q (frequency of bad sites in the random distribution case) favors S allele (Figure 4). If there are much more good sites (i.e., smaller q), more individuals are initially assigned to good sites. In this case, frequently changing sites in response to few times of failure would not be a good strategy. Likewise, if there are much more bad sites (i.e., greater q), moving from a bad site to a bad site frequently occurs. In that case, staying at a bad site would be better than costly moving. Therefore, anxious moving is favored in a diverse environment (i.e., intermediate q). Further numerical analysis suggests that the allelic dimorphism is favored when the difference between w_G and w_B was large.

3.2 Stable allelic dimorphism is never found in the depression model

The depression model revealed that the environmental condition of each site converges over time to a stationary distribution, in which the proportion of bad sites approaches an equilibrium state $q_{\mathrm{D}}^{*} = \frac{u_{\mathrm{GB}}}{u_{\mathrm{GB}}+u_{\mathrm{BG}}}$. This convergence is driven by the geometric decay factor $r_{\mathrm{D}} = 1 - u_{\mathrm{GB}} - u_{\mathrm{BG}}$, which satisfies $-1 < r_{\mathrm{D}} < 1$ under biologically plausible assumptions (i.e., both transition probabilities are strictly between 0 and 1). As a result, the expected frequency of bad sites at each round, denoted $q_{\mathrm{D}}^{(n)}$, approaches q_{D}^{*} in a predictable manner (Figure 2A).

This environmental process was incorporated into a model of individual behavior, where the quitting rate x determines the probability that an individual chooses to become inactive (i.e., stop trying to gain reward from the environment). The total expected gain for an individual adopting quitting rate x is given by a linear function $f_{\mathrm{D}}(x) = -asA_{\mathrm{D}}x + N - (1-a)A_{\mathrm{D}}$, where the coefficient A_{D} summarizes the expected gain per round, weighted by environmental quality.

The analysis showed that A_D is always positive, ensuring that the shape of the fitness function $f_{\mathrm{D}}(x)$ is determined entirely by the sign of the parameter a. When $a > 0$, the fitness function is monotonically decreasing with respect to x, meaning that individuals who persist (i.e., do not quit) are favored. Conversely,

when $a < 0$, quitting becomes advantageous, and higher values of x are selectively favored. Thus, the evolutionary dynamics are qualitatively different depending on whether continued engagement with a deteriorating environment is beneficial or harmful to fitness.

In particular, when fitness declines with continued exposure (i.e., when $a < 0$), the model predicts that the quitting strategy will be fixed in the population, corresponding to fixation of the S-allele associated with a high quitting rate. On the other hand, when persistence is rewarded (i.e., $a > 0$), the model favors fixation of the L-allele, corresponding to low quitting. These results are consistent with the interpretation that dormancy-like behavior—conceptually similar to depressive immobility—can be adaptive when sustained engagement with a harmful environment reduces overall fitness (Figure 2D).

3.3 When depression is an inevitable side effect of anxiety, dimorphism is more likely to be maintained

In the combined model, we can show that the probability that the player with quitting rate x is in a bad site at a given round n, $q_{\mathrm{C}}(x,n)$ is the same as the anxiety model, $q_{\mathrm{A}}(x,n)$. On the other hand, the range of rounds in which L/S is favored is wider than the anxiety model (Figure 2F).

We numerically found that larger κ yields a broader parameter region within which allelic dimorphism is maintained (Figure 5). Notably, dimorphism is maintained even when $N = 2$, with which dimorphism is not seen in the anxiety model, with a sufficiently large κ. This is because S/S homozygotes entail a greater risk of depression, which reduces accumulated gain as long as $a > 0$, than L/S heterozygotes. In contrast, the value of ρ has small effect on the outcome.

Figure 6 shows a typical pattern of change in the S allele frequency with q, frequency of bad sites in the random distribution case, in the combined model. Though not shown, similar plots with a bit more extreme frequencies were obtained with the anxiety model. As expected from the above parameter region plots, the S allele frequency is a one-humped function of q with a maximum point at an intermediate value of q, with which variance of site conditions is high.

4. Discussion

We developed three models capturing dynamics of a stress-sensitive allele frequency in a prehistoric human population, anxiety, depression, and combined models, to investigate mechanism maintaining genetic polymorphism and relationship between anxiety and depression. Individuals

engage in multiple trials, the failure probability of which depend on condition of “sites” for hunting, gathering, or farming. An individual carrying stress-sensitive alleles is assumed to have a greater probability of quitting a trial if he/she failed in it. After the quitting, he/she (i) moves to another site that may or may not be in a better condition than the previous one in the anxiety model, (ii) stays at the same site, during which the site condition may change, (iii) probabilistically move or stay in the combined model. It turned out that the stress-sensitive allele can fix in all three models if failure is accompanied by damage rather than reduced benefit. In addition, the anxiety and combined model, the stress-sensitive allele gives evolutionary advantage if both the number of chance for changing sites and the frequency of sites in good conditions take intermediate values. The anxiety model predicted that there can be stable polymorphism of stress-sensitive and stress-insensitive alleles, while the depression model did not. In the combined model, parameter regions within which polymorphism was observed was broader than the anxiety model.

The most remarkable prediction from the anxiety model is that frequency of the stress-sensitive allele is positively correlated with the degree of environmental diversity, not with absolute badness of environment. Given that several stress-sensitive alleles (e.g., the S allele of 5-HTTLPR and 136Ile of SLC18A1) show higher frequencies in Eurasia as compared to Africa and, it follows that Eurasia and Africa may have had higher and lower, respectively,

environmental diversity. Here, the lower diversity has twofold possibilities: most situations are good or they are bad. The previous arguments on the geological gradient of stress-sensitive allele frequency seem to have implicitly assumed that there is more danger and threat in the region of higher stress-sensitive allele frequency (Caspi et al., 2003). Moreover, some documents noted an association between 5-HTTLPR polymorphism and mechanisms of adaptation to extreme climates (Savostyanov et al., 2021). According to the model prediction, however, it is possible that environmental pressure in such a region is milder. For example, the Jomon period in Japan, which is known to have higher frequency of the S allele of 5-HTTLPR, is characterized by environmental stability and abundant resources, leading to a much longer settlement at one site than in Africa (Imamura, 2016).

The anxiety model showed that the number of chances for changing sites significantly affected the results. This suggests that a stress-sensitive allele evolves only in species with relatively long-life spans or those that have to make decisions repeatedly. Note that longer life spans and more chances for decision-making in today's world than ever before (Misuraca et al., 2024) not necessarily means that stress-sensitive individuals performed better today. The present result is obtained only if individuals can move to another site when they get stressed. This condition would not usually hold in the current environmental context. Moreover, the magnitude and type of stress experienced in the present

day may differ significantly from those in prehistoric times. Consequently, the effects of stress-sensitive alleles may be masked, thereby concealing the association between genotype and depression incidence (Border et al., 2019). In addition to the chronic data analysis, psychological experiments and animal experiments are necessary in order to achieve a comprehensive understanding of the evolutionary role of stress sensitivity.

The combined model, in which the probability of being depressed with probability was positively correlated with probability of occurrence of having an active response to change the situation, exhibited the widest range of parameter regions for stable polymorphism among the present three models. It follows that the combined model is most likely given the world-wide prevalence of polymorphisms of the stress-sensitivity genes. That in turn supports the view that depression shares several genetic basis with anxiety and it is an inevitable byproduct of anxiety.

The present model assuming a single infinite population does not consider migration–selection balance, which is particularly important when there is environmental variation among local populations (Booker, 2024). In addition, phylogenetic analysis of mitochondrial DNA suggests that human migration out of Africa was not a one-way process; rather, ancestors from western Eurasia also entered southern Africa via eastern Africa (Pickrell et al., 2014). This back-migration could play a role in maintaining polymorphism in

each local population by reintroducing genetic variation that might otherwise have been lost.

The present model also did not consider inter-individual interaction, which may provide another and non-exclusive explanation for the polymorphism. Interaction is often accompanied by frequency-dependent selection, leading to coexistence of multiple alleles at an equilibrium point. In this context, it is noteworthy that association between the S allele frequency and the degree of collectivism is reported (Chiao & Blizinsky, 2010; but see also Eisenberg & Hayes, 2011). Such a model should also consider the relationship between rate of depression and hierarchy (Fan et al., 2023; Nesse & Schulkin, 2019; Tseng et al., 2023).

Finally, the present model considering repetitive resource-seeking behavior may be also applied to studies on attention deficit hyperactivity disorder (ADHD), with which individuals exhibit increased levels of resource-seeking behavior (Barack et al., 2024). Given that anxiety disorders and ADHD are often comorbid, it would be valuable to explore how these conditions interact at the genetic and environmental levels (Swanepoel et al., 2022). A comprehensive understanding of these overlapping mental health conditions are obviously important (Esteller-Cucala et al., 2020).

In summary, this study highlights the geographic gradient in the frequency of stress-sensitive alleles, with a clear ascent from Africa to Eurasia. Outcomes of three evolutionary models indicate that stress-sensitive alleles are favored in a moderate environment, not in a very dangerous environment. They also support the view that anxiety and depression share genetic factors. Further theoretical studies incorporating individual interactions and psychological experiments will provide deeper insights into the seemingly counterintuitive evolution of stress-sensitive alleles.

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Appendix

Allele frequency dynamics and local stability analysis for equilibrium states.

Denote frequencies of the L allele and the S allele among gametes at generation t as $1-p(t)$ and $p(t)$, respectively. As we assume random mating, frequencies of the three genotype, L/L, L/S, and S/S are calculated as $\big(1-p(t)\big)^2$, $2\big(1-p(t)\big)p(t)$, and $p(t)^2$, respectively. The gametes of genotype S gametes at generation $t+1$ are produced by the L/S and S/S individuals. The amount produced by the

former is half as many as that produced by the latter. The frequency p_{t+1} is calculated as

$$p(t+1) = g(p) = \frac{1}{\bar{w}(p)}[(1-p)pF_1 + p^2F_2], \quad \text{(A.1)}$$

where $\bar{w}(p)$ is mean fitness for all individuals calculated as follows:

$$\bar{w}(p) = (1-p)^2F_0 + 2(1-p)pF_1 + p^2F_2. \quad \text{(A.2)}$$

Using the above difference equation and the initial value p_1, we can calculate the allele frequencies at any generation.

Define $\hat{p}$ as the S allele frequency at an equilibrium, the state at which the allele frequencies do not change over generations. From (A.1), $\hat{p}$ is obtained by solving $\hat{p} = g(\hat{p})$. This equation has three solutions, $\hat{p} = 0$, 1, and p^*, where

$$p^* = \frac{F_1 - F_0}{2F_1 - F_0 - F_2}. \quad \text{(A.3)}$$

That is biologically feasible (i.e., $0 < p^* < 1$) if and only if

$$F_1 < \min\{F_0, F_2\}. \quad \text{(A.4)}$$

or

$$F_1 > \max\{F_0, F_2\}, \quad \text{(A.5)}$$

Each equilibrium is locally stable if

$$-1 < \left(\frac{\partial g}{\partial p}\right)_{p=p^*} < 1. \quad \text{(A.6)}$$

The trivial equilibria $p = 0$ and $p = 1$ are stable if $F_1 < F_0$ and $F_1 < F_2$, respectively. The two trivial equilibria are simultaneously locally stable (called bistable) if (A.4) is satisfied, in which case $p = p^*$ exists as an unstable internal equilibirum. The non-trivial, dimorphic equilibrium $p = p^*$ is locally stable if (A.5) holds, in which case $p = 0$ and $p = 1$ are both unstable.

Obtaining fitness functions for the three models.

Let $\phi(w, x)$ be expected one-round gain increment for an individual that has probability x (one of x_0, x_1, and x_2) at a site with failure rate w (either w_{G} or w_{B}). It is calculated as

$$\begin{aligned}\phi(w, x) &= 1 - w + wa[1 - x + x(1 - s)] \\ &= -aswx + 1 - (1 - a)w\end{aligned}.$$

Let $f_i(x)$ be the expected cumulative gain for individuals with quitting rate x when the final N-th round has ended. We assume that expected fitness is calculated as follows:

$$F_i = 1 + \varepsilon f(x_i); i \in \{0,1,2\},$$

where $0 < \varepsilon \ll 1$ so that fitness is positive even when $f(x_i)$ takes a negative value.

The depression model

Let $q_{\mathrm{D}}(n)$ be the probability that the environment is bad in round n. By definition $q_{\mathrm{D}}(1) = q_1$. For $n \geq 2$, $q_{\mathrm{D}}(n)$ is calculated as:

$$\begin{aligned} q_{\mathrm{D}}(n) &= \left(1 - q_{\mathrm{D}}^{(n-1)}\right)u_{\mathrm{GB}} + q_{\mathrm{D}}^{(n-1)}(1 - u_{\mathrm{BG}}) \\ &= (1 - u_{\mathrm{GB}} - u_{\mathrm{BG}})q_{\mathrm{D}}^{(n-1)} + u_{\mathrm{GB}} \end{aligned}. \quad \text{(B.1)}$$

Note that $q_D^{(n)}$ does not include w_{G}, w_{B} and x. This makes sense given the assumption of the depression model that environment affects but is not affected by the outcome of trials and individual behavior.

The general solution of $q_{\mathrm{D}}^{(n)}$ is

$$\begin{aligned} q_{\mathrm{D}}(n) &= (q - q_{\mathrm{D}}^{*})r_{\mathrm{D}}^{n-1} + q_{\mathrm{D}}^{*} \\ &= r_{\mathrm{D}}^{n-1}q + (1 - r_{\mathrm{D}}^{n-1})q_{\mathrm{D}}^{*}, \end{aligned} \quad \text{(B.2)}$$

where

$$r_{\mathrm{D}} = 1 - u_{\mathrm{BG}} - u_{\mathrm{GB}}, \quad \text{(B.3)}$$

$$q_{\mathrm{D}}^{*} = u_{\mathrm{GB}}/(u_{\mathrm{BG}} + u_{\mathrm{GB}}). \quad \text{(B.4)}$$

Since $-1 < r_{\mathrm{D}} < 1$, $q_{\mathrm{D}}^{(n)}$ monotonically or asymptotically approach q_{D}^{*} as n increases.

The expected gain accumulated until the end (i.e., round N) for individuals with quitting rate x, $f_{\mathrm{D}}(x)$, is obtained as follows. First, let $f_{\mathrm{D}}^{(n)}(x)$ denote the expected gain in round n. If the site condition is good and bad, their expected gain is $\phi(w_{\mathrm{G}}, x)$ and $\phi(w_{\mathrm{B}}, x)$, respectively. Therefore, using the probability $q_{\mathrm{D}}^{(n)}$ we have

$$f_{\mathrm{D}}^{(n)}(x) = \left(1 - q_{\mathrm{D}}^{(n)}\right)\phi(w_{\mathrm{G}}, x) + q_{\mathrm{D}}^{(n)}\phi(w_{\mathrm{B}}, x) \tag{B.5}$$

It follows:

$$\begin{aligned} f_{\mathrm{D}}(x) &= \sum_{n=1}^{N} f_{\mathrm{D}}^{(n)}(x) \\ &= \phi(w_{\mathrm{G}}, x)\sum_{n=1}^{N} 1 - \left(\phi(w_{\mathrm{G}}, x) - \phi(w_{\mathrm{B}}, x)\right)\sum_{n=1}^{N} q_{\mathrm{D}}^{(n)} \\ &= [(1 - q_{\mathrm{D}}^{*})\phi(w_{\mathrm{G}}, x) + q_{\mathrm{D}}^{*}\phi(w_{\mathrm{B}}, x)]N - (q - q_{\mathrm{D}}^{*})\left(\phi(w_{\mathrm{G}}, x) - \phi(w_{\mathrm{B}}, x)\right)\sum_{n=1}^{N} r_{\mathrm{D}}^{n-1} \end{aligned} \tag{B.6}$$

Equation B.6 is further calculated by replacing $\phi(w_{\mathrm{G}}, x)$ and $\phi(w_{\mathrm{B}}, x)$ with the right-hand side of equation as follows:

$$f_{\mathrm{D}}(x) = -aA_{\mathrm{D}}sx + N - (1 - a)A_{\mathrm{D}} \tag{B.7}$$

$$\begin{aligned} A_{\mathrm{D}} &= [w_{\mathrm{G}}(1 - q_{\mathrm{D}}^{*}) + w_{\mathrm{B}}q_{\mathrm{D}}^{*}]N + (q - q_{\mathrm{D}}^{*})(w_{\mathrm{B}} - w_{\mathrm{G}})\sum_{n=1}^{N} r_{\mathrm{D}}^{n-1} \\ &= \frac{1}{u_{\mathrm{GB}} + u_{\mathrm{BG}}}\left\{(w_{\mathrm{G}}u_{\mathrm{BG}} + w_{\mathrm{B}}u_{\mathrm{GB}})N - [(1 - q)u_{\mathrm{GB}} - qu_{\mathrm{BG}}](w_{\mathrm{B}} - w_{\mathrm{G}})\frac{1 - (1 - u_{\mathrm{GB}} - u_{\mathrm{BG}})^{N}}{u_{\mathrm{GB}} + u_{\mathrm{BG}}}\right\} \end{aligned} \tag{B.8}$$

Note that we can show $A_{\mathrm{D}}(x) > 0$ as follows:

$$\begin{aligned} A_{\mathrm{D}} &= \sum_{n=1}^{N}[w_{\mathrm{G}}(1 - q_{\mathrm{D}}^{*}) + w_{\mathrm{B}}q_{\mathrm{D}}^{*} + (q - q_{\mathrm{D}}^{*})(w_{\mathrm{B}} - w_{\mathrm{G}})r_{\mathrm{D}}^{n-1}] \\ &= \sum_{n=1}^{N}\{w_{\mathrm{G}}[1 - q_{\mathrm{D}}^{*}(1 - r_{\mathrm{D}}^{n-1})] + w_{\mathrm{B}}q_{\mathrm{D}}^{*}(1 - r_{\mathrm{D}}^{n-1}) + q(w_{\mathrm{B}} - w_{\mathrm{G}})r_{\mathrm{D}}^{n-1}\} \end{aligned} \tag{B.9}$$

The summation term reflects transient deviations from the equilibrium environment and incorporates environmental volatility.

Therefore, $f_{\mathrm{D}}(x)$ is a monotonically increasing and decreasing function of x when $a < 0$ and $a > 0$, respectively.

The anxiety model

The anxiety model shares much of its structure with the depression model. The former has a unique expected probability for individuals with quitting rate x to be at a bad site in round n, $q_{\mathrm{A}}(x, n)$, in place of $q_{\mathrm{D}}(n)$ of the depression model. It is calculated as follows.

$$q_{\mathrm{A}}(x, 1) = q_1, \tag{B.10}$$

$$q_{\mathrm{A}}(x, n) = [1 - (w_{\mathrm{G}} v_{\mathrm{GB}} + w_{\mathrm{B}} v_{\mathrm{BG}})x] q_{\mathrm{A}}^{(n-1)}(x) + w_{\mathrm{G}} v_{\mathrm{GB}} x. \tag{B.11}$$

Note that (B.11) is obtained by replacing u_{GB} and u_{BG} in (B.1) with $w_{\mathrm{G}} v_{\mathrm{GB}} x$ and $w_{\mathrm{B}} v_{\mathrm{BG}} x$, respectively. Using the same replacement, we obtain the counterparts of those in the depression model as follows:

$$\begin{aligned} q_{\mathrm{A}}(x, n) &= \left(q_1 - q_{\mathrm{A}}^*(x)\right) r_{\mathrm{A}}^{n-1} + q_{\mathrm{A}}^*(x) \\ &= \left(r_{\mathrm{A}}(x)\right)^{n-1} q_1 + \left[1 - \left(r_{\mathrm{A}}(x)\right)^{n-1}\right] q_{\mathrm{A}}^*(x) \end{aligned} \tag{B.12}$$

$$q_{\mathrm{A}}^*(x) = \begin{cases} q_1 \text{ if } x = 0 \\ \dfrac{v_{\mathrm{GB}}}{v_{\mathrm{GB}} + (w_{\mathrm{B}}/w_{\mathrm{G}}) v_{\mathrm{BG}}} \text{ otherwise} \end{cases} \tag{B.13}$$

$$r_{\mathrm{A}}(x) = 1 - (w_{\mathrm{B}} v_{\mathrm{BG}} + w_{\mathrm{G}} v_{\mathrm{GB}})x \tag{B.14}$$

Note that $-1 < r_{\mathrm{A}}(x) < 1$ holds and $q_{\mathrm{A}}(x,n)$ monotonically or oscillatory approaches q_{A}^{*} as n increases unless x equals zero. Note also that the equilibrium state q_{A}^{*} is independent from x while the quitting rate x affects convergence speed toward the equilibrium. This means that the anxiety model partially guarantees a type of rationality of the anxious moving; individuals can reduce the probability of being in a bad site by repeating the outcome-based escapes (Figure 2b; supplementary text).

$$\begin{aligned} f_{\mathrm{A}}(x) &= -aA_{\mathrm{A}}(x)sx + N - (1-a)A_{\mathrm{A}}(x) \\ &= -(asx + 1 - a)A_{\mathrm{A}}(x) + N \end{aligned} \tag{B.15}$$

$$\begin{aligned} A_{\mathrm{A}} &= \left[w_{\mathrm{G}}\left(1 - q_{\mathrm{A}}^{*}(x)\right) + w_{\mathrm{B}} q_{\mathrm{A}}^{*}(x)\right]N + \left(q_1 - q_{\mathrm{A}}^{*}(x)\right)(w_{\mathrm{B}} - w_{\mathrm{G}}) \sum_{n=1}^{N} \left(r_{\mathrm{A}}(x)\right)^{n-1} \\ &= \sum_{n=1}^{N} \left[w_{\mathrm{G}}\left\{1 - q_{\mathrm{A}}^{*}\left[1 - \left(r_{\mathrm{A}}(x)\right)^{n-1}\right]\right\} + w_{\mathrm{B}} q_{\mathrm{A}}^{*}\left[1 - \left(r_{\mathrm{A}}(x)\right)^{n-1}\right] + q_1(w_{\mathrm{B}} - w_{\mathrm{G}})\left(r_{\mathrm{A}}(x)\right)^{n-1}\right] > 0 \end{aligned} \tag{B.16}$$

In addition, for $x > 0$, equation B.16 can be rewritten as follows:

$$A_{\mathrm{A}}(x) = \frac{CN}{V} - \frac{B}{V}\sum_{k=0}^{N-1}(-1)^k V^k X_{\mathrm{E}}^{(k)}, \tag{B.17}$$

where

$$B = [(1-q)w_{\mathrm{G}} v_{\mathrm{GB}} - q w_{\mathrm{B}} v_{\mathrm{BG}}](w_{\mathrm{B}} - w_{\mathrm{G}}), \tag{B.18}$$

$$C = w_{\mathrm{G}} w_{\mathrm{B}}(v_{\mathrm{GB}} + v_{\mathrm{BG}}), \tag{B.19}$$

$$V = w_{\mathrm{G}} v_{\mathrm{GB}} + w_{\mathrm{B}} v_{\mathrm{BG}}, \tag{B.20}$$

$$X_{\mathrm{A}}^{(k)} = \binom{N}{k+1} x^k. \tag{B.21}$$

Note that C and V are positive, and $X_{\mathrm{A}}^{(k)}$ is non-negative, whereas B can be negative. The cumulative gain $f_{\mathrm{A}}(x)$ is rewritten using these quantities as follows:

$$\begin{aligned} f_{\mathrm{A}}(x) &= -(asx + 1 - a)\left\{\frac{CN}{V} - \frac{B}{V}\sum_{k=0}^{N-1}(-V)^k X_{\mathrm{A}}^{(k)}\right\} + N \\ &= \frac{B}{V}\left\{asx\sum_{k=0}^{N-1}(-V)^k X_{\mathrm{A}}^{(k)} + (1-a)\sum_{k=0}^{N-1}(-V)^k X_{\mathrm{A}}^{(k)}\right\} - as\frac{CN}{V}x - (1-a)\frac{CN}{V} + N \end{aligned} \tag{B.22}$$

This form more clearly indicates that $f_{\mathrm{A}}(x)$ is an N-th degree polynomial of x.

Analysis of the case of $N = 2$ in the anxiety model.

When $N = 2$, equation B.22 becomes

$$f_{\mathrm{A}}(x) = -asBx^2 - [2asD + (1-a)B]x + 2[1 - (1-a)D], \tag{B.23}$$

where

$$D = \frac{C-B}{V} = (1-q)w_{\mathrm{G}} + qw_{\mathrm{B}}. \tag{B.24}$$

Note that $D > 0$. The first and second derivatives of $f_{\mathrm{A}}(x)$ are calculated as

$$f_{\mathrm{A}}'(x) = -2asBx - [2asD + (1-a)B], \tag{B.25}$$

$$f_{\mathrm{A}}''(x) = -2asB. \tag{B.26}$$

The quadratic function $f_{\mathrm{A}}(x)$ takes its extreme value (either maximum or minimum) at $x = x_{\mathrm{E}}$, where

$$f'_{\mathrm{A}}(x_{\mathrm{E}}) = 0 \leftrightarrow x_{\mathrm{E}} = -\left(\frac{D}{B} + \frac{1-a}{2as}\right). \tag{B.27}$$

Equation B.26 indicates that $f_{\mathrm{A}}(x_{\mathrm{E}})$ is the maximum and the minimum if $aB > 0$ and $aB < 0$, respectively.

It can be shown that $aB > 0$ and $0 < x_{\mathrm{E}} < 1$ do not hold simultaneously, which means that $f_{\mathrm{A}}(x)$ does not take a maximum within the range from zero to one, as follows. Suppose $aB > 0$, which is equivalent to either $0 < a < 1$ and $B > 0$ or $a < 0$ and $B < 0$. In the former case, it is clear from equation B.27 that x_{E} is negative. In the latter case, x_{E} is greater than one because

$$x_{\mathrm{E}} - 1 = -\left(\frac{B+D}{B} + \frac{1-a}{2as}\right), \tag{B.28}$$

and

$$B + D = (1-q)w_{\mathrm{G}}[1 + v_{\mathrm{GB}}(w_{\mathrm{B}} - w_{\mathrm{G}})] + qw_{\mathrm{B}}[1 - v_{\mathrm{BG}}(w_{\mathrm{B}} - w_{\mathrm{G}})] > 0. \tag{B.29}$$

In conclusion, stable allelic dimorphism resulted from overdominance does not occur in the anxiety model with $N = 2$.

The combined model

Here we make a constraint that y is a monotonically increasing function of x as follows:

$$y = h(x) = \rho\left(\frac{x}{x_{max}}\right)^{\kappa}, \tag{B.30}$$

where

$$x_{max} = \max\{x_0, x_1, x_2\}, \tag{B.31}$$

and κ and ρ are positive real parameters satisfying $\rho < 1 - x_{max}$

The combined model is almost the same as the anxiety model. The former assumes a greater quitting rate for individuals with moving rate $x(> 0)$ than the latter does. The same quantities $q_{\mathrm{A}}^{(n)}(x)$, $q_{\mathrm{A}}^{*}(x)$, $r_{\mathrm{A}}(x)$ as the anxiety model can be applied. On the other hand, the increased quitting rate yields reduced gain as follows:

$$f_{\mathrm{C}}^{(n)}(x) = \left(1 - q_{\mathrm{D}}^{(n)}\right)\phi\left(w_{\mathrm{G}}, x + h(x)\right) + q_{\mathrm{D}}^{(n)}\phi\left(w_{\mathrm{B}}, x + h(x)\right) \tag{B.32}$$

$$f_{\mathrm{C}}(x) = \sum_{n=1}^{N} f_{\mathrm{C}}^{(n)}(x) \tag{B.33}$$

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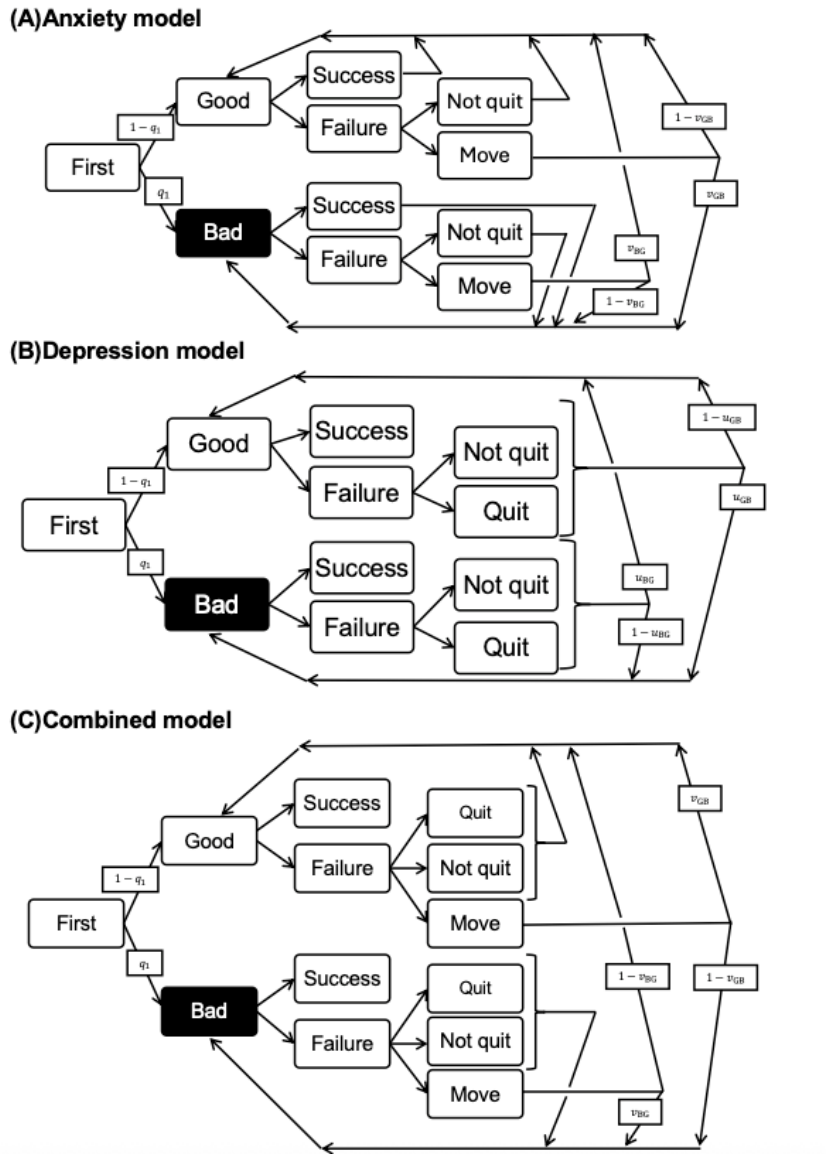
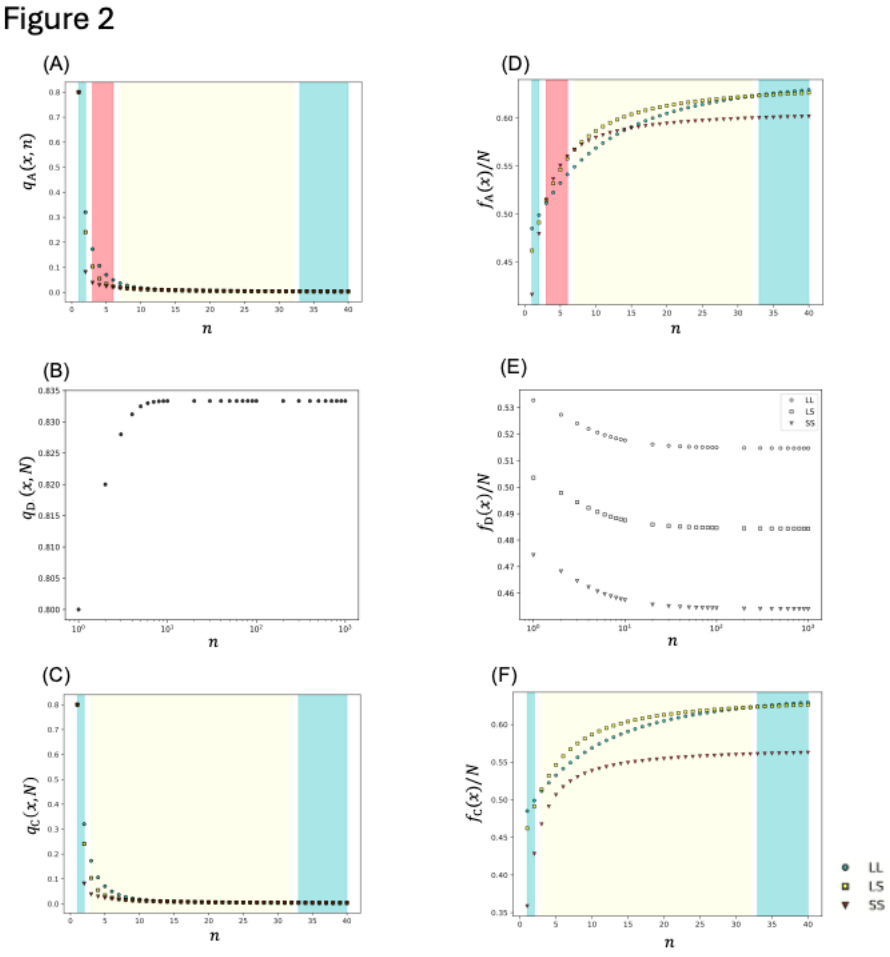
Figure Captions

Fig. 1. Flow of individual behavior. in the anxiety model (A), the depression model (B), and the combined model (C).



An individual is assigned to a site with condition good or bad. Result of each trial is twofold: success or failure. Failure probabilistically induces quitting. If the individual has quit the trial, he/she either move to another site (**A**, **C**) or stay at the same site (**B**, **C**). The above process is repeated *N* times.

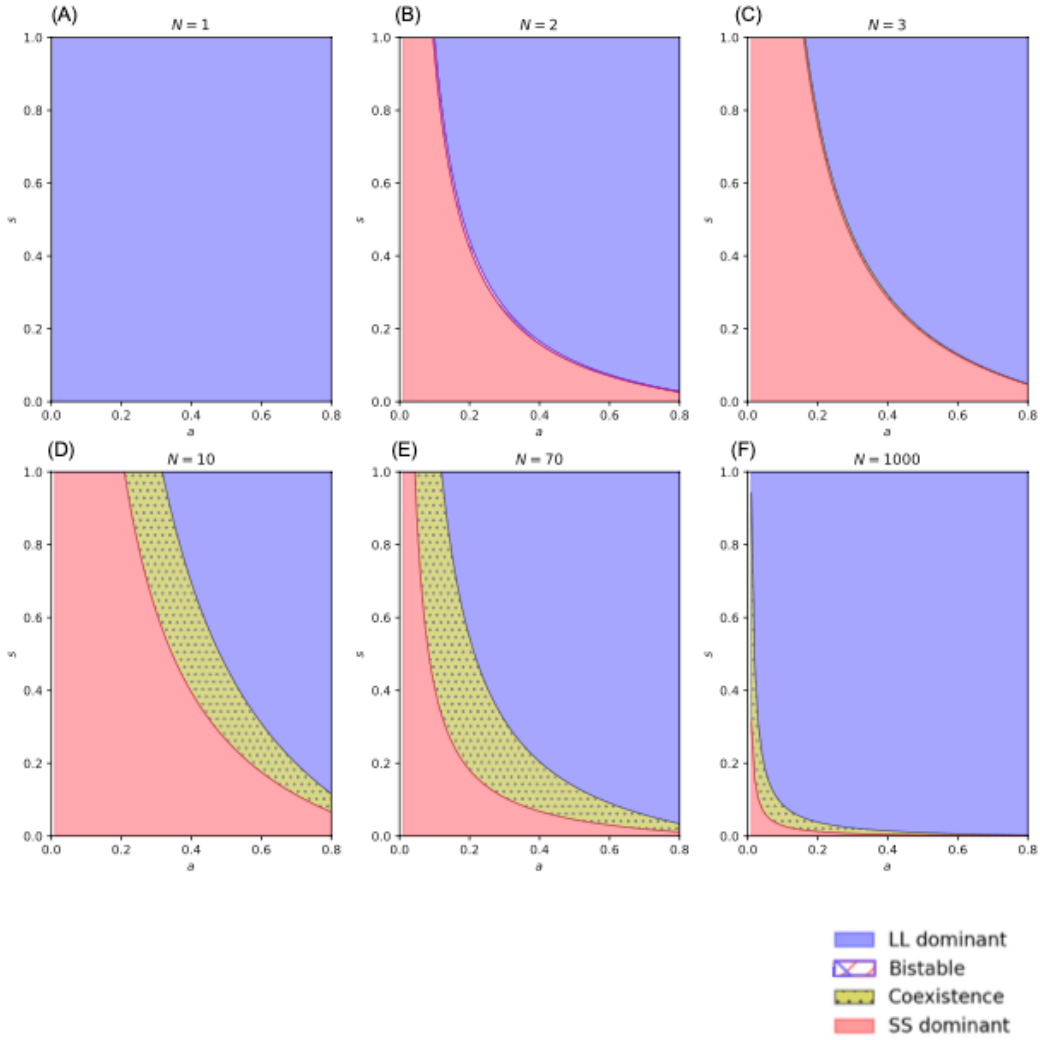
Fig. 2. Within-generation dynamics in the three model.



Frequency of individuals that are at the bad site among those sharing the same genotype, $q^{(n)}(x_i)$ (**A**–**C**), and the expected accumulated gain, $f(x_i)$, normalized by the number of rounds experienced so far (**D**–**F**) were plotted against the number of rounds, n, in the anxiety model (**A**, **D**), the depression model (**B**, **E**), and combined model (**C**, **F**). Background colors indicate the genotype with the highest gain: L/L(blue), L/S(yellow) and S/S(red). In the anxiety and combined models, different genotypes approach the same equilibrium frequency with different convergence rate (**A**, **C**), and the genotype with the greatest cumulative

gain depends on the round number (**D**, **F**). In the depression model, the convergence rate is independent of genotype (**B**), with one homozygote (L/L in this numerical example) always providing the greatest cumulative gain (**D**). Parameter values are $w_{\mathrm{G}} = 1/2$, $s = 35/100$, $v_{\mathrm{BG}} = 4/5$, $v_{\mathrm{GB}} = 1/5$ and $x_2 = 4/5$ for the anxiety model (**A**, **D**), and $w_{\mathrm{G}} = 1/20$, $s = 1/2$, $u_{\mathrm{BG}} = 1/10$ $u_{\mathrm{GB}} = 1/2$, and $x_2 = 3/5$ for the depression model (**B**, **E**). The other parameters are $a = 2/5$, $w_{\mathrm{B}} = 9/10$, $x_0 = 1/5$, and $x_1 = 2/5$. The same parameter values as the anxiety model, $\rho = 1/2$, and $\kappa = 20$ and were used for the combined model (**C**, **F**).

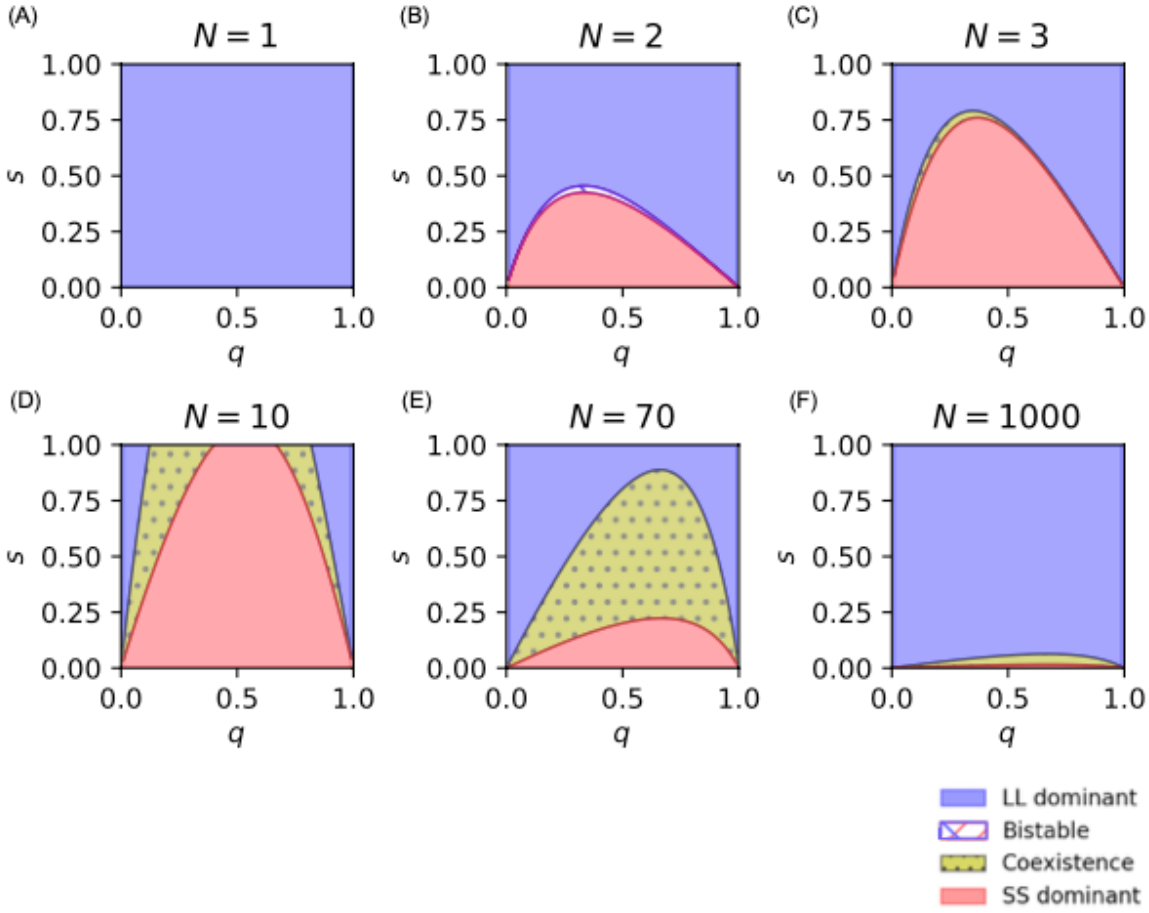
Fig. 3. Dependency of evolutionarily stable states in the anxiety model on the environmental factors.



Various values were substituted into total number of rounds (N), the maximum gain for individuals that have failed in a trial (a), and cost for anxiety movement (s). Specifically, $N = 1$ (**A**), 2 (**B**), 3 (**C**), 10 (**D**), 70 (**E**), and 1000 (**F**), the values of a vary between 0 to $4/5$ (the horizontal axis), and the values of s vary between 0 to 1 (the vertical axis). The blue and red areas indicate the parameter regions in which the L and S alleles, respectively, are fixed. The yellow area indicates the

region in which dimorphism of the L and S alleles is maintained depending on values of the other parameters. The white area indicates the region in which either the L or S allele is fixed depending on the initial allele frequency. When $N = 1$ (**A**), the L allele is fixed as long as $a > 0$. When $N = 2$ (**B**), the regions are also found in which S is fixed or the bistable dynamics are observed. When $N \geq 3$ (**C**–**F**), there is the region in which dimorphism is maintained. Area of the dimorphic region is wider when intermediate N is substituted (D and F). The other parameters are $w_{\mathrm{B}} = 4/5$, $w_{\mathrm{G}} = 1/5$, $v_{\mathrm{BG}} = 7/10$, $v_{\mathrm{GB}} = 3/10$, $x_0 = 1/5$ $x_1 = 2/5$, and $x_2 = 3/5$.

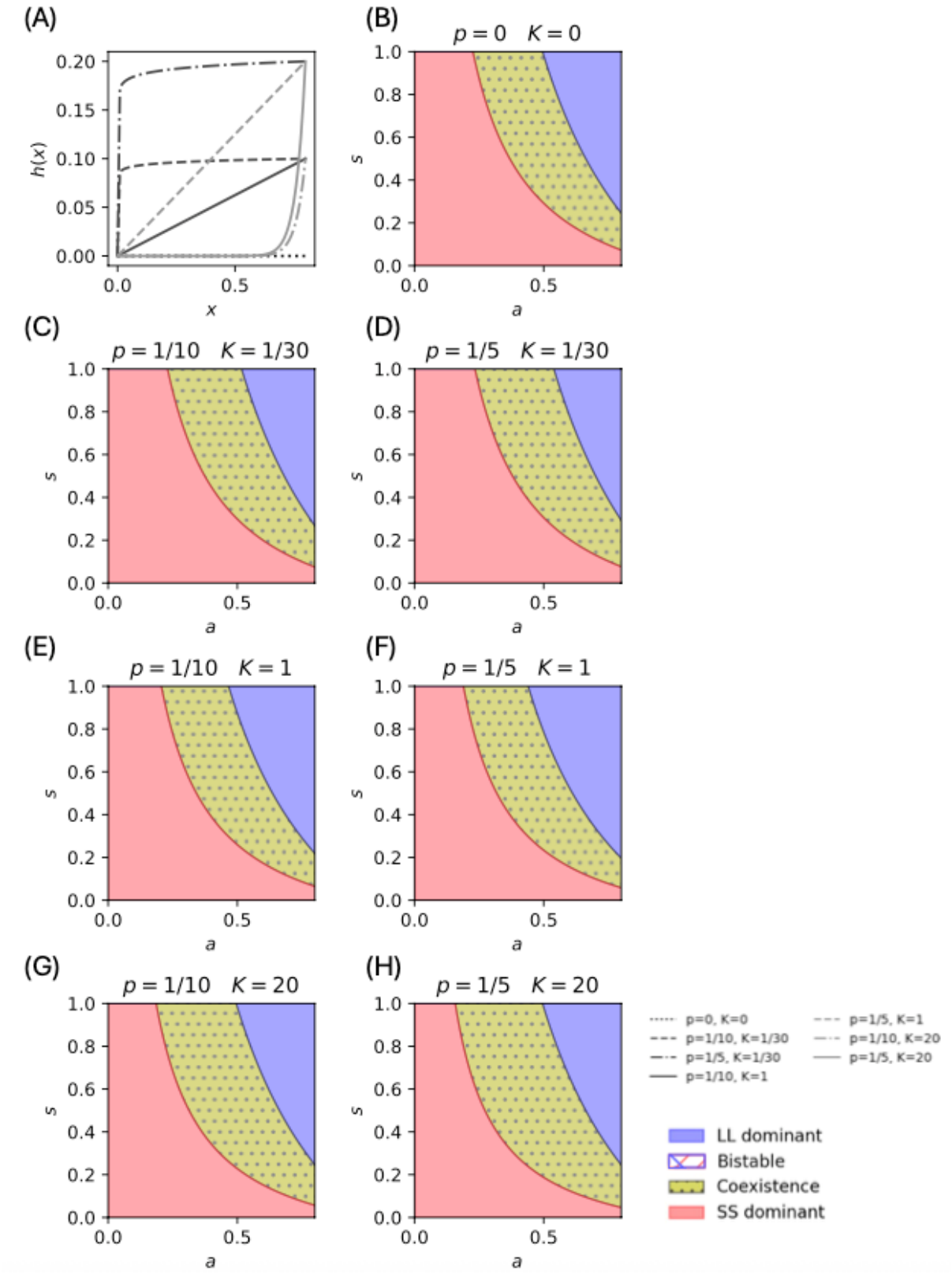
Fig. 4. Dependency of evolutionarily stable states in the anxiety model on the environmental factors.



Various values were substituted into the total number of rounds (N), the frequency of bad sites (q), and cost for anxiety movement (s). In the random distribution case, $q_1 = v_{\mathrm{GB}} = q$ and $v_{\mathrm{BG}} = 1 - q$ are assumed. Specifically, $N = 1$ (**A**), 2 (**B**), 3 (**C**), 10 (**D**), 70 (**E**), and 1000 (**F**), the values of q vary between 0 to 1 (the horizontal axis), and the values of s vary between 0 to 1 (the vertical axis). The blue and red areas indicate the parameter regions in which the L and S alleles, respectively, are fixed. The yellow area indicates the region in which

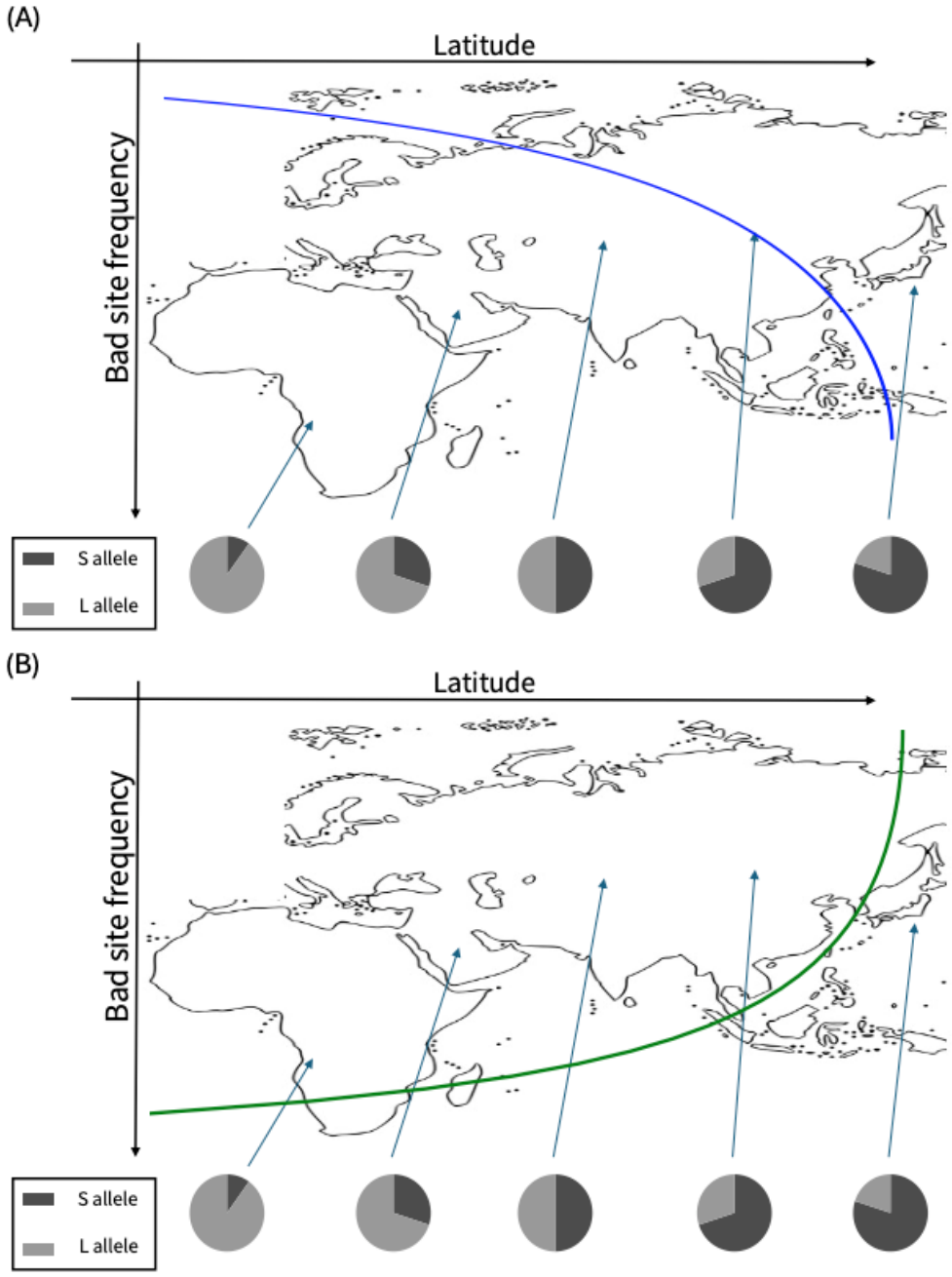
dimorphism of the L and S alleles is maintained depending on values of the other parameters. The white area indicates the region in which either the L or S allele is fixed depending on the initial allele frequency. When $N = 1$ (**A**), the L allele is fixed as long as $a > 0$. When $N = 2$ (**B**), the regions are also found in which S is fixed or the bistable dynamics are observed. When $N \geq 3$ (**C**–**F**), there is the region in which dimorphism is maintained. Area of the dimorphic region is wider when intermediate q is substituted. The value of q realizing the broadest parameter region for dimorphism in turn depend on N. The other parameters are $a = 1/5$, $w_{\mathrm{B}} = 4/5$, $w_{\mathrm{G}} = 1/5$, $x_0 = 1/5$ $x_1 = 2/5$, and $x_2 = 4/5$.

Fig. 5. Dependency of evolutionarily stable states in the combined model on the degree of association between anxiety and depression.



Various values were substituted into the parameters determining association between moving rate and depression rate (ρ and κ), the maximum gain for individuals that have failed in a trial (a), and cost for anxiety movement (s). In (**A**), the association between the moving rate (x) and the depression rate ($h(x)$) were plotted with various ρ and κ. In (**B**–**H**), the blue and red areas indicate the parameter regions in which the L and S alleles, respectively, are fixed. The yellow area indicates the region in which dimorphism of the L and S alleles is maintained depending on values of the other parameters. The white area indicates the region in which either the L or S allele is fixed depending on the initial allele frequency. The parameter values are $\rho = 0$ (**B**), $1/10$ (**C**, **E**), or $1/5$ (**D**, **F**), $\kappa = 0$ (**B**), $1/30$ (**C**, **D**), or 1 (**E**, **F**) , the values of a vary between 0 to $3/4$ (the horizontal axis), and the values of s vary between 0 to 1 (the vertical axis), $w_{\mathrm{B}} = 4/5$, $w_{\mathrm{G}} = 1/5$, $q_1 = 1/2$, $v_{\mathrm{BG}} = 1/2$, $v_{\mathrm{GB}} = 1/10$, $N = 30$, $x_0 = 1/5$, $x_1 = 2/5$, and $x_2 = 4/5$.

Fig. 6. Two possible environmental gradients realizing the same allele-frequency gradient.



In both panels, local variation in environmental conditions is assumed to be small in Africa and high in Eurasia, and pie charts represent equilibrium allele frequencies in each area predicted by the combined model. However, the local

variation is small in Africa because most sites are in good condition (**A**) or they are in bad condition (**B**). In both scenarios, the stress-sensitive S allele frequency is higher in Eurasia. The parameter q was varied between $34/100$ and $4/5$ in (**A**), and between $5/100$ and $31/100$ in (**B**). The other parameters are $a = 1/5$, $w_{\mathrm{B}} = 4/5$, $w_{\mathrm{G}} = 1/5$, $N = 70$, $s = 3/10$, $x_0 = 1/5$, $x_1 = 2/5$, and $x_2 = 4/5$.