

Robustness increases heritability: implications for familial disease

Steven A. Frank¹

Robustness protects organisms in two ways. Homeostatic buffering lowers the variation of traits caused by internal or external perturbations. Tolerance reduces the consequences of bad situations, such as extreme phenotypes or infections. This article shows that both types of robustness increase the heritability of protected traits. Additionally, robustness strongly increases the heritability of disease. The natural tendency for organisms to protect robustly against perturbations may partly explain the high heritability that occurs for some diseases.

Keywords: Quantitative genetics, genetic variability, tolerance, homeostasis, developmental variability

Introduction

Robustness protects against perturbation. For example, checkpoints in the cell cycle sense certain types of DNA damage and prevent clonal expansion of aberrant cells. Robustness mechanisms reduce disease within individuals and, by protecting traits against the consequences of perturbation, may also influence patterns of genetic and developmental variability (Visser et al., 2003).

In this article, I show that robustness alters variability in ways that increase heritability. I start with the heritability of any trait protected by robustness. I then describe how, in theory, robustness may enhance the heritability of disease (Frank, 2004, 2019). Heritability is high for many diseases (Sadée et al., 2014). Perhaps robustness explains some part of that high heritability.

1. Department of Ecology and Evolutionary Biology, University of California, Irvine, CA 92697–2525, USA
email: safrank@uci.edu

Heritability

Consider a simple description of the heritability of a trait, z , as the ratio of the additive genetic variance, σ_g^2 , to the total trait variance, σ_z^2 , as

$$h = \frac{\sigma_g^2}{\sigma_z^2} = \frac{\sigma_g^2}{\sigma_g^2 + \sigma_d^2}. \quad (1)$$

I split the total variance into a genetic component and a developmental component, σ_d^2 . Nongenetic aspects are often called the *environmental* component. Here, I use *development* to emphasize processes within the individual that may be protected by robustness mechanisms, such as perturbations that alter the ways in which disease may develop within an individual. I assume that genetic and developmental effects act independently on phenotype. One may also consider a third component of the total variance, σ_e^2 , for the other environmental factors acting independently of genetic and developmental components. However, this article focuses on the developmental component as defined here, and so I ignore the other environmental factors. See Table 1 for list of variables and parameters.

Increase in heritability

Robustness reduces developmental variation

Robustness mechanisms tend to buffer developmental fluctuations and random perturbations within individuals. For example, new DNA damage or perturbations to cellular environments can increase the tendency for clonal expansions. Cell cycle checkpoints act as homeostatic robustness mechanisms that reduce developmental variation in cell growth rates.

From eqn 1, any homeostatic robustness mechanism that reduces the developmental variance, σ_d^2 , causes an increase in heritability when holding constant the genetic variance, σ_g^2 . However, I show in a later section that a decrease in σ_d^2 often decreases σ_g^2 . Evaluating the ultimate consequence of reducing developmental variability requires some analysis. It turns out that decreasing developmental variability does tend to increase heritability.

Robustness reduces deleterious effects

Robustness may raise heritability by reducing the effect of a potentially deleterious trait. For example, the heat shock protein Hsp90 helps amino acid sequences to fold properly into functional proteins. In

the absence of Hsp90, a particular sequence may misfold. In the presence of Hsp90, the same sequence may fold properly (Queitsch et al., 2002; Rutherford & Lindquist, 1998).

In general, as the deleterious effect of trait variants declines, the population will accumulate more genetic variation for that trait. For example, mutations leading to poorly folding amino acid sequences will be removed from the population relatively slowly when protected by the enhanced folding efficacy caused by Hsp90. Over time, the genetic variance, σ_g^2 , that causes poor folding in the absence of Hsp90 will increase (Queitsch et al., 2002; Rutherford & Lindquist, 1998).

Any robustness mechanism that reduces the deleterious effects of trait variation will have the same consequence of raising σ_g^2 . In eqn 1, as σ_g^2 rises, heritability increases when holding all else constant.

However, robustness mechanisms that reduce deleterious effects alter the relation between character values and fitness. To understand the full consequences, we must analyze how all variables respond evolutionarily to changes in robustness. In a later section, I show that reducing deleterious effects and increasing an individual's tolerance to character variation does typically raise heritability.

Heritability of disease

This section highlights properties of key variables and definitions to evaluate the heritability of disease. The following sections show how robustness increases the heritability of disease. All models focus on asexual haploid genetics to emphasize the main qualitative trends in the simplest way.

Offspring phenotype given parental phenotype

Phenotype is the sum of independent genetic and developmental components, written as $z = g + d$. Suppose those components have normal distributions, $g \sim \mathcal{N}(0, \sigma_g^2)$ and $d \sim \mathcal{N}(0, \sigma_d^2)$, so that $z \sim \mathcal{N}(0, \sigma_z^2)$, with $\sigma_z^2 = \sigma_g^2 + \sigma_d^2$.

To analyze the heritability of disease, we need to analyze progeny phenotype given parental phenotype. The first step is to describe the conditional distribution for the genetic value of the parent given its phenotype, $g|z$. From the derivation in the Supplementary Information (Frank, 2022), we obtain

$$g|z \sim \mathcal{N}\left(zh, \sigma_g^2(1-h)\right). \quad (2)$$

Progeny inherit their parent's genotype, $g|z$. For a progeny's phenotype given its parent's phenotype, the value is $y|z = g|z + d$, in which progeny developmental component, d , is independent of

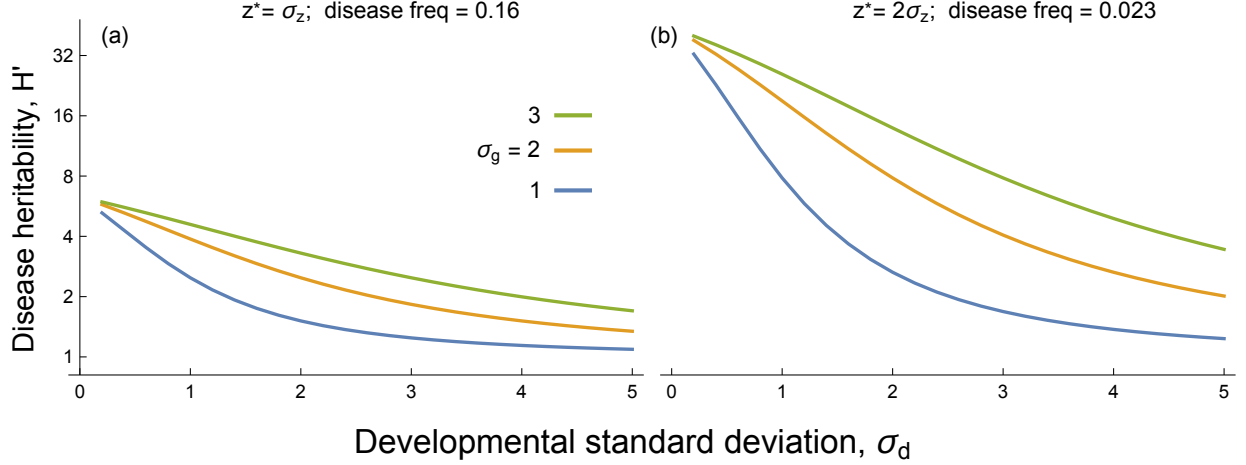


Figure 1: Robustness increases the heritability of disease. Typically, robustness tends to decrease developmental variance, σ_d^2 , increase genetic variance, σ_g^2 , and decrease the frequency of disease, D . The curves in both panels show the heritability of disease, H' , as the odds ratio of F , the probability that an offspring suffers disease given that its parent suffered disease, relative to D , the population-wide probability of disease. In all cases, any decrease in developmental variance, σ_d^2 , caused by robustness leads to an increase in the heritability of disease. The different colored curves in each panel show an increase in genetic variance from bottom to top. Any increase in genetic variance caused by robustness leads to an increase the heritability of disease. Panel (b) has a lower population-wide disease frequency than panel (a), because an increase in the phenotypic threshold for disease, z^* , associates with fewer individuals in the diseased upper tail of the phenotypic distribution. By setting the threshold to multiples of the phenotypic standard deviation, σ_z , the disease frequency is constant within each panel over the various values of genetic and developmental variance.

its inherited genetic value. Thus, the conditional distribution of progeny phenotype, y , given parental phenotype, z , is

$$y|z \sim \mathcal{N}\left(zh, \sigma_g^2(1-h) + \sigma_d^2\right). \quad (3)$$

Heritability of disease

Suppose any phenotype greater than z^* suffers disease. To simplify the analysis and without loss of generality, I limit disease to the upper tail of the phenotypic distribution. Let the familial measure of disease, F , be the probability that an offspring suffers disease, $y|z > z^*$, given that its parent suffered disease, $z > z^*$. Let the population-wide measure of disease, D , be the frequency of disease in the population, which is the probability that $z > z^*$. Define the heritability of disease as

$$H = \log_2\left(\frac{F}{D}\right), \quad (4)$$

which is \log_2 of the odds ratio of offspring disease given parent disease, F , relative to the baseline disease probability in the population, D . Alternatively, one can use the odds ratio directly

$$H' = 2^H = \frac{F}{D}, \quad (5)$$

as in Fig. 1. Here, I am using an odds ratio as a measure of parent-offspring similarity. Although the analysis of variance form in eqn 1 is the most commonly used expression for heritability, for the study disease or extreme phenotypes, the odds ratio provides a more useful expression for this particular analysis.

The definition, simple in concept, requires five calculations. The Supplementary Information (Frank, 2022) shows the derivation. Here, I emphasize the main steps. In the first step, the probability that $y|z > z^*$ is the upper tail above z^* of the distribution in eqn 3. In the second step, we weight the probability that $y|z > z^*$ by the probability that the parent's value is z and then sum over all parental values $z > z^*$. In the third step, we divide by the probability that $z > z^*$. These three steps give us F .

The fourth step sets the population-wide probability of disease, D , as the probability that $z > z^*$. The fifth step applies eqn 4 to obtain the \log_2 odds ratio of the probability that an offspring suffers disease given that its parent suffered disease, F , relative to the population-wide probability of disease, D .

We can express the calculations for F and D mathematically as

$$F = \left(\int_{z^*}^{\infty} s_1(z) f(z) dz \right) / D$$

$$s_1(z) = \int_{z^*}^{\infty} \phi(y|z) dy$$

$$D = \int_{z^*}^{\infty} f(z) dz,$$

in which the function $f(z)$ is the probability density of $\mathcal{N}(0, \sigma_z^2)$, and the function $\phi(y|z)$ is the probability density of the distribution given in eqn 3.

Robustness increases heritability of disease

The final value for the heritability of disease depends on the genetic and developmental variances, σ_g^2 and σ_d^2 , and on $z^* > 0$, the threshold phenotypic value to be classified as disease.

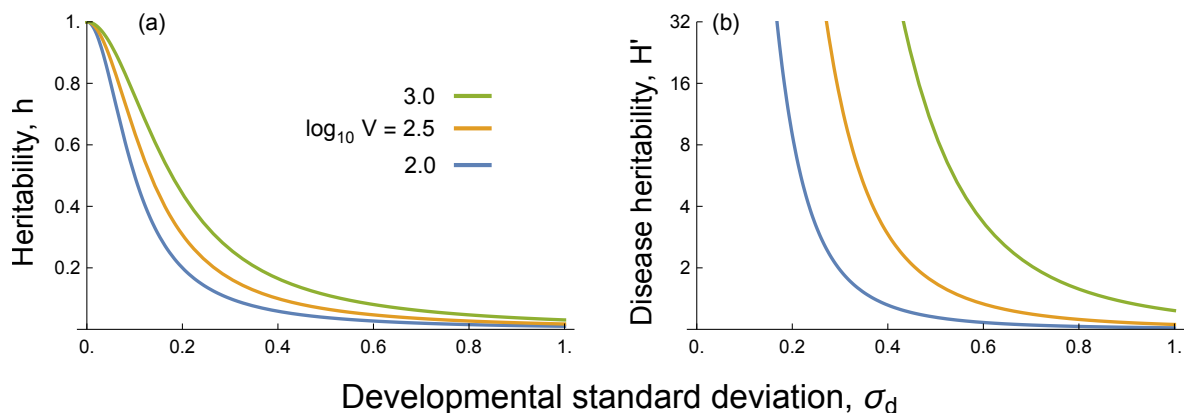


Figure 2: Evolutionary equilibrium accounting for interactions between variables. (a) The general heritability from eqn 9. (b) The heritability of disease, calculated by the steps outlined in the text and demonstrated in the Supplementary Information (Frank, 2022). Robustness causes decreasing developmental variance with decline in σ_d or weakening intensity of selection by tolerance with rising V . Either process increases heritability. For both panels, $c = 0.1$ and $\mu = 10^{-4}$. In (b), $\gamma = 0.9$.

Figure 1 shows how changes in one factor alter the heritability of disease when holding all other factors constant. Robustness may decrease developmental variance, increase genetic variance, or increase the phenotypic threshold for disease. The figure shows that any of these trends typically causes an increase in the heritability of disease when holding the other factors constant.

This partial analysis clarifies the components of the system. The following section considers how the various factors influence each other as they respond evolutionarily to changes in robustness.

Evolutionary feedback

Full analysis must consider how changes in one aspect of robustness or variation alter other components. Consider, for example, a robustness mechanism that provides greater tolerance for extreme phenotypes. Weakened selection increases the genetic variance, increasing the frequency of individuals with phenotypes above a threshold, z^* . However, with greater tolerance, the threshold z^* may no longer be the correct transition point to disease. Instead, the threshold shifts to a larger value.

How does robustness influence the heritability of disease when taking into account these feedbacks between the various key values? This section illustrates how to solve this problem. Each subsection considers a different robustness mechanism and its consequences.

Background

We need a few general definitions and results before turning to specific robustness mechanisms. To begin, define the fitness of a phenotype, z , as

$$w(z) = \exp\left(\frac{-z^2}{2V}\right). \quad (6)$$

This expression assumes stabilizing selection with a maximum at $z = 0$. Then we can write the expected fitness of an individual with genetic value g as

$$w|g = \int w(z)f(z|g)dz \propto \exp\left(\frac{-g^2}{2(V + \sigma_d^2)}\right),$$

in which $z|g \sim \mathcal{N}(g, \sigma_d^2)$ describes the developmental variation that determines the distribution of phenotype values, z , for a given genetic value, g , the function f is the probability density function, and ‘ \propto ’ denotes *proportional to*.

To relate the genetic variance, σ_g^2 , to the intensity of selection and the developmental variance, σ_d^2 , assume that the population is at mutation-selection balance. A classic model of mutation-selection equilibrium assumes that mutations causing a change in genetic value of $\pm c$ happen with frequency μ in each generation, and the selection intensity is set by the scaling of character value, c , and the denominator of the exponential that defines fitness (Kimura, 1965; Lande, 1975; Frank & Slatkin, 1990). For example, using $w|g$ for the fitness of genotypes, the selection intensity is $s = c^2/2(V + \sigma_d^2)$.

When mutation is stronger than selection, $g \sim \mathcal{N}(0, \sigma_g^2)$, with

$$\sigma_g^2 = c^2 \sqrt{\frac{\mu}{2s}} = \sqrt{c^2 \mu (V + \sigma_d^2)}. \quad (7)$$

This expression relates the genetic variance, the developmental variance, and the intensity of selection on phenotypes given by V . The Supplementary Information (Frank, 2022) provides details and also analyzes the case in which selection is stronger than mutation (Turelli, 1984; Frank & Slatkin, 1990).

Finally, we must consider how the threshold for disease, z^* , may change as evolution alters the other factors. I will assume that $z^* > 0$ is the phenotypic value at which fitness is $0 < \gamma < 1$, ignoring the symmetric point in the lower tail to keep things simple. Using $w(z)$, the value of z at which fitness is γ is

$$z^* = -\log(\gamma)\sqrt{V/2}. \quad (8)$$

Increase in tolerance of phenotypic variants

In eqn 6, an increase in V flattens the fitness surface and weakens selection for a given phenotypic deviation from peak fitness. Weakened selection associated with larger V increases the genetic variance (eqn 7). A rise in genetic variance enhances heritability. Using the equilibrium genetic variance in eqn 7, heritability is

$$h = \frac{\sigma_g^2}{\sigma_g^2 + \sigma_d^2} = \frac{\sqrt{c^2 \mu (V + \sigma_d^2)}}{\sqrt{c^2 \mu (V + \sigma_d^2) + \sigma_d^2}}, \quad (9)$$

which increases with a rise in V (Fig. 2a).

Decrease in developmental variance

Heritability increases with a decline in developmental variance because $dh/d\sigma_d^2 < 0$, as shown in the Supplementary Information (Frank, 2022). The magnitude of the decline in heritability will depend on the parameters c , μ , and V . From eqn 9, we can plot heritability versus developmental variance for different values of V , as shown in Fig. 2a.

Heritability of disease

Figure 2b shows that increasing robustness raises the heritability of disease. In particular, a greater tolerance of phenotypic variation, increasing V , and a homeostatic decrease in developmental variance, declining σ_d^2 , increase the heritability of disease. In Fig. 2b, the different component factors adjust to each other, leading to an evolutionary equilibrium, whereas in Fig. 1 each factor was changed holding the others constant. The same qualitative trends hold in the two cases.

Discussion

A good test would compare two populations. The more robust population would have greater tolerance for phenotypic variants or greater homeostatic reduction of developmental variants. The theory predicts that the more robust population would have greater general heritability of the tolerated or variant trait and greater heritability of disease.

I do not know of any existing data that provide such comparison. I mention a few promising candidates for future study.

Plant tolerance to herbivory and disease has been widely discussed (Simms & Triplett, 1994; Strauss & Agrawal, 1999; Monson et al., 2022). Many cases of phenotypic plasticity are considered within the context of tolerating environmental challenges (Pfennig, 2021). Comparison between populations or species that differ in tolerance may be interesting.

Microbial exodigestion arises when individual cells secrete enzymes (Zimmerman et al., 2013). When diffusion is sufficiently fast, local digestion depends on the average secretion rate per cell in the neighborhood, independently of the variation between cells. The developmental variation of secretion rate is robustly buffered by local averaging. By contrast, in viscous environments with slow diffusion, the effective neighborhood shrinks. Group averaging no longer buffers individual cellular variation (Frank, 2013).

Comparing fast versus slow diffusion, the fast diffusion situation favors greater heritability of secretion rate per cell and greater heritability of extreme phenotypic variants that may suffer reduced fitness, an expression of disease.

Protections against cancer seem to differ between species (Seluanov et al., 2018). Larger or longer-lived species may have greater protection for a given tissue. If so, then the heritability of disease may be greater in those species with greater protection. However, because the genetics of disease likely differs between such species, clarity about mechanism may be required to make a clear comparison.

Supplementary information

Two files are available online (Frank, 2022). The file `heritable.nb` provides a Wolfram Mathematica notebook that can be used to follow the steps in derivations and to evaluate alternative quantitative assumptions. A printed version of that notebook in the file `heritable.pdf` can be read without using the Mathematica software (Wolfram Research, 2022).

Acknowledgments

The Donald Bren Foundation, National Science Foundation grant DEB-1939423, and DoD grant W911NF2010227 support my research.

Conflict of interests

The author declares no conflicts of interest.

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Table 1: Definitions of key symbols and concepts

Symbol	Definition	Equation
σ_z^2	Total variance of the character, z	(1)
σ_g^2	Variance associated with genetic factors, g	(1)
σ_d^2	Variance associated with developmental factors, d	(1)
h	Heritability as the fraction of variance associated with genes	(1)
\mathcal{N}	Normal distribution with given mean and variance	(2)
$g z$	Offspring genetic value, g , given parent's phenotype, z	(2)
$y z$	Offspring phenotype, y , given parent's phenotype, z	(3)
z^*	Phenotypes $z > z^*$ suffer disease	(4)
F	Probability of offspring disease given parent disease	(4)
D	Population-wide probability of disease	(4)
H	\log_2 of family transmission, F , relative to baseline, D	(4)
H'	Heritability of disease as odds ratio, $2^{H'} = F/D$	(5)
$w(z)$	Fitness of phenotypic value, z	(6)
V	Inverse selection intensity when written as $d \log w/dz \propto 1/V$	(6)
s	An expression for selective intensity from several factors	(7)
μ	Mutation rate	(7)
c	Phenotypic change caused by a mutation	(7)
$1 - \gamma$	Fitness loss at disease threshold, z^*	(8)