The Population Genetics of Biological Noise

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Abstract

Information transmission is intrinsic to life, and noise is intrinsic to information transmission. Biological noise underlies some human diseases, but is also essential for the flexibility and plasticity of individual organisms and for their evolution. Recent technological advances in our ability to characterize many sources of biological noise have demonstrated that its amount is often heritable. Here, we treat the population genetics of all loci that influence the amount of biological noise. While analogous theory for heritable changes in mean trait values has been established for nearly a century, to our knowledge this is the first general treatment of the evolution of heritable changes in their statistical distributions. This represents a critical theoretical contribution to this important and rapidly growing domain of inquiry. It also sheds light on the hypothesis that natural selection can increase evolvability, and generalizes modifier theory used in the tradition of Feldman and colleagues.

Introduction

Information transmission is intrinsic to biology: during development, information from an offspring's inheritance informs its phenotype, and during reproduction, information flows to the next generations' inheritance (Figure 1A, Maynard Smith [1999]). But noise is inevitable. During development it results in stochastic fluctuations in biochemical, cellular and organismal phenotypes [Eling, Morgan, and Marioni 2019], and during reproduction it causes a newborn's inheritance to differ from that of its parent(s). Critically, while biological noise is random, its amount can be heritably influenced. For example, promoter alleles can differ in gene expression noise (e.g., Duveau et al. [2018]), and DNA polymerase alleles can differ in their fidelity of genome replication (e.g., Matic et al. [e.g. 1997]).

This raises the possibility that alleles that influence the amount of biological noise (hereafter, *noise alleles*) may in some cases be subject to natural selection [e.g. Viney and Reece 2013, Richard and Yvert 2014]. We might guess that biological noise is unconditionally deleterious [Sturtevant 1937, Wang and Zhang 2011], but it can also be beneficial [Tawfik 2010, Tsimring 2014]. Here, we present a simple model for the fitness effects of noise that captures both possibilities. Our model predicts the existence of an equilibrium amount of biological noise, the location of which depends on four factors: the rate of environmental change, the timescale of association between noise allele and induced phenotype, the form of selection, and population size. We argue that this result may be robust to model specifics, and conclude by connecting it to previous art.

Results

The distinction between developmental and reproductive noise (Figure 1A) motivates us to distinguish between *developmental* and *reproductive noise alleles*, which reside respectively at *developmental* and *reproductive noise loci*. Figure 1B schematically illustrates how developmental noise alleles influence phenotypic variation among offspring with identical inheritance. And Figure 1C shows how reproductive noise alleles affect random variation in inheritance among offspring of the same parent. (We assume throughout that variation in inheritance causes phenotypic variation.) Table 1 presents many mechanisms for both classes of biological noise.

Modeling the fitness effects of biological noise

Since the phenotypic consequence of biological noise is random, we introduce the stochastic model shown in Figure 2A. We assume a one-dimensional, normally distributed phenotype z:

$$z \sim N(z_0, \sigma^2_{phenotype}), \tag{1}$$

where $\sigma_{phenotype}$ is our proxy for the amount of phenotypic noise and z_0 is the organism's expected phenotype averaged over noise (equivalently, $z_0 = \mathbb{E}[z]$). Equation 1 is shown at the bottom of Figure 2A.

Following others [e.g. Charlesworth 2013], we next assume that fitness (r) drops quadratically in z from an optimal phenotype ($z_{optimum}$), written $r(z) = r_{optimum} - (z_{optimum} - z)^2$. Without loss of generality, we set the optimal phenotype $z_{optimum} = 0$. Thus, the fitness effect of a phenotypic perturbation to z in an organism with expected phenotype z_0 is

$$\Delta r(z, z_0) = r(z_0) - r(z) = z_0^2 - z^2. \tag{2}$$

These ideas are illustrated in the center of Figure 2A. Note that our model assumes that biological noise influences only a single phenotype that is sampled exactly once each generation. We address both assumptions in the Discussion.

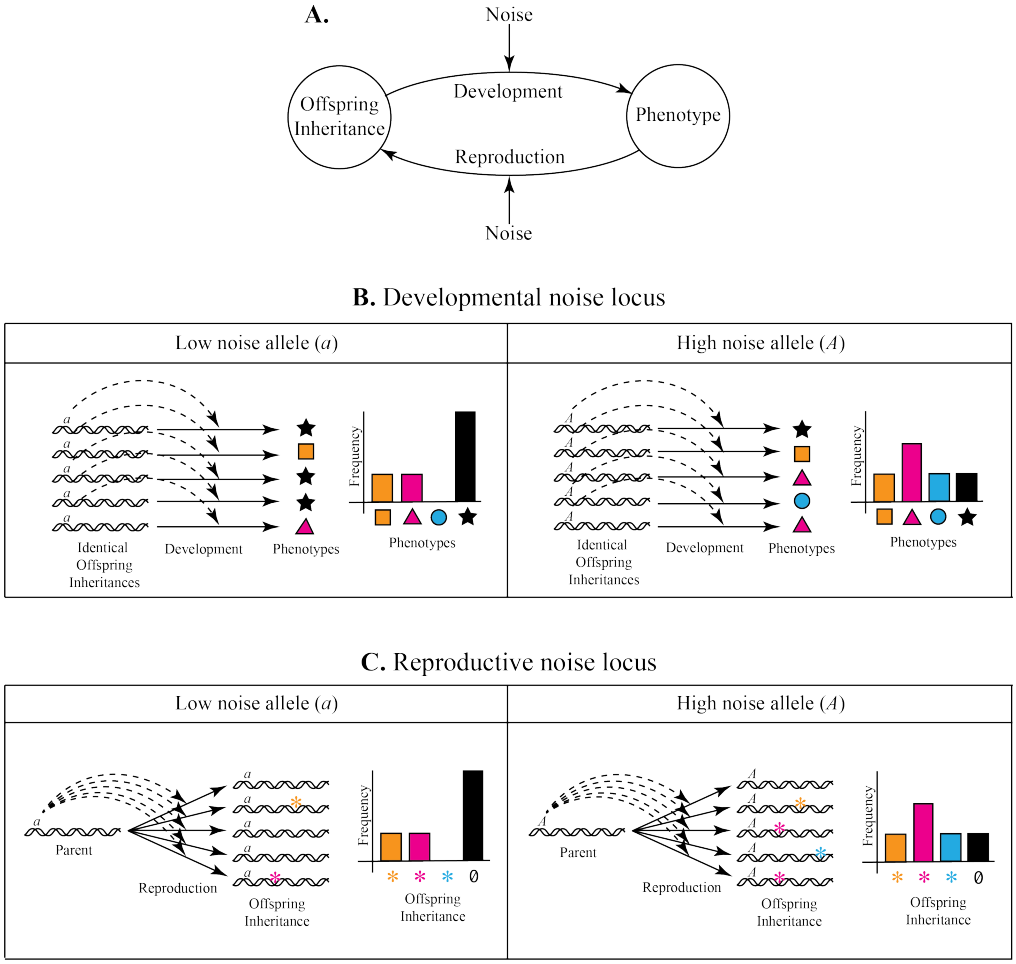

Figure 1: Classes and genetic control of biological noise **A.** During development, information flows from the offspring's inheritance to its phenotype, and during reproduction it flows back from the parent to the next generation's inheritance. This implies that biological noise can emerge during development or during reproduction, correspondingly implying two classes of genetic loci that influence the amount of biological noise. **B.** Holding environment constant, low and high developmental noise alleles (designated *a* and *A*) differentially influence the amount of phenotypic variation (represented by colored shapes) among offspring with identical inheritances. **C.** Again holding environment constant, low and high reproductive noise alleles (designated *a* and *A*) differentially influence the amount of variation among offspring inheritances (represented by colored asterisks) from a single parent.

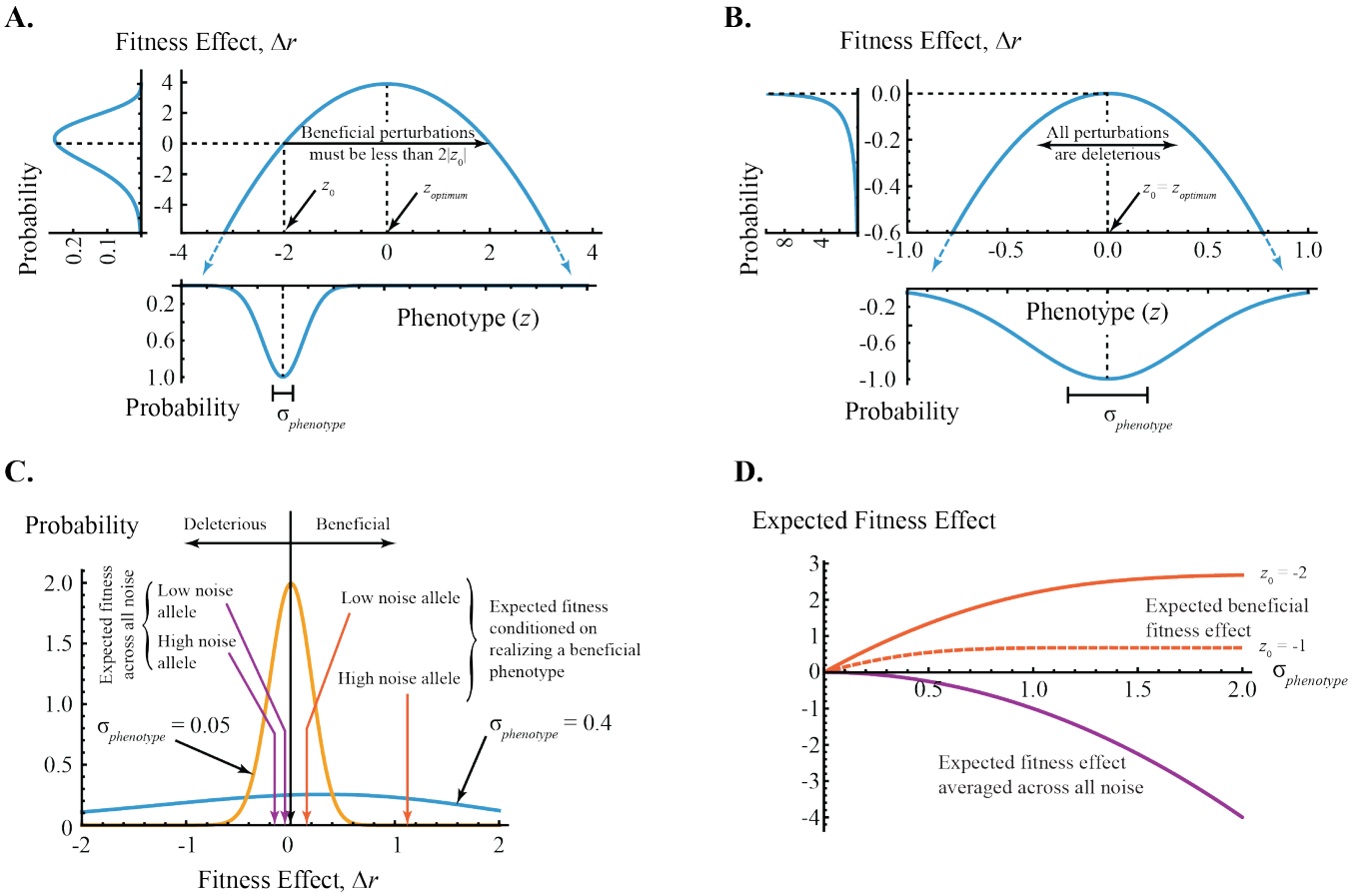

Figure 2: Fitness effects of phenotypic noise. **A.** Model introduced in text. Lower plot: Normally distributed phenotypic noise (Equation 1) with expectation $z_0 = \mathbb{E}[z] = -2$ and phenotypic noise $\sigma_{phenotype} = 0.4$. Center plot: Quadratic phenotype-to-fitness function (Equation 2). Without loss of generality we set the phenotypic fitness optimum $z_{optimum} = 0$. Left plot: resulting probability density function of fitness effects Δr (Equation A1 in Appendix). **B.** All phenotypic noise is deleterious if an organism's expected phenotype is at the fitness optimum ($z_0 = \mathbb{E}[z] = z_{optimum} = 0$). All other parameters as in panel A, though the x-axis has been rescaled for emphasis. **C.** The probability density functions of fitness effects induced by high (blue, $\sigma_{phenotype} = 0.4$, as in panel A) and low (orange, $\sigma_{phenotype} = 0.05$) noise alleles. All other parameters as in panel A, though the x-axis has been rescaled for emphasis. In expectation, noise is deleterious. This can be seen by comparing the two purple arrows with the vertical black arrow. But as noise goes up, so does the expected fitness effect of beneficial phenotypes. This can be seen by comparing two red arrows with the vertical black arrow. **D.** Expected fitness averaged over all phenotypes (purple, given by Equation A2; this is independent of expected phenotype z_0) and conditioned on beneficial phenotypes (red, Equation A3; shown for two values of expected phenotype) as a function of phenotypic noise ($\sigma_{phenotype}$). In the latter case, solid line correspond to the case when expected phenotype $z_0 = -2$ (as also shown in panels A and C) while dashed line show result when expected phenotype $z_0 = -1$.

Finally, the change-of-value technique (Appendix) yields an expression for the probability density function of fitness effects (Equation A1) for given expected phenotype (z_0) and phenotypic noise ($\sigma_{phenotype}$). Typical results are shown at the left of Figure 2A and B, and in 2C.

Biological noise is deleterious on average. In our model, all phenotypic perturbations larger than $2|z_0|$ are deleterious (Figure 2A), and since we assume that noise is symmetric in z, only half the remainder are beneficial. Moreover, for a given phenotypic perturbation less than $2|z_0|$, deleterious outcomes will be more deleterious than beneficial outcomes are beneficial. This effect, called Jensen's inequality [Jensen 1906], follows because fitness effect Δr is concave down. (Algebraically, in this case $\mathbb{E}[\Delta r(z,z_0)] < \Delta r(\mathbb{E}[z],z_0)$.) Thus on expectation, fitness goes down as noise goes up, an effect confirmed quantitatively by Equation A2 in the Appendix.

The limiting case is an organism at the phenotypic fitness optimum ($z_0 = \mathbb{E}[z] = z_{optimum}$). Here, all perturbations are deleterious (Figure 2B). Indeed, even in populations at equilibrium between natural selection, mutation, recombination, migration and demographic stochasticity within lineages (called *random genetic drift*), noise due to mutation, migration, or recombination is deleterious [Altenberg,

Liberman, and Feldman 2017]. This result is called the *reduction principle*, and we speculate that it generalizes to all sources of biological noise.

Noise can sometimes be beneficial. But while the fitness effect of noise averaged across all phenotypes goes down as noise goes up, in the more general case of an organism not at the phenotypic fitness optimum, increased noise also increases access to high fitness phenotypes. This can be seen by comparing the low noise and high noise probability density functions in Figure 2C. We quantify this by also computing the expected fitness effects conditioned on the realization of a beneficial phenotype (Equation A3 in the Appendix). As suggested at the outset, the tension between these *unconditioned* and *conditioned fitness expectations* (algebraically, $\mathbb{E}[\Delta r(z, z_0)]$ and $\mathbb{E}[\Delta r(z, z_0) \mid \Delta r(z, z_0) > 0)]$, respectively) is critical to understanding the evolutionary fate of noise alleles.

Figure 2D illustrates the dependence of both expectations on $\sigma_{phenotype}$ under our model. The expected fitness across all phenotypes (purple) goes down without limit as noise goes up (as per Jensen's inequality). Interestingly, this effect is independent of expected phenotype z_0 (Equation A2). In contrast, the conditioned expectation (red) goes up before approaching a plateau, although that plateau goes down as the expected phenotype approaches $z_{\text{optimum}} = 0$.

The equilibrium amount of biological noise

The two features of our model represented by the changing slopes of the purple and red lines in Figure 2D suggest the existence of an equilibrium amount of biological noise. From there, higher noise alleles will be selectively disfavored because their now more modest conditioned fitness advantage is more than offset by their greater unconditioned fitness cost. And at the same time, lower noise alleles will also be selectively disfavored, because their inability to capitalize on anomalously high fitness phenotypic realization is not offset by their reduced unconditioned fitness cost. We identify four determinants for the location of this equilibrium: the rate of environmental change, the timescale of association between noise alleles and the phenotypic perturbations they induce, the form of natural selection, and population size.

Rate of environmental change. Under our model, the scope for fitness improvement induced by biological noise goes down as an organism's expected phenotype z_0 approaches the phenotypic fitness optimum $z_{optimum} = 0$ (compare solid and dashed red lines in Figure 2D.) Now relaxing the assumption that the environment (and hence, the fitness function) is invariant in time, we imagine an evolving population as lagging behind its moving phenotypic fitness optimum in phenotypic space by an amount that goes up with the rate of environmental change. Thus, we predict that the equilibrium amount of biological noise similarly goes up with the rate of environmental change.

Timescales of phenotypic association. Indirect selection (Box 1) can only distinguish between segregating noise alleles in a population via whatever directly selected phenotypic differences they happen to have recently induced in their carriers. Thus, indirect selection's influence on the amount of biological noise in a population must somehow depend on the timescale of association (in organismal generations) between noise alleles and their resulting phenotypic perturbations. Put another way, indirect selection's efficacy will depend on the correlation between parent and offspring phenotype.

One limit is represented by the case of alleles that influence mutation rate in non-recombining organisms. These remain permanently associated with whatever phenotypic perturbations they cause via mutations elsewhere in the genome. Thus here, phenotypic correlation between parent and offspring is maximized, allowing indirect selection to distinguish between competing noise alleles until one reaches fixation and the other is lost. This is why high noise mutation rate alleles (or *mutators*) often reach fixation in asexual microbial populations evolving in novel lab environments [Sniegowski, Gerrish, and Lenski 1997, Giraud et al. 2001, Lamb et al. 2008, Raynes, Gazzara, and Sniegowski 2011, Swings et al. 2017, Bedhomme et al. 2019]. This also explains the converse observation: low noise mutation rate alleles (or *antimutators*) often reach fixation in asexual populations evolving in an environment to which they are already well adapted (Tröbner and Piechocki [1984], Giraud et al. [2001], McDonald et al. [2012], Wielgoss et al. [2013], Swings et al. [2017], though see Johnson et al. [2021]). (These two results are consistent with our prediction that the equilibrium amount of biological noise should be positively correlated with the pace of environmental change.)

At the other limit, consider a noise allele for which parent and offspring phenotypes are entirely uncorrelated. In this case Gillespie [1974] showed that indirect selection always disfavors high noise alleles. This follows because while still rare, the risk that the high noise allele is lost in the next generation as a consequence of sampling a deleterious phenotype is of much greater evolutionary significance than is the (one-generation) benefit of increased frequency as a consequence of its sampling a beneficial one.

In between these limits, the probability of success for a new high noise allele goes up with the timescale of association with its induced phenotypes [Carja and Plotkin 2017], since this allows indirect selection to "see" its occasionally beneficial phenotypic consequences for more generations. Thus, all else equal, we predict that the equilibrium amount of biological noise similarly goes up with the timescale of association.

This timescale is determined by two biological processes: the rate of dissociation between noise allele and induced phenotype (e.g., via recombination in the case of mutator alleles, Otto [2013]), and the lability of the induced phenotype itself. To illustrate this latter process, consider a locus in a single-celled organism that influences the variance in cellular concentration of some biomolecule. Now imagine an individual in which a high noise allele has induced a selectively favorable, anomalously high (or low) concentration of that molecule. While subsequent cell divisions will dilute such perturbations back toward its expectation, that decay will be roughly exponential, meaning that indirect selection

Box 1: Direct and indirect selection Classical population genetic models of natural selection disregard biological noise, instead assuming that any given allele has the identical phenotypic effect on every otherwise identical organism in which it appears. In this case, the fate of an allele can be modeled by recursively applying that effect to every descendant carrier in which it may appear [Graves and Weinreich 2017]. Extending earlier usage (e.g., Karlin and McGregor [1974], Otto [2013], Sniegowski et al. [2000]), we say that such alleles are under *direct selection*.

In contrast, noise alleles induce stochastic fitness perturbations in their carriers as a consequence of stochastic perturbations in phenotype. So two copies of the same noise allele may be regarded differently by natural selection. Again extending earlier usage (e.g., Karlin and McGregor [1974], Otto [2013], Sniegowski et al. [2000]), we say that such alleles are under *indirect selection*. (This is also sometimes called *second order selection*, e.g., Karlin and McGregor [1972], Tenaillon et al. [1999], Woods et al. [2011].) Indirect selection influences the frequency of any given copy of a noise allele in any generation via direct selection on whatever phenotype it happens to have most recently induced in the carrier. But critically, that effect can vary among carriers of the same noise allele.

Importantly, noise alleles can also be directly selected. For example, fitness in some RNA viruses depends in part on replication rate [Elena and Sanjuán 2005, Furió, Moya, and Sanjuán 2005]. Thus, an RNA polymerase allele that is faster because it lacks a proofreading activity can accelerate genome replication, thereby uniformly increasing fitness in all carriers. Such direct selection is independent of any indirect selection mediated by the phenotypic consequences of whatever additional mutations the error-prone polymerase introduces. Similarly, on the premise that misfolded proteins are metabolically or physiologically costly, alleles that reduce chaperone protein expression will be uniformly deleterious in all carriers. Again, this direct effect is independent of any indirect selection acting on the phenotypic consequences of a decrease in the proportion of misfolded proteins.

The distinction between direct and indirect selection goes back to Fisher [1932]. Following others [e.g. Feldman 1972, Karlin and McGregor 1974], here we simplify by assuming that noise alleles only experience indirect selection. Algebraically, this means we assume that cosegregating noise alleles only differ in $\sigma_{\text{phenotype}}$ and not in z_0. The interested reader is directed to Otto [2013] and Ferrare and Good [2024], who explicitly relax this assumption. See also Sniegowski and Murphy [2006], Deloupy et al. [2020], and Wagner [2022], who argue that this simplification may sometimes be biologically untenable.

will favor the high noise allele for a few cell generations. Similarly, transgenerational phenotypic plasticity in multicellular organisms often persists for several generations after the environmental cue (reviewed in Bell and Hellmann [2019]), again offering indirect selection a reliable signal with which to distinguish between competing noise alleles.

Finally, recall that the number of generations from appearance to fixation of a directly selected beneficial mutation is roughly the reciprocal of its fitness advantage [Desai and Fisher 2007]. Thus, indirect selection's capacity to favor high noise alleles is maximized as soon as phenotypic association times are at least that long.

The form of selection. Results thus far have assumed fitness-proportional selection, meaning that the probability that an organism contributes to the next generation is proportional to its fitness in the current one. But other effects are possible. For example, when males compete for reproductive access to females, all individuals that exceed some phenotypic threshold can have an equal probability of contributing to the next generation. This is called truncation selection, and it emerges in many biological situations (reviewed in Kolodny and Stern [2017], Morsky and Bauch [2019]).

Interestingly, Kolodny and Stern [2017] showed that truncation selection can cause indirect selection to favor high noise alleles even if phenotypes are resampled every generation. In this case, individuals contributing to the next generation will include carriers of high noise alleles that happen by good luck to have sampled a phenotype above the threshold, even if their expected phenotype is below that value. Put another way, truncation selection reduces the fitness penalty induced by high noise alleles. Indeed, even less extreme departures from fitness-proportional selection can be sufficient to favor high noise alleles in the absence of any persistent association with induced phenotype [Kolodny and Stern 2017]. Consequently, we predict that the amount of noise expected at the selective equilibrium will go up as selection goes from fitness-proportional toward truncation.

Population size. For a population at its phenotypic fitness optimum, all noise is deleterious (Figure 2B). And since the strength of random genetic drift scales inversely with population size [Fisher 1930, Wright 1931], in this case we predict that the equilibrium amount of noise should go down as population size goes up. This is Lynch's *drift barrier* hypothesis, [Lynch et al. 2016]), which is consistent with the pattern observed for mutation rate across cellular life ($r^2 \approx 0.8$, [Lynch 2010]). The analogous signal is weaker for single-point transcription [Meer et al. 2020, Li et al. 2023] and splicing [Saudemont et al. 2017] error rates. Though we might not be surprised: the consequence of mutational noise are transmitted to all offspring, whereas transcription and splicing noise only affect the products of individual mRNA molecules.

Importantly, the picture is more complicated in the general case of populations not at the phenotypic fitness optimum, because some stochastic phenotypic fluctuations are now beneficial (Figure 2A, C). The strength of random genetic drift still goes down as population size goes up, and assuming that most phenotypic perturbations are deleterious, indirect selection against high noise alleles will be the first effect to overcome drift [Raynes, Burch, and Weinreich 2021]. Thus we still predict a drift barrier effect in populations of moderate size. But as population size continues to increase, the strength of indirect selection in favor of high noise alleles will eventually come to exceed both random genetic drift and indirect selection against them [Raynes, Burch, and Weinreich 2021]. Thus, we predict that at above some critical population size, the equilibrium amount of noise will go up with population size.

This non-monotonicity in the direction of selection acting on noise alleles is called *sign inversion* [Raynes et al. 2018]. It emerges from the double-edged nature of biological noise and has been observed in several systems [Masel 2005, King and Masel 2007, Whitlock et al. 2016, Raynes et al. 2018, Raynes and Weinreich 2021, Zhou and Xue 2022, Polizzi et al. 2024, Weissman et al. 2025]. We speculate all noise alleles will exhibit sign inversion in populations not at their phenotypic fitness optimum.

Discussion

Our treatment of the population genetics of biological noise is predicated on an intrinsic tension between the beneficial phenotypes that noise occasionally induces and its much more common, deleterious consequences. We have argued that for any biological mechanism susceptible to noise, there will exist an equilibrium amount at which these opposing effects are precisely balanced. This result depends on the distinction between direct and indirect selection (Box 1), which is also central to two other active domains of intellectual inquiry.

First, indirect selection is central to theory that explores the evolution of *evolvability*, a population's capacity to generate heritably adaptive phenotypic variants [Wagner and Altenberg 1996, Burch and Chao 2000, Sniegowski and Murphy 2006, Masel and Trotter 2010]. More specifically, the distinction between evolvability-as-byproduct and evolvability-as-adaptation [Sniegowski and Murphy 2006, Lynch 2007] is equivalent to the distinction between direct and indirect selection acting on evolvability. Critically however, evolvability-as-adaptation arguments risk teleological critiques, since an evolving population cannot "anticipate" what phenotypes are likely to be beneficial in the future [e.g. Weber 1996, Sniegowski and Murphy 2006, Pigliucci 2008, Paaby and Testa 2018].

Reframing the problem of indirect selection on evolvability in terms of biological noise appears to resolve this concern, since noise is inherently a double-edged sword. As we have shown, indirect selection increases biological noise only when increasing the population's capacity to generate adaptive phenotypic variants (i.e., its evolvability) outweigh the concomitant cost of generating deleterious variants. Otherwise, indirect selection will reduce biological noise because this reduction in the population's capacity to generate deleterious phenotypes (what might be called its *antievolvability*) now outweighs the possibility of generating adaptive phenotypes.

Indirect selection is also fundamental to a body of evolutionary literature called *modifier theory*. This work be-

gins from the observation that population genetic parameter values such as mutation and recombination rate are genetically encoded, mutable, and thus can evolve. Modifier theory dates to the 1960s [Nei 1967, Karlin and McGregor 1972, Feldman 1972], and the field remains quite active [e.g. Masel 2005, Altenberg, Liberman, and Feldman 2017, Baumdicker, Sester-Huss, and Pfaffelhuber 2020, Zhou and Xue 2022]. Importantly, all previously examined modifier models can be seen to influence biological noise (Table 1), and we speculate that the population genetics of biological noise developed here generalizes modifier theory. Moreover, our focus on mechanisms of noise rather than on parameter values in population genetic models suggests that modifier theory may be much more broadly applicable than previously appreciated. These ideas will be explored in a forthcoming contribution.

Importantly, our model makes several strong assumptions. For example, in contrast to Figure 2, noise alleles can have multidimensional phenotypic consequences, such as when they influence the pleiotropic effects of mutations [Draghi and Wagner 2008, Pavlicev, Cheverud, and Wagner 2011, Watson and Szathmáry 2016, Do O and Whitlock 2023]. Moreover, regardless of dimensionality, we have limited intuition for the distribution of fitness effects of phenotypic noise. And experimental access to these distributions is difficult for most of the mechanisms in Table 1, though surveys of the distribution of mutational fitness effects are one exception [e.g. Eyre-Walker and Keightley 2007, Firnberg et al. 2014, Kemble, Nghe, and Tenaillon 2019].

Nevertheless, our prediction of an equilibrium amount of biological noise may be quite robust to model specifics. First, the existence of a nearby optimum on the fitness function appears to us to be sufficient for the conditioned, beneficial effect of noise to approach a plateau as noise goes up. Second, recent work on mutational interactions reveals that as fitness goes up, the advantage of beneficial mutations often decline while the costs of deleterious mutations go up (reviewed in Johnson, Reddy, and Desai [2023], Diaz-Colunga et al. [2023]). By Jensen's inequality, such negative curvature in the phenotype-to-fitness function is sufficient to cause the unconditioned fitness of noise alleles to go down with noise. It remains to be seen whether the fitness function induced by other forms of biological noise also exhibit negative curvature, although there are principled reasons to suppose that they may [Meiklejohn and Hartl 2002, Wang and Zhang 2011, Cotto and Day 2023, Lo et al. 2024]).

Another critical issue outside our treatment is the interplay between the rate of environmental variation and that of organismal development. Our model assumes that organisms sample phenotypes once in their lifetime. However, physiology can change depending on the environment, and development is not an instantaneous process. So noise may influence phenotype (and thus fitness) more than once during an individual's lifetime. This is perhaps especially important in long-lived organisms with distinct developmental phases. Moreover, the distributions from which these perturbations are sampled can themselves vary over an organism's lifetime [e.g. Bulté and Bennoun 1990, Dupont et al. 2024]. Similarly, in multicellular organisms developmental noise can be sampled independently across cells [Bravo, Belkhir, and Paget-Bailly 2024] or cell types [Wolf et al. 2023]. It appears plausible that if the environment varies substantially within a generation, changes in the phenotype may magnify the evolutionary importance of developmental noise alleles, but much work remains to be done in this area.

The population genetics of alleles that influence mean trait values have been well established for almost a century. Here we propose an original framework for understanding the population genetics of alleles that influence the amount of biological noise around those means. This work is extremely timely because technological advances are revolutionizing empirical access to this phenomenon at the cellular, subcellular and molecular levels (Table 1). We are optimistic that the ideas introduced here will soon lead to a much deeper understanding of the forces responsible for observed levels of biological noise in nature.

Acknowledgments

This work emerged from a graduate seminar at Brown University that DMW taught during the spring semester of 2020, and we thank Nigel Anderson, Alan Denadel, Gabriella Ferra, Lourdes Gomez, Jiaying Lai, Robert Lamb, Miles, David Morgan, Chibuikem Nwizu, Maya Weissman and Hannah Weller for early contributions. Guillaume Achaz, Christina Burch and Ricardo Azevedo provided several trenchant suggestions late in the writing. DMW is grateful for financial support from the Brown University Faculty Research Fund during his Fall 2024 sabbatical in Montpellier, France, during which much of this work was completed. He also acknowledges space and intellectual support during that visit from the *Équipe Génétique et Écologie Évolutive* at the *Centre d'Écologie Fonctionnelle et Évolutive* in Montpellier, and by members of the *Maladies Infectieuses et Vecteurs: Écologie, Génétique, Évolution et Contrôle* laboratory in Montpellier. IGB was supported by the European Union's Horizon 2020 Research and Innovation Program (ERC-CoG-647916).

Author Contributions

DMW conceived the idea for this manuscript, DMW, CP, TS, YR and IGB developed the conceptual framework, DMW wrote and solved the model, and DMW, CP, TS and IGB wrote the manuscript. DMW, CP, HB, EC, and SR conducted the literature review.

Competing interests

The authors declare no competing interests.

Table 1: Mechanisms and Consequences of Biological Noise

Mechanism	Consequence	Representative citations
	Noise introduced during development[1]	
Gene expression noise	Variation in RNA or protein number among genetically identical cells over time or space	Hill, Vande Zande, and Wittkopp [2021], Hansson [2025]
Protein sequence variation[2]	Variation in protein sequence among genetically identical cells over time or space	Drummond and Wilke [2009], Evans et al. [2018]
Enzyme promiscuity[3]	Variation in substrate binding affinity and/or catalytic rate.[4]	Copley [2017]
Protein fold-switching	Heterogeneity in protein structure over time or space[5]	Porter [2023]
Network topology[6]	Variation in network dynamics	Bruggeman and Teusink [2018]
Environmental robustness[7]	Limited phenotypic response to environmental variation	Gursky, Surkova, and Samsonova [2012]
Phenotypic plasticity[8]	Distinct phenotypic responses in response to environmental cues	Paaby and Testa [2018]
Seasonal migration[9]	Variation in environmental conditions encountered	Winger et al. [2019]
	Noise introduced during reproduction	
Genetic mutation[10]	Genetic variation among offspring from a single parent	Sniegowski et al. [2000]
Mendelian segregation[11]	Genetic variation among genotypes from a single parent	Chasnov [2000]

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[1]Includes physiological noise in single-celled organisms

[2]Includes mis-transcription, post-transcriptional modification, tRNA-charging errors, mis-translation and post-translational modification.

[3]We follow Copley [2017] and restrict the term to enzymes that also catalyze physiologically irrelevant secondary reactions. We thus distinguish between promiscuous enzymes and those with broad, physiologically important substrate specificity.

[4]Structural proteins can also exhibit binding promiscuity [Rebeiz et al. 2011, Atkins 2015].

[5]Also called metamorphic proteins [Murzin 2008] or extant fold-switching [Porter and Looger 2018], this effect is closely related to evolved fold-switching (e.g., Chakravarty et al. [2023]), in which alternative fold structures come to be separated by only very few mutations. However, evolved fold-switching means that the local fitness landscape experienced by an evolving population has evolved. Put another way, the evolution of fold-switching influences the distribution of mutational fitness effects and is thus a modifier of reproduction.

[6]Single-cell systems biology has clarified how different network motifs influence the amount of noise in a network's behavior [Cağatay et al. 2009], and these ideas may apply equally to gene regulation networks, cell signaling networks, metabolic networks, and ecological networks.

[7]Or environmental canalization. Often in opposition to diversified bet hedging.

[8]Following others (e.g., Simons [2011]), we restrict phenotypic plasticity to cases where environmental cues trigger specific phenotypic responses, sometimes also described by norms of reaction. We thus distinguish phenotypic plasticity from random environmentally triggered phenotypic perturbations such as diversified bet hedging (previous). Transgenerational phenotypic plasticity is sometimes realized via mechanisms of non-genetic inheritance outlined above [Bell and Hellmann 2019]. Thus, it is a form of Lamarkian inheritance of acquired phenotypes.

[9]Modifiers of dispersal increase variation in environment experienced, while modifiers of seasonal migration reduce variation in environment experienced.

[10]DNA polymerase alleles can also vary in mutational bias, e.g. Couce, Guelfo, and Blázquez [2013], Serero et al. [2014], Melde, Bao, and Sharp [2022], Sane et al. [2023], sometimes with evolutionary consequences [Couce and Tenaillon 2019]. See also Tenaillon and Matic [2020] for cases where mutation and recombination rates can be tuned locally. Vertebrate immunity loci and microbial contingency loci [Moxon, Bayliss, and Hood 2006] have similar properties. Finally, mitotic mutations introduce developmental noise.

[11]We distinguish between modifiers of Mendelian segregation and modifiers of recombination rate (next). Mendelian segregation incurs many of the direct fitness costs of sex

Mechanism	Consequence	Representative citations
Chromosomal crossover[12]	Genetic variation among gametes from a single parent	Otto and Lenormand [2002], Becks and Agrawal [2010]
Segregation distortion[13]	Allelic variation among gametes from a single parent	Hartl [1975]
Bias in genetically determined sex ratio	Variation in sex among offspring from a single parent	Fisher [1930], Otto [2013]
DNA methylation and histone modification	Epigenetic variation among offspring from a single parent	Pujadas and Feinberg [2012]
Cytoplasmic inheritance[14]	Variation in cytoplasmic content of daughter cells produced by a single mitosis	Ackermann et al. [2007]
Other forms of non-genetic inheritance	Fidelity of vertical transmission of somatic (including prions, and the microbiomes of plants and animals), nutritional, environmental and learned behavioral features of an organism	Bonduriansky and Day [2009], Henry et al. [2021]
Ploidy	Genetic variation among genotypes from a single mating; also influences dominance coefficients acting on mutations.	Raynes and Weinreich [2021]
Proportion of time each generation spent in the haploid phase	Proportion of time each generation during which mutations are subject to haploid selection	Otto and Gerstein [2008]
Assortative mating	Proportion of individuals in which mutations are subject to homozygote selection	De Cara, Barton, and Kirkpatrick [2008]
Distribution of fitness effects[15]	Variation in fitness effects of mutation	Ferrare and Good [2024]
Epistasis[13]	Variation in fitness effect of an allele as a function of alleles elsewhere in the genome	Liberman and Feldman [2006]
Dominance[13]	Variation in fitness effect of an allele as a function of the allele at homologous locus elsewhere in the genome	Fisher [1928], Otto [2013]
Pleiotropy	Variation in phenotypic consequence of a single mutation	Draghi and Wagner [2008], Pavlicev, Cheverud, and Wagner [2011]
Dispersal[16]	Variation in environment experienced by offspring from a single parent	Balkau and Feldman [1973]

including that of finding mates, risk of predation and disease, and the 2-fold cost of sex (e.g., Otto and Lenormand [2002]).

[12]Unlike modifiers of Mendelian segregation (previous), modifiers of recombination rate influence the probability of recombination between loci, which can occur in haploids as well as in obligate sexual diploids. Direct costs here include the energetic costs of meiosis (e.g., Otto and Lenormand [2002]).

[13]Complicated by the fact that these alleles are also intrinsically directly selected.

[14]It is perhaps formally interesting to notice that with cytoplasmic segregation, increasing asymmetry increases noise, whereas in the case of genetic segregation distortion (above), increasing asymmetry reduces noise. In the present case, transmission is zero-sum: one daughter cell inherits whatever the other does not. Whereas with genetic segregation, asymmetry means increasing the number of copies of the driver allele in the population.

[15]These includes modifiers of mutational robustness, genetic (de)canalization, and evolutionary capacitors. More abstractly, this class of modifier loci can cause populations to systematically move across the fitness landscape in response to indirect selection, i.e., to cause the local fitness landscape experienced by an evolving population to evolve (e.g., Wilke et al. [2001] but see also Archetti [2009]).

[16]Modeled as a per-generation probability of migration m; an environment is heritable for $1/m$ generations. In contrast, modifiers of seasonal migration act within generations.

Appendix

If phenotype $z \sim N(z_0, \sigma^2)$ (Equation 1) and fitness effect $\Delta r(z, z_0) = z_0^2 - z^2$ (Equation 2), we first find the probability density function for fitness effects $\Delta r(z)$:

$$f_{\Delta r}(\Delta r; z_0, \sigma) = \frac{\mathrm{e}^{-\frac{(-\sqrt{z_0^2-\Delta r}-z_0)^2}{2\sigma^2}} + \mathrm{e}^{-\frac{(\sqrt{z_0^2-\Delta r}-z_0)^2}{2\sigma^2}}}{2\sqrt{2\pi}\sigma\sqrt{|\Delta r + z_0^2|}}. \tag{A1}$$

This yields the expected fitness effect over all phenotypic perturbations:

$$\mathbb{E}[\Delta r(z_0, \sigma)] \equiv \int_{-\infty}^{r(0,z_0)} f_{\Delta r}(\Delta r; z_0, \sigma)\Delta r \mathrm{d}\Delta r = -\sigma^2. \tag{A2}$$

(Recall that without loss of generality we set $z_{\text{optimum}} = 0$, making $r(0,z_0)$ the appropriate upper limit of integration.)

Finally, the expected fitness effect conditioned on a beneficial phenotype reads

$$\mathbb{E}[\Delta r(z_0, \sigma)|\Delta r(z_0, \sigma) > 0] \equiv \frac{\int_0^{r(0,z_0)} f_{\Delta r}(\Delta r; z_0, \sigma)\Delta r \mathrm{d}\Delta r}{\int_0^{r(0,z_0)} f_{\Delta r}(\Delta r, z_0, \sigma)\mathrm{d}\Delta r}$$
$$= \frac{2|z_0|\sqrt{\frac{2}{\pi}}\sigma + (z_0^2 + \sigma^2)\left(\mathrm{Erf}\left[\frac{z_0-|z_0|}{\sqrt{2}\sigma}\right] - \mathrm{Erf}\left[\frac{z_0+|z_0|}{\sqrt{2}\sigma}\right]\right)}{\mathrm{Erf}\left[\frac{|z_0|\sqrt{2}}{\sigma}\right]} + z_0^2. \tag{A3}$$

Methods

Equation A1 was found using the change-of-value technique, shown here. All calculations were performed in Mathematica, as was the production of Figure 2. That code is available here under GNU General Public License (GPLv3), and can be examined with the free Wolfram Player application. Equations A1-A3 match simulation results developed in MatLab (not shown; available on request from daniel_weinreich@brown.edu).

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