The Adaptive Potential of Nonheritable Somatic Mutations

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ABSTRACT: The adaptive potential of nonheritable somatic mutations has received limited attention in traditional evolutionary theory because heritability is a fundamental pillar of Darwinian evolution. We hypothesized that the ability of a germline genotype to express a novel phenotype via nonheritable somatic mutations can be selectively advantageous and that this advantage will channel evolving populations toward germline genotypes that constitutively express the phenotype. We tested this hypothesis by simulating evolving populations of developing organisms with an impermeable germline-soma separation navigating a minimal fitness landscape. The simulations revealed the conditions under which nonheritable somatic mutations promote adaptation. Specifically, this can occur when the somatic mutation supply is high, when few cells with the advantageous somatic mutation are required to increase organismal fitness, and when the somatic mutation also confers a selective advantage at the cellular level. We therefore provide proof of principle that nonheritable somatic mutations can promote adaptive evolution via a process we call "somatic genotypic exploration." We discuss the biological plausibility of this phenomenon as well as its evolutionary implications.

Keywords: somatic mutations, Weissman, evolutionary theory, development, adaptive landscape, multilevel selection.

Introduction

During the development of most animals, an early distinction occurs between the germline (the population of cells that are fated to differentiate into gametes) and the soma (the cells composing the rest of the body). August Weismann (1893) noted that any variation arising in the soma during the lifetime of an organism would be temporary and nonheritable because it would not be present in the reproductive cells. The nonheritability of somatic variation weakened Lamarckian arguments concerning the role of acquired variation in adaptation and set the stage for a neo-Darwinian take on evolution (Mayr 1985; Morange 2017). Within this paradigm, the somatic organism came to be viewed as a mere "excrescence" (Bergson 1907) or a "dead-end replicator" (Dawkins 1982), and the nonheritable genetic variation arising in it as an evolutionary cul-de-sac (Dawkins 1982; Buss 1983*b*; Otto and Hastings 1998; Jablonka and Lamb 2005). Consequently, studies of somatic mutation in animal evolution mainly focused on their deleterious consequences at the level of the organism in which they arise, such as in cancer and senescence (Medawar 1957; Cairns 1975; Kirkwood 1977; Kirkwood and Rose 1991; Kennedy et al. 2012; Erten and Kokko 2020), and on the evolutionary dynamics of tumors (Greaves and Maley 2012).

Somatic mutations are ubiquitous, thus effectively making multicellular organisms a genetic mosaic (Reusch et al. 2021), and more often than not these mutations are harmless (De 2011; Martincorena and Campbell 2015; Yizhak et al. 2019; Wijewardhane et al. 2021). Somatic mutations are detected at different frequencies within the soma, partly depending on whether they arise early or late during development (Behjati et al. 2014; Ju et al. 2017; Lee-Six et al. 2018; Osorio et al. 2018) and partly because of the selective competitiveness of mutant cells (Martincorena and Campbell 2015; Martincorena et al. 2018*a*; Martincorena et al. 2018*b*; Lawson et al. 2020), meaning that somatic mutations can increase in frequency within the body when they confer a higher proliferative potential or lower mortality to the cells carrying them (Hanahan and Weinberg 2011). Although the clonal expansion resulting from this somatic selective process is one of the characteristics of the evolutionary dynamics of cancers (Greaves and Maley 2012), positive selection of cells with somatic mutations can also occur

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without causing any apparent disease phenotypes in the tissues containing the mutant cells (Martincorena and Campbell 2015; Martincorena et al. 2015, 2018*b*; Yizhak et al. 2019; Colom et al. 2020; Lawson et al. 2020).

In some cases, somatic mutations are beneficial not only for individual cells but also for the entire multicellular organism. A classic example is the adaptive immune system of jawed vertebrates, in which somatic mutants are selected within the body based on their affinity to the pathogens they help deter (Burnet 1976; Tonegawa 1976). Somatic mutations can be beneficial in other physiological contexts as well, such as in the liver, where they can promote regeneration after injury, protect against toxins, and prevent malignant transformation (Zhu et al. 2019). They can also ameliorate the consequences of deleterious mutations that cause hematopoietic diseases (Revy et al. 2019) or serious developmental syndromes (Bar et al. 2017). In such cases, somatic mutations may facilitate the persistence of deleterious germline mutations by buffering their negative effects on organismal fitness until a compensatory or reversion mutation arises in the germline (De 2011).

Research on the evolutionary consequences of somatic variation that is beneficial above the cellular level has mainly focused on plants (Whitham and Slobodchikoff 1981; Antolin and Strobeck 1985; Gill et al. 1995; Schoen and Schultz 2019; Cruzan et al. 2020) as well as other modular organisms, such as corals (Van Oppen et al. 2011) and red algae (Monro and Poore 2009). However, somatic variation in these taxa may be partly heritable, either because there is a blurry germline-soma distinction or because they can reproduce clonally (Buss 1983*a*; Leria et al. 2019; Cruzan et al. 2020; Yu et al. 2020; Reusch et al. 2021). Here, we argue that there is also evolutionary potential in somatic variation that is strictly nonheritable. Indeed, if nonheritable somatic mutations can confer a fitness advantage to the organism carrying them, selection can act on the potential to acquire such mutations, as evidenced by the evolution of mechanisms that direct or intensify the production of somatic genetic variation, such as the molecular processes driving the recombination and mutagenesis of genes involved in the adaptive immune system (Odegard and Schatz 2006; Müller et al. 2018) and the somatic activation of transposable elements (McClintock 1950; Singer et al. 2010). These mechanisms tend to target specific genomic regions and function in specialized cell types, and what ultimately gets selected is the mechanisms producing the somatic mosaicism rather than the somatic mutant genotypes themselves (Whitham and Slobodchikoff 1981; Caporale 2000; Jablonka and Lamb 2005; Singer et al. 2010; Müller et al. 2018).

Here, we envision a complementary general model in which adaptation is facilitated by selection acting on genotypes with a potential to acquire nonheritable somatic mutations that are beneficial to the organism, even in the absence of a mechanism to intensify somatic diversity. Given the sheer number of cells in the soma and their increased mutation rates relative to the germline (Lynch 2010; Murphey et al. 2013; Milholland et al. 2017; Moore et al. 2020), we reason that beneficial mutations often first arise in the soma. Similar to so-called phenotypic mutations (Whitehead et al. 2008), which arise because of errors in transcription or translation, nonheritable genotypes that are similar in sequence to a heritable beneficial genotype may occasionally confer the fitness benefit of the heritable beneficial genotype to an organism via somatic mutation. Placing this model in the context of an adaptive landscape (Wright 1932), the germline genotype can be one or more mutations away from an adaptive peak, and somatic mutations can confer a fitness benefit to an organism by producing nonheritable beneficial genotypes that are closer to or atop the adaptive peak. This can cause a smoothing of the fitness landscape (Frank 2011; Van Egeren et al. 2018), which may promote adaptation toward an adaptive peak by increasing the probability that the beneficial mutation arises as a germline variant. This is because precursor genotypes that are near the adaptive peak are more likely to be selected, as they exhibit a positive epistatic interaction with somatic mutations, thus increasing their frequency in the population relative to genotypes that are farther away from the peak. We thus hypothesize that nonheritable somatic mutations causing a fitness advantage may channel evolving populations toward adaptive peaks, thus promoting adaptation.

Results

Model Overview

To study the potential of nonheritable somatic mutations to promote adaptation, we modeled an evolving population of N multicellular organisms with an impermeable germline-soma separation navigating a minimal fitness landscape. We used a haploid two-locus, two-allele model with alleles a and A for the first locus and b and B for the second locus to represent a landscape with a single adaptive peak at genotype AB, which confers a selective advantage s_{organism} to the organism relative to the other genotypes in the landscape (fig. 1*A*; "Methods"). We simulated evolution with nonoverlapping generations, starting from an initial population composed exclusively of organisms with the ab genotype. Each generation consisted of a developmental phase followed by a reproductive phase (fig. 1*B*; "Methods"). In the developmental phase, the soma of each individual developed from a single cell with a given zygotic genotype in D developmental cycles until reaching the final somatic size of 2^D cells. For each cell division, somatic

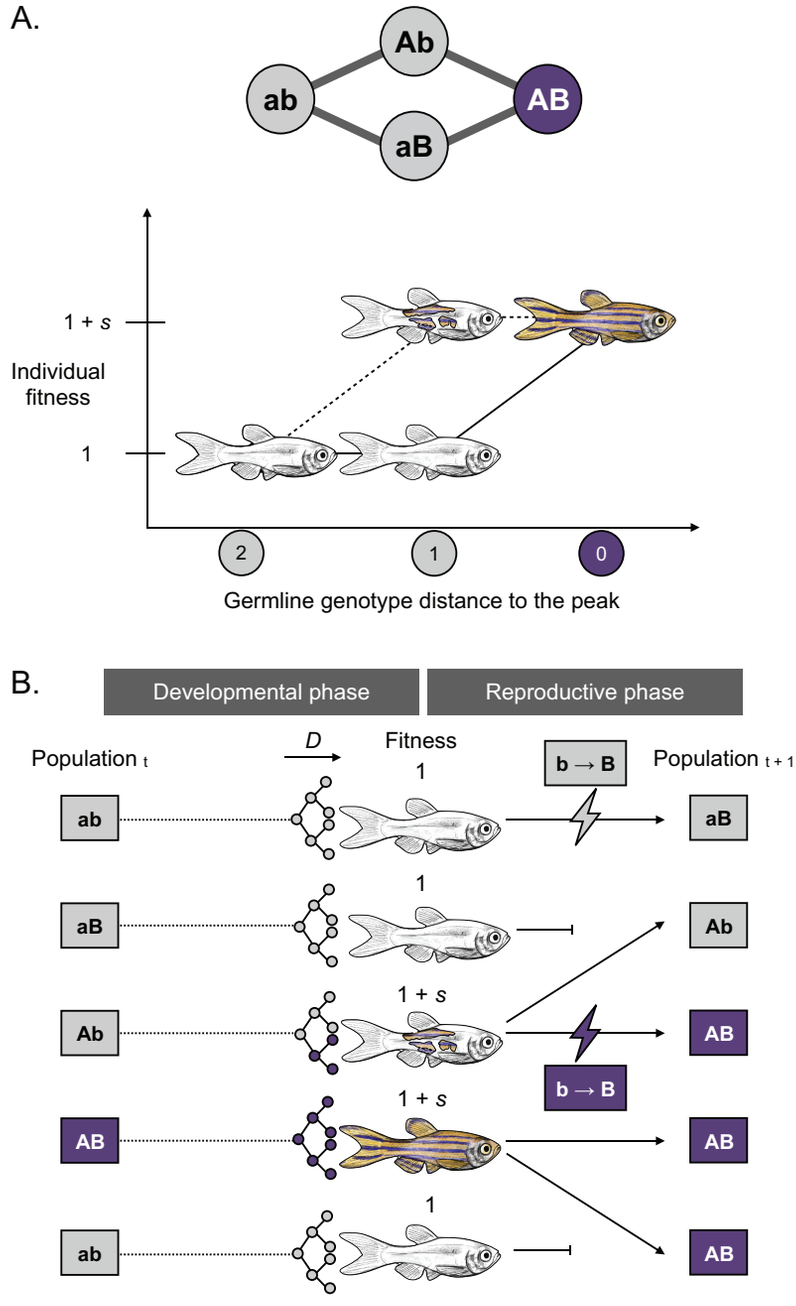

Figure 1: Baseline model. *A*, Fitness landscape represented as a two-locus, two-allele model. Each line connecting genotypes at silver and purple nodes corresponds to a single mutational step. Genotype AB (purple, peak genotype) confers a higher fitness to its carrier, whereas all other genotypes confer no selective advantage in the absence of somatic mutations. The Cartesian axes represent the individual fitness value as a function of the distance of the heritable germline genotype to the peak. Solid lines represent evolutionary trajectories toward the peak from ab, in which somatic mutations are either not present or produce no selective advantage, such as in our control simulations. Dashed lines show how beneficial somatic mutations can smooth the fitness landscape by increasing the organismal fitness of individuals with somatic mutations to the peak genotype. *B*, Representation of a single generation in our simulations. At generation t, individuals in a population of size N enter a developmental phase. During this phase, starting from a single cell with each individual's germline genotype, D developmental cycles occur until the final somatic size 2^D is reached. At each developmental cycle, somatic mutations occurring at rate μ_{soma} can modify the distance to the peak of each somatic cell. Based on a fitness function, at the end of the developmental phase the final genotypic composition of the soma defines the fitness of each individual. During the reproductive phase, the population is sampled on the basis of the individual fitness values to create a new population for the next generation. Before entering the developmental phase of generation $t + 1$, germline mutations may occur at rate μ_{germline}, represented by purple and silver lightning bolts in our diagram.

mutations occurred at rate μ_{soma} per locus per daughter cell. Organismal fitness was defined by the proportion of somatic cells carrying the AB genotype at the end of development. As such, we allowed somatic mutations only during development and did not model the mature life span of organisms. In the reproductive phase, organismal reproductive success was proportional to fitness, and germline mutations occurred at rate $\mu_{germline}$ per locus.

Nonheritable Somatic Mutations Can Promote Adaptation

We ran two versions of our model across a range of somatic and germline mutation rates. In the first version, somatic mutations did not confer an organismal selective advantage. This served as a control and as a point of comparison with traditional population genetic models that disregard somatic development. We implemented this version of our model by simulating each generation using only the reproductive phase, thus ignoring somatic mutations that could arise during the developmental phase. Fitness was therefore defined by the germline genotype alone. In the second version, somatic mutations conferred an organismal selective advantage. Such an advantage could arise via somatic mutations influencing cell signaling or spatial patterning during development, as we later discuss. We implemented this version of our model using a fitness function in which an individual attained the full selective advantage $s_{organism}$ if at least one somatic cell had the peak genotype AB at the end of the developmental phase—an assumption we later relax. Fitness was therefore defined by the somatic composition of the organism.

The evolutionary outcomes of these simulations for a range of germline and somatic mutation rates are shown in figure 2*A*–2*D*. In the control simulations, the mean fitness of the population increased for germline mutation rates beyond 5×10^{-7} mutations per locus per generation (fig. 2*A*; annex I). Under these high germline mutation rates, populations converged on the peak genotype via stochastic tunneling, which occurs when the double-mutant AB arises in a neutral or deleterious aB or Ab background before the latter becomes extinct (Iwasa et al. 2004; Ashcroft et al. 2015; fig. 2*C*). When somatic mutations conferred a selective advantage to the organism, the mean fitness of the population increased with both the germline and the somatic mutation rate, thus expanding the parameter space in which higher fitness evolved relative to the control simulations (compare fig. 2*A* and 2*B*). For low somatic mutation rates, this expansion manifested via a decreased threshold on the germline mutation rate past which populations converged on the peak genotype (fig. 2*D*). In contrast, for higher somatic mutation rates, fitness increases were not due to convergence on the peak genotype in the germline. Rather, germline genotypes remained one or two mutations away from the adaptive peak, but the peak fitness was nevertheless obtained because of somatic mutations (fig. 2*D*). Additionally, the presence of somatic mutations increased the rate of convergence to the peak genotype in parameter regions where the peak was reached in both versions of our model (fig. 2*E*).

We note that empirical mutation rates from mouse and human cells ($\mu_{soma} \sim 5 \times 10^{-9}$, $\mu_{germline} \sim 1 \times 10^{-8}$; Milholland et al. 2017) fall within the range of mutations rates where somatic mutations can promote adaptation via convergence on the peak germline genotype (fig. 2*A*–2*D*, circles). For these mutation rates, an initial stage of drift with low frequencies of the Ab and aB genotypes was often followed by two consecutive selective sweeps toward the AB genotype (fig. 2*F*). In contrast, in control simulations, genetic drift dominated the evolutionary dynamics, such that populations remained two mutations from the peak (fig. 2*G*).

Taken together, these results provide proof of principle that nonheritable somatic mutations can promote adaptation, even under biologically realistic germline and somatic mutation rates.

Somatic Mutation Supply Determines Evolutionary Outcomes

The results presented above revealed three distinct evolutionary outcomes depending on the somatic and germline mutation rates (fig. 3*A*): (i) populations did not increase in fitness and remained two mutations away from the peak, (ii) populations increased in fitness by converging on the peak, and (iii) populations increased in fitness but the germline genotype either remained one mutation away from the peak as Ab or aB or two mutations away from the peak as ab.

The mutation rate thresholds for each of the three outcomes can be estimated probabilistically (annex I). At low somatic mutation rates ($\mu_{soma} = 1 \times 10^{-10}$, $D = 25$; fig. S1), the probability of acquiring the peak AB genotype via somatic mutation from an intermediate aB or Ab germline genotype is essentially zero, so there is no selective advantage of genotypes Ab or aB over ab. At intermediate somatic mutation rates ($1 \times 10^{-10} < \mu_{soma} < 1 \times 10^{-7}, D = 25$; fig. S1), somatic mutations to the peak AB genotype from intermediate aB and Ab germline genotypes occur with sufficient frequency to give the intermediate germline genotypes an average selective advantage over the germline ab genotype. However, these somatic mutation rates are not high enough to guarantee the somatic evolution of the AB genotype, rendering the AB germline genotype more fit than the intermediate aB and Ab genotypes. In contrast, at high somatic mutation rates, somatic evolution of the AB genotype is essentially guaranteed from the ab germline genotype

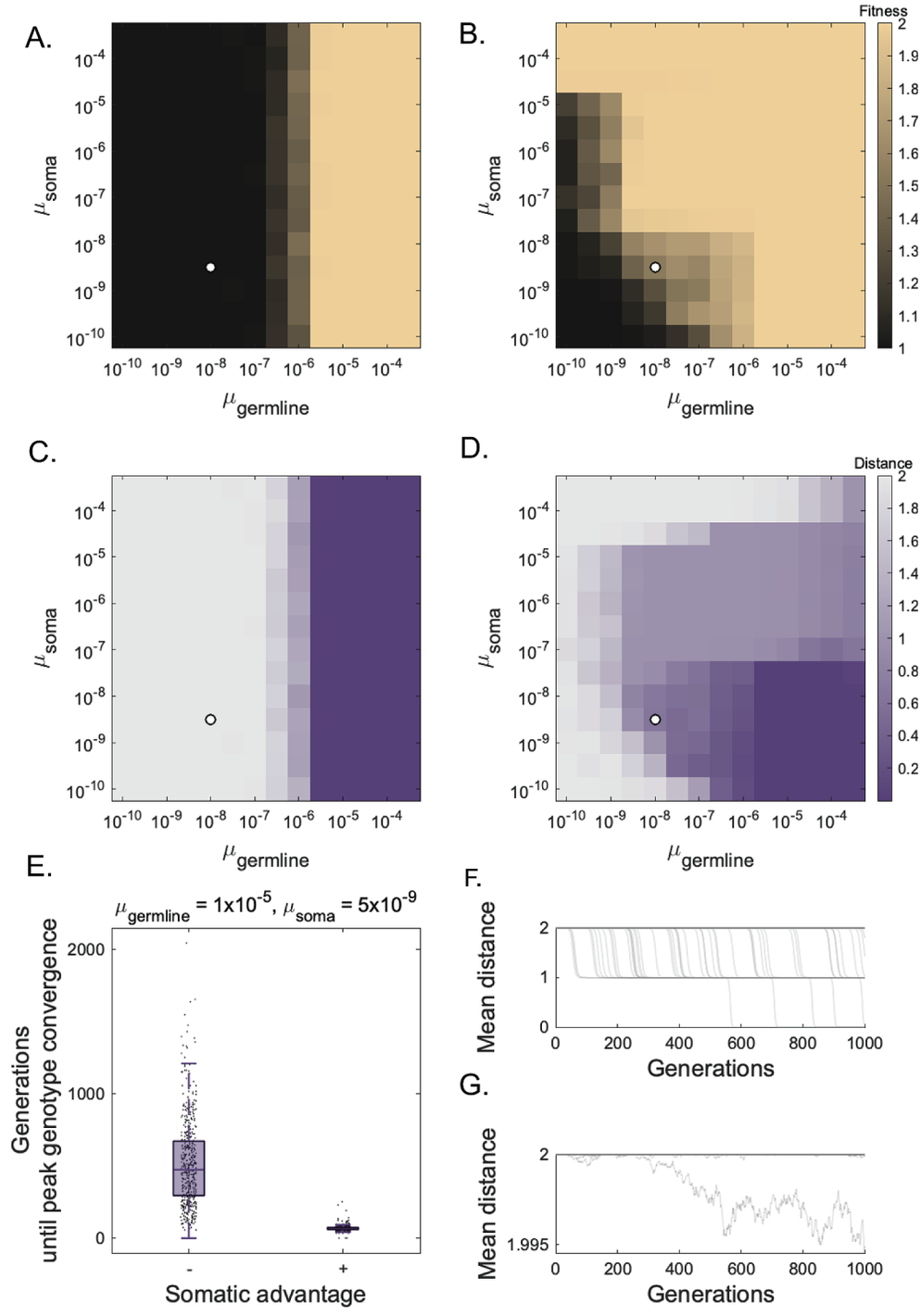

Figure 2: Nonheritable somatic mutations can promote adaptation. *A*–*D*, Mean fitness of populations (*A*, *B*) and mean mutational distance to the peak (*C*, *D*) after 5,000 generations when somatic peak genotypes did not provide an organismal selective advantage (*A*, *C*) and when they did (*B*, *D*), for a range of somatic mutation rates (mutations per locus per cell division) and germline mutation rates (mutations per locus per generation). The rows and columns that are not marked by a tick correspond to values of μ with a mantissa of 5. The values shown are the mean across 500 replicates for each parameter combination. White circles indicate the combination of $\mu_{soma} = 5 \times 10^{-9}$ and $\mu_{germline} = 1 \times 10^{-8}$, which approximates empirically estimated mutation rates from mouse and human cells (Milholland et al. 2017). *E*, Distribution of the number of generations required to converge on the peak genotype in 500 simulations for $\mu_{soma} = 5 \times 10^{-9}$ and $\mu_{germline} = 5 \times 10^{-5}$ when somatic peak genotypes provided a selective advantage (+) and when they did not (−). *F*, *G*, Evolutionary trajectories over the first 1,000 generations for 100 randomly chosen replicates when somatic peak genotypes provided a selective advantage (*F*) and when they did not (*G*), under the mutation rates indicated by the asterisks in *A*–*D*. Notice that the limits on the *Y*-axes differ in *F* and *G*. We ran all simulations with a population size $N = 100{,}000$, a selective advantage $s_{organism} = 1$, and a number of developmental cycles $D = 25$.

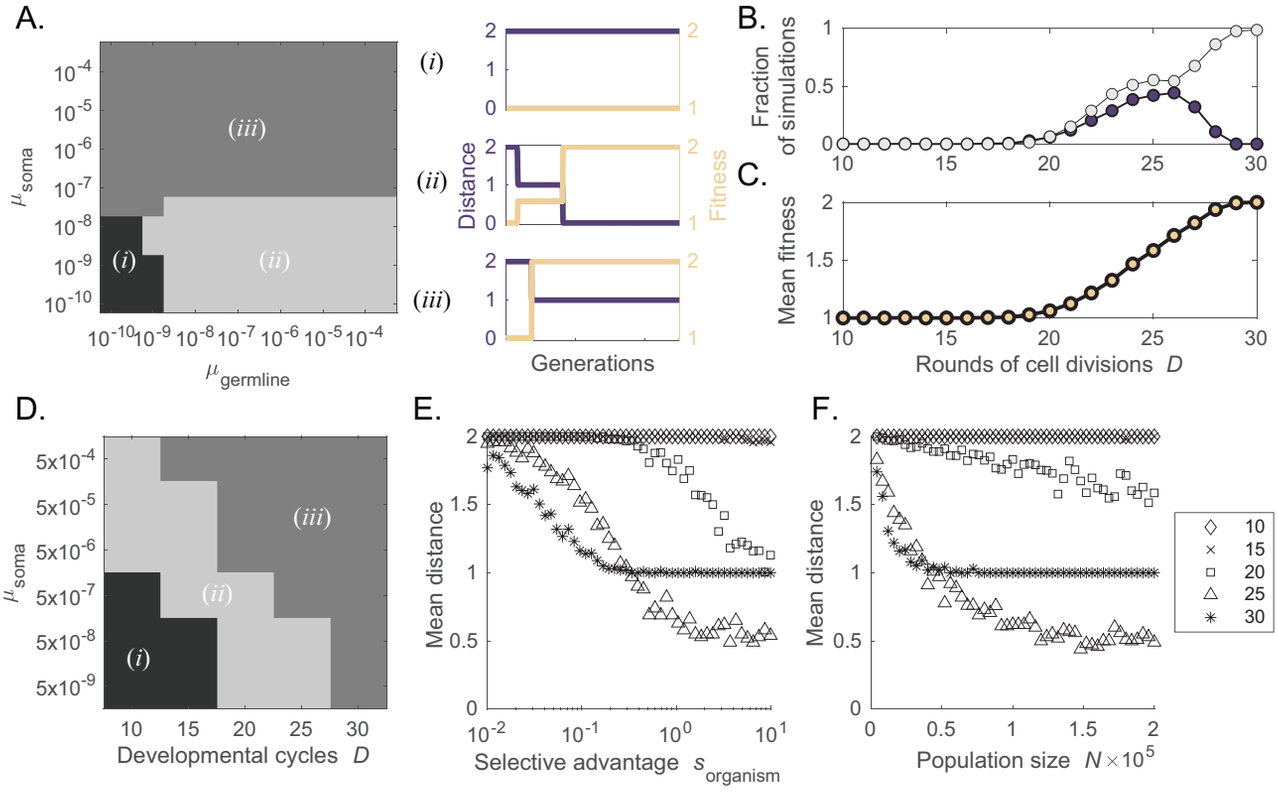

Figure 3: Evolutionary outcomes in relation to model parameters. *A*, Three distinct evolutionary outcomes emerge in our model: (i) populations do not evolve the maximum fitness of $1 + s_{organism}$ after 5,000 generations, (ii) populations evolve the maximum fitness of $1 + s_{organism}$ after 5,000 generations and converge on the peak genotype, and (iii) populations evolve the maximum fitness of $1 + s_{organism}$ after 5,000 generations but do not converge on the peak genotype. Regions are shaded according to the outcome realized by the simulations for each parameter combination. The rows and columns that are not marked by a tick correspond to values of μ with a mantissa of 5. Subpanels to the right show the trajectories for mean distance to the peak (purple) and mean fitness (beige) in representative simulations for each of the three evolutionary outcomes. *B*, Fraction of simulations in which the population reached the peak genotype (purple) or remained one mutation away from the peak genotype (silver) after 5,000 generations shown in relation to *D*. *C*, Mean population fitness after 5,000 generations of the same simulations as in *B*. *D*, Evolutionary outcomes i, ii, and iii for different combinations of somatic mutation rates and developmental cycles. *E*, *F*, Mean distance of the germline genotype to the peak after 5,000 generations across a range of values for selective advantage on a log scale (*E*) and population size (*F*). The different symbols correspond to different numbers of developmental cycles *D*, as shown in the key for *F*. For *D*–*F*, we performed 100 simulations for each combination of parameters. The baseline parameters were $N = 100{,}000$, $s_{organism} = 1$, $\mu_{soma} = 5 \times 10^{-9}$, and $\mu_{germline} = 1 \times 10^{-8}$.

($\mu_{soma} > 1 \times 10^{-4}$, $D = 25$; fig. S1) or from the intermediate aB and Ab germline genotypes ($\mu_{soma} > 1 \times 10^{-7}$, $D = 25$; fig. S1), rendering all germline genotypes selectively equivalent. The latter scenario is exemplified by the adaptive immune system of jawed vertebrates. Given the hypervariability induced by VDJ recombination and elevated rates of somatic mutation during affinity maturation, there is reduced selective pressure to evolve an exact germline memory of past encounters with pathogens.

Somatic mutation supply can thus determine which evolutionary outcome emerges. Another factor that influences somatic mutation supply beside somatic mutation rate is the number of cells in the soma, which in our model is determined by the number of developmental cycles *D*. To assess how somatic mutations influence adaptation for organisms of different size, we modified our baseline model to include a range from $D = 10$ to $D = 30$, which produces final somatic cell counts between $2^{10} = 1{,}024$ and $2^{30} = 1.07 \times 10^9$, respectively—values that approximate the number of cells in tissues, organs, and entire animals (table 1). Modifying the mutation supply in this way resulted in similar evolutionary outcomes as when varying somatic mutation rates (fig. 3*B*, 3*C*). Specifically, after 5,000 generations, no populations increased in fitness when $D < 19$, populations tended to increase in fitness by evolving the peak genotype when $19 \leq D \leq 28$,

Table 1: Representative biological examples

Developmental cycle (D)	Somatic size (2^D cells)	Representative biological examples
10	1,024	Somatic cells of adult *Caenorhabditis elegans* (Kenyon 1988)
15	32,768	Adult tardigrade (Seki and Toyoshima 1998), wing disk of fruit fly at metamorphosis (Day and Lawrence 2000)
20	1.05×10^6	Mouse pituitary gland (Gleiberman et al. 2008)
25	3.36×10^7	Adult mouse cerebellum (Surchev et al. 2007)
30	1.07×10^9	Newborn rat (Cairns 1975)

Note: We study a range of developmental cycles D, which yield somas spanning the size of an adult worm to a newborn rat. These examples provide biological intuition for our model parameter D, although we emphasize that the functional effects of somatic mutations will often be restricted to the tissue in which they arise.

and populations increased to a maximum fitness of $1 + s_{\text{organism}}$ without reaching the peak germline genotype when $D > 28$. These outcomes can again be described probabilistically, since by extending the developmental phase of the simulation the opportunities for the adaptive mutations to occur somatically also increase, making them likely for intermediately sized somas and guaranteed for larger somas (annex I; fig. S1). As expected under this logic, by varying the somatic mutation rate together with the number of developmental cycles, we observed that the evolutionary outcome of our model depended on the interaction between these two components of somatic mutation supply (fig. 3*D*). For example, high somatic mutation rates facilitated convergence on the peak genotype even for populations of organisms with the smallest soma considered ($D = 10$, which approximates the somatic size of an adult *Caenorhabditis elegans*; table 1).

To explore the importance of somatic mutation supply relative to other factors affecting evolutionary dynamics in our model, we additionally varied the population size N and the selection coefficient s_{organism} of the AB genotype ("Methods"). The number of populations converging on the peak genotype increased as either of these parameters increased, but only for some intermediately sized somas (fig. 3*E*, 3*F*). Notably, even though our baseline values for s_{organism} were relatively high, reflecting scenarios in which a single mutation more than doubles fitness components like survival or reproductive maturation (e.g., Karageorgi et al. 2019; Lanno et al. 2019), we also observed somatic mutations promoting adaptation under more conservative selection coefficients between 0.01 and 0.1 and slightly higher empirical measurements of selection coefficients, such as those measured for missense mutations enhancing insecticide resistance in mosquitoes ($s_{\text{organism}} = 0.16$; Lynd et al. 2010) and improving camouflage in wild mice ($s_{\text{organism}} = 0.32$; Barrett et al. 2019; fig. 3*E*). Overall, although population size N and selection coefficient s_{organism} can influence the probability with which a population converges on the peak germline genotype, it is ultimately the somatic mutation supply, defined by the somatic mutation rate and the size of the organism, that primarily influences which of the three evolutionary outcomes emerge.

Another factor that can influence the adaptive potential of nonheritable somatic mutations is the ruggedness of the fitness landscape. Thus far, we studied a fitness landscape with three genotypes of equal fitness (ab, Ab, and aB) and a fourth genotype (AB) with a selective advantage s_{organism} (fig. 1*A*). Considering instead a rugged fitness landscape with two adaptive peaks separated by an adaptive valley (Ab and aB; "Methods"; annex II; fig. S2*A*), we found that somatic mutations could promote adaptation by facilitating valley crossing (fig. S2*B*, S2*C*). Which of the three evolutionary outcomes emerged depended on the mutation supply, the depth of valley, and the selective advantage of the peak genotype AB (fig. S2*D*). These results suggest that somatic mutations not only promote adaptation on neutral networks but also aid in the exploration of rugged fitness landscapes, which can otherwise hinder adaptive evolution as populations become trapped on local adaptive peaks (Gokhale et al. 2009).

Alternative Fitness Functions Restrict the Adaptive Potential of Somatic Mutations

So far, we have used a fitness function in which a single somatic cell with the peak genotype is sufficient to confer the full selective advantage s_{organism}. Relaxing this assumption to account for more realistic biological scenarios, we considered alternative functions in which the fitness of a given organism is proportional to the fraction of somatic cells with the peak genotype, σ_{peak}, so that the fraction F_i of s_{organism} attained by an individual i is

$$F_i(\sigma_{\text{peak}}) = (\sigma_{\text{peak}})^f, \tag{1}$$

where f is a constant defining the shape of the function. The function is concave when $f > 1$, convex when $0 < f < 1$, and linear when $f = 1$ (fig. 4*A*). Concave functions

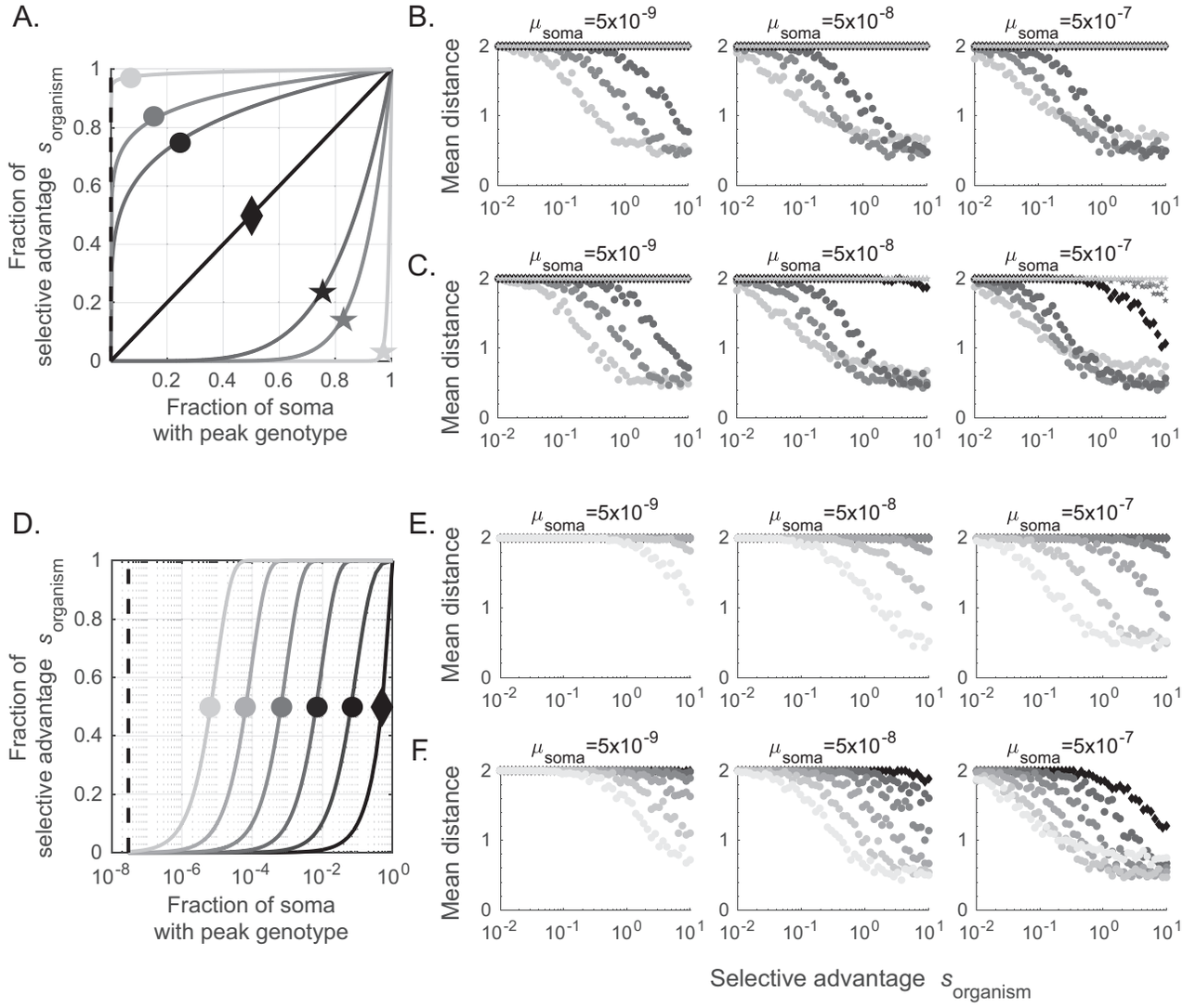

Figure 4: Influence of alternative fitness functions and cell lineage selection on the adaptive potential of somatic mutations. *A*, *D*, Fraction of the selective advantage conferred to an individual as a function of the fraction of cells in the soma with the peak genotype. In *A*, there are three concave functions (circles), three convex functions (stars), and a linear function (diamond), generated with equation (1) for different values of f ("Methods"). In *D*, we show different concave diminishing-returns fitness functions of different shape, generated with equation (2) using different values of g ("Methods"). The shades of gray from light to dark indicate the distance to the linear fitness function, which is black. Note that the linear function is the same in both *A* and *D* and that *D* is presented on a log scale on the *X*-axis. The black dashed line indicates the value of $1/2^{25}$, which is the minimum fraction of somatic cells with peak genotypes that are needed to confer the full selective advantage in the baseline model with $D = 25$ developmental cycles. *B*, *E*, Mean distance to the peak in populations after 5,000 generations across a range of selective advantages under each of the different fitness functions from *A* and *D* in *B* and *E*, respectively. Each point represents the mean across 50 replicate simulations for each parameter combination. The shade and symbols of each point refer to the fitness functions presented in *A* and *D*. For *C* and *F*, we modified the simulations such that cells with peak genotypes had a fitness advantage $s_{cell} = 2$ over cells with other genotypes. We performed the simulations in *B*, *C*, *E*, and *F* with the somatic mutation rates indicated above the graphs, while the remaining parameters were $N = 100{,}000$, $D = 25$, and $\mu_{germline} = 1 \times 10^{-8}$.

require relatively few somatic cells with the peak genotype to confer the full selective advantage $s_{organism}$, whereas convex functions require a large number of somatic cells with the peak genotype to confer the full selective advantage.

Figure 4*B* shows the probability of converging on the adaptive peak in relation to the selection coefficient $s_{organism}$ for three different somatic mutation rates using seven parameterizations of the fitness functions given in

equation (1). In the range of parameters explored, concave functions tended to promote adaptation across different values of μ_{soma} and $s_{organism}$, whereas linear or convex functions did not (fig. 4*B*).

Exploring further the evolutionary outcomes under different kinds of concave functions, we also considered a series of diminishing-returns fitness functions with different thresholds for the number of cells needed to increase fitness, which was defined by a constant g so that

$$F_i(\sigma_{peak}) = \frac{(\sigma_{peak} + 1)^{1-g} - 1}{2^{1-g} - 1}. \quad (2)$$

We studied six of these fitness functions with different values for g (fig. 4*D*; "Methods"). Under our baseline somatic mutation rate, beneficial somatic mutations promoted adaptation only at relatively high values of $s_{organism}$ for the two fitness functions that required the fewest somatic cells with the peak genotype to confer the full selective advantage (fig. 4*E*). With these fitness functions, in a soma of 2^{25} cells, ~30 and ~300 cells with the peak genotype are needed to confer 10% of the selection coefficient $s_{organism}$, respectively, and at least ~3,000 and ~30,000 cells (representing less than 0.01% of the total somatic cells) with the peak genotype are needed to confer the full selection coefficient $s_{organism}$, respectively. For the same fitness functions, increasing the somatic mutation rate by one or two orders of magnitude (fig. 4*E*, second and third graphs) increased the probability of converging on the adaptive peak for all values of $s_{organism}$. Moreover, this increase in the somatic mutation rate expanded the set of fitness functions under which somatic mutations promoted convergence to the peak genotype.

Thus, even under high somatic mutation rates and with high selection coefficients, somatic mutations are unlikely to promote adaptation if more than a small fraction of somatic cells with the peak genotype are required to confer the full selective advantage $s_{organism}$.

The Adaptive Potential of Nonheritable Somatic Mutations under Multilevel Selection

We have so far assumed that somatic mutations confer a selective advantage to the organism but not to the cell. Yet cell lineage selection is common in development, and it biases mosaic and chimeric cellular compositions (Morata and Ripoll 1975; Simpson 1979; Buss 1982; Otto and Orive 1995; Otto and Hastings 1998; Extavour and García-Bellido 2001; Schwarz and Cadavid 2007; Schoen and Schultz 2019; Yu et al. 2020), helping to explain why some somatic mutations are recurrently detected across different individuals (Melton et al. 2015). Cells can attain increased fitness if they better respond to signals in their developmental environment, make better use of resources, induce apoptosis of neighboring cells, proliferate more, or die less (Moreno et al. 2002; Kim and Jain 2020). We therefore included cell lineage selection in our model, reasoning that it might expand the set of fitness functions under which nonheritable somatic mutations promote adaptation by increasing the number of cells with the peak genotype in the soma. We assumed that somatic cells with peak genotypes had a cellular fitness advantage s_{cell} ("Methods") but kept the final size of the soma at 2^D cells, inspired by systems with determinate growth (Hariharan 2015). In other words, we assumed that cells with a fitness advantage increased in frequency without affecting the final size of the organism. After applying these modifications to our model, we ran simulations using the same fitness functions as described above (fig. 4*A*, 4*D*).

Doubling the cellular proliferative advantage of somatic peak genotypes ($s_{cell} = 2$) expanded the conditions under which nonheritable somatic mutations promoted adaptation, even when the fitness function was linear or convex (fig. 4*C*, second and third graphs). In the case of the concave diminishing-returns functions, increases in the proliferation of somatic mutants with the peak genotype expanded the set of functions in which somatic mutations promoted adaptation, even for the lowest somatic mutation rate considered (fig. 4*F*, first graph), and increasing the somatic mutation rate by one or two orders of magnitude expanded the set even further, to the point that across all considered functions some populations converged on the peak germline genotype (fig. 4*F*, second and third graphs). Thus, when a somatic mutation simultaneously benefits the organism and the somatic mutant cell within the context of development, nonheritable somatic mutations can promote adaptation across a broader range of conditions.

Discussion

Somatic mutations are abundant and sometimes increase organismal fitness (Bar et al. 2017; Revy et al. 2019; Zhu et al. 2019). Nonetheless, because of their nonheritability, they are typically neglected as a source of adaptation in traditional evolutionary theory (Buss 1983*a*, 1983*b*). Here, we provide proof of principle that nonheritable somatic mutations can promote adaptation and help traverse fitness valleys. They do so by exposing adaptive genotypes to selection ahead of their emergence in the germline, thus channeling populations toward peaks in adaptive landscapes, a process we refer to as "somatic genotypic exploration." Below, we discuss the biological plausibility of somatic genotypic exploration given the simplifications in our model and the restrictions it uncovered, as well as the implications of this process for adaptive evolution.

Biological Plausibility of Somatic Genotypic Exploration

Our model makes assumptions that simplify many intricacies of organismal biology. We modeled organisms as haploid individuals with asexual reproduction, whose somas develop through consecutive symmetric and synchronized cell divisions. Complexifying the model could make somatic genotypic exploration more or less likely, depending on the circumstances. For example, if the organism was diploid, the chances of acquiring somatic peak genotypes would be doubled because there would be two copies of each allele per cell, but if the peak allele was recessive, somatic mutations would be less effective in revealing adaptive phenotypes. Moreover, the fate of somatic mutants can be affected by tissue architecture and growth dynamics (Frank and Nowak 2004; West et al. 2021). More realistic developmental models accounting for differentiation, asymmetrical divisions, and stem cells will likely affect how somatic genotypic exploration influences adaptation. For example, somatic mutations could have greater influence if they arise in stem cells that contribute substantially to the composition of a tissue, but if somatic mutations are beneficial only if they arise in cells with specialized functions, then acquiring the somatic mutations in specific developmental contexts where they are adaptive would be less likely.

We also made the simplifying assumption that fitness depends on two biallelic loci. One consequence of this assumption is that valley crossing requires the traversal of just a single deleterious intermediate. This assumption underlies most models of valley crossing, including those addressing the roles of mutation rates (Komarova et al. 2003; Iwasa et al. 2004), population sizes (Weinreich and Chao 2005), recombination (Michalakis and Slatkin 1996; Christiansen et al. 1998; Weissman et al. 2010; Altland et al. 2011), population structure (Ben-Tal et al. 2014), cooperation (Obolski et al. 2017), environmental fluctuations (Hadany 2003), and nongenetic phenotypic variation (Van Egeren et al. 2018). We anticipate that somatic genotypic exploration is less likely to facilitate the crossing of valleys that comprise multiple deleterious intermediates, as has been observed in other modeling frameworks (Weissman et al. 2009; Komarova 2014; Ram and Hadany 2014). The reason is the "foresight" afforded by somatic genotypic exploration is limited to a small mutational radius around the germline genotype, which may not be sufficiently large to explore genotypes on the other side of wide valleys. A direction for future research is therefore to incorporate more than two loci in our model, which would also help us understand how somatic genotypic exploration influences population diffusions on neutral networks (Maynard Smith 1970; Schuster et al. 1994), with implications for the evolution of mutational robustness (van Nimwegen et al. 1999) and genetic diversity (Wagner 2007).

Despite these simplifications, our model is suggestive of the biological conditions under which somatic genotypic exploration is expected to influence adaptive evolution in nature. For example, our model suggests that nonheritable somatic mutations can promote adaptation when the somatic mutation supply is high, which can occur by an increased number of cellular divisions in development and by an increased somatic mutation rate. One could object that an increased somatic mutation rate would cause deleterious mutations elsewhere in the genome, thus offsetting any beneficial effects of somatic mutations. However, mutation rates are highly heterogeneous across the genome, sometimes varying by several orders of magnitude even among neighboring loci (Hodgkinson and Eyre-Walker 2011; Makova and Hardison 2015), which produces mutational hot spots that can be sources of evolutionary adaptations (Galen et al. 2015; Xie et al. 2019). Similarly, these hot spots may confer the elevated somatic mutation rates suggested by our model to promote adaptation via nonheritable somatic mutation, without increasing the mutation load elsewhere in the genome. In our model, we studied beneficial nonheritable somatic mutations, although deleterious somatic mutations could also influence the evolutionary trajectories of populations. Extending our model to include deleterious mutations elsewhere in the genome will illuminate how somatic genotypic exploration steers a population through an adaptive landscape, not only toward adaptive peaks but also away from adaptive valleys via the purging of deleterious genetic variation, akin to what has been shown for other types of nonheritable variation (Bratulic et al. 2017; Kosinski and Masel 2020; Zheng et al. 2021).

Our model also suggests that nonheritable somatic mutations can promote adaptation when a small number of cells with the adaptive somatic mutation are required to confer a selective advantage to the organism. Cell signaling offers a promising example of a biological process where this may occur because a small number of cells with a somatic peak genotype influencing signal emission could orchestrate the behavior of many more cells with alternative genotypes. For example, somatic mutations in organs with endocrinological functions can drastically alter individual physiology and development (Richter-Unruh et al. 2002; Kim and Kim 2019), even when those mutations do not cause enhanced cell proliferation and are in normal nontumoral tissue (Azizan et al. 2013; Nishimoto et al. 2015). In a developmental context, small disturbances from signals could trigger the formation of new patterns in embryos (Schweisguth and Corson 2019), disturbances that could come about from somatic mutations affecting paracrine signaling in few cells among a population of cells that do not have the somatic mutation.

As an illustrative example of a system in which a few mutant cells can have major phenotypic consequences,

consider the development of the striped pattern of zebrafish. This pattern arises from the precise arrangement of different pigmented cell types that dynamically interact with each other and with themselves to coordinate their positioning and proliferation (Patterson and Parichy 2019; Owen et al. 2020). Mutations to specific genes are capable of altering interactions between cell types or preventing their differentiation entirely, which result in major differences in the pattern phenotypes (Singh and Nüsslein-Volhard 2015; Podobnik et al. 2020). We presumed that if these mutations could occur or be reversed somatically during development, they could influence pattern formation. We tested this using a computational model of the cellular interactions between pigment cells that accurately predicts the pattern of wild-type fish and that of different mutants (Owen et al. 2020). Adding a single somatic mutant cell during the development of a fish that could not produce stripes re-created completely or partially the pattern of the striped wild-type zebrafish, depending on the timing of the mutation during development (fig. 5). Supporting these outcomes, Maderspacher and Nüsslein-Volhard (2003) reported the rescue of a wild-type striped phenotype in mutant zebrafish incapable of producing stripes, enabled by a small number of wild-type cells derived from grafting their progenitors into the mutant embryo. This is evidence supporting the potential of a small number of somatic mutant cells to substantially affect the development of a selectable phenotype.

Our model shows that nonheritable somatic mutations are more likely to promote adaptation when they confer a selective advantage not only to the organism but also to the somatic cells in their developmental context. In other words, somatic genotypic exploration is facilitated if somatic mutations that are beneficial to the organism also confer a competitive advantage to the cells in which they arise, allowing these cells to increase in frequency within the organism. The further study of this angle of somatic genotypic exploration will greatly benefit from current approaches to the study of cancer in which the development of tumors based on clonal expansions is thought of as an ecological process in the tissue and cellular context where somatic variants arise (Lloyd et al. 2016; Neinavaie et al. 2021; Somarelli 2021) and from the general study of cell competition during development (Morata and Ripoll 1975; Otto and Hastings 1998; Extavour and García-Bellido 2001; Moreno et al. 2002). Phenotypes that could be affected by somatic genotypic exploration facilitated by proliferative somatic mutant cells include the many morphological innovations in animal evolution that resulted from changes in cell proliferation during development and the parameters controlling its onset and cessation (Alberch et al. 1979; Conlon and Raff 1999). For example, differences in cell proliferation in the facial development of some species of phyllostomid bats help explain the different lengths of their snouts in relation to the shape of the flowers they feed on (Camacho et al.

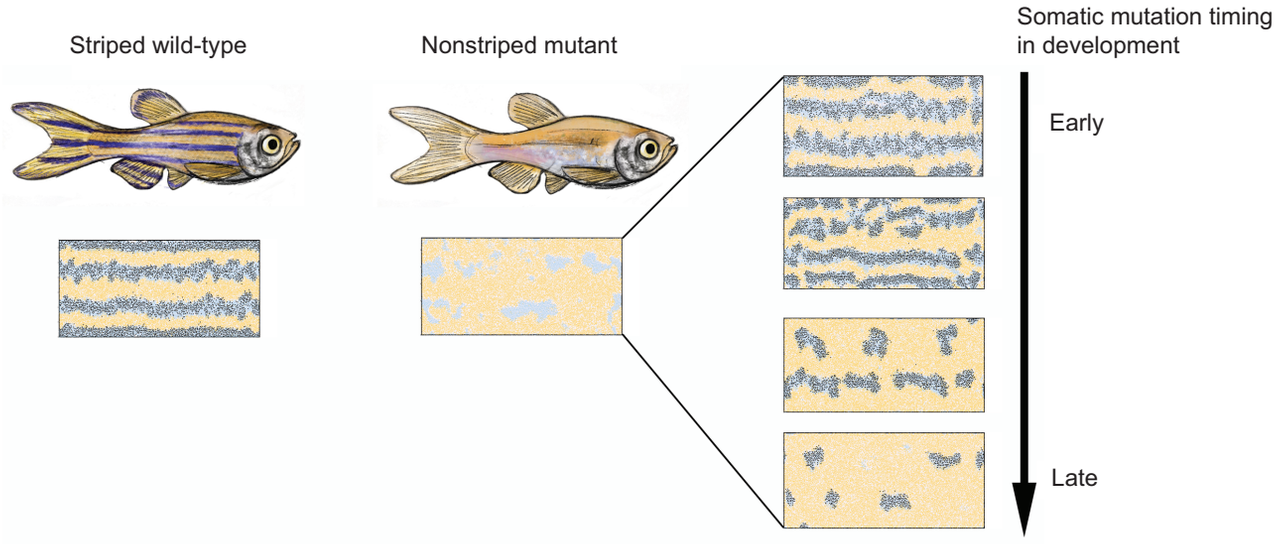

Figure 5: Nonheritable somatic mutations influence pattern formation in a model of zebrafish development. We modified a model of developmental patterning in zebrafish (Owen et al. 2020) to include somatic mutations (annex III). Developing from a nonstriped germline *nacre* mutant, the emergence of a single somatic mutation can cause stripe formation. The extent of stripe formation depends on when during development the somatic mutation arises, such that early-arising somatic mutations replicate the wild-type stripe pattern, whereas late-arising somatic mutations cause a more diffuse stripe pattern. This example highlights a biological scenario in which only a few somatic mutations are required to cause drastic changes in a selectable phenotype.

2020), and genes involved in cell proliferation show indications of positive selection in animals of relatively large size, such as capybaras (Herrera-Álvarez et al. 2020). Conceivably, different degrees of cell proliferation revealing beneficial phenotypes, as in these examples, might have arisen first from prolific somatic variants, and selection acting on those variants eventually promoted their emergence in the germline.

Ultimately, the biological plausibility of somatic genotypic exploration is an empirical question, one that future work could address with a natural case study or by means of laboratory experiments. Identifying a natural case study may prove challenging because of the need to pinpoint somatic variants that cause beneficial phenotypes. However, this may eventually be possible using single-cell genomics technologies, which are advancing rapidly (Dou et al. 2018). Alternatively, laboratory experiments with developing animals may provide a path forward. For example, gene-editing technologies can be used to identify somatic mutations that induce measurable changes in organismal phenotypes, such as in the aforementioned example of stripe formation in zebrafish, which is a well-characterized developmental system for which precise gene-editing techniques are already available (Rosello et al. 2021). Additionally, laboratory evolution experiments could be carried out using developing model organisms that have short generation times, such as nematodes or flies, in which the somatic functionalization of a reporter gene could be selected.

Evolutionary Implications of Somatic Genotypic Exploration

Somatic genotypic exploration can impact evolution in at least four ways. First, somatic genotypic exploration can make the vast supply of nonheritable genetic diversity adaptively relevant. As was pointed out by Frank (2009), the cell lineage history of the development of a single human individual is tremendous, exceeding the lineage history of hominids. Given empirical rates of somatic mutations, a single body can thus harbor immense genetic diversity, which is only now starting to be explored in depth with sequencing technologies (Martincorena et al. 2015; Blokzijl et al. 2016; Lee-Six et al. 2018; Martincorena et al. 2018*a*; García-Nieto et al. 2019; Zhu et al. 2019; Moore et al. 2020; Abascal et al. 2021). Such diversity cannot directly enter the germline, but by fueling somatic genotypic exploration it could still influence evolutionary trajectories. Indeed, as our model shows, nonheritable somatic mutations can steer evolving populations toward adaptive peaks as well as increase the rate of adaptation to these peaks. Although our study has focused on organisms with an impermeable germline-soma separation, we speculate that somatic genotypic exploration can also accelerate adaptation in organisms that do not have such a strict barrier between the germline and soma because even in these organisms, most somatic mutations are not inherited. It would be interesting to adapt our model to explore how somatic genotypic exploration could influence adaptation of populations in which somatic variants are occasionally inherited, thus expanding on what is known about the influence of somatic mutations in the evolution of such organisms (Reusch et al. 2021).

Second, somatic genotypic exploration allows selection to act on the potential of genotypes to produce nonheritable adaptive phenotypes, facilitating the eventual fixation of those phenotypes via germline mutations. This makes somatic genotypic exploration akin to the genetic assimilation of plastic phenotypes triggered by environmental conditions (Waddington 1942; Waddington 1953; Pigliucci et al. 2006; Crispo 2007), by the stochasticity or "noise" of cellular processes (Kaern et al. 2005; Whitehead et al. 2008; Payne and Wagner 2019; Schmutzer and Wagner 2020), or by epigenetic modifications (Klironomos et al. 2013). Within this context, the so-called look-ahead effect (Whitehead et al. 2008) is particularly relevant; in this model, phenotypic mutations caused by transcription or translation errors create potentially adaptive protein variants, offering a mechanism for channeling populations toward adaptive genotypes, as in our model. However, because somatic genotypic exploration relies on the exploratory potential of somatic mutations that arise during development, it can act on substantially different phenotypes via substantially different biological processes. For instance, the effect of cell lineage selection would be irrelevant in the absence of some degree of intraorganismal inheritance, which is provided by somatic mutations, but would be mostly absent in the transcriptional and translational errors enabling the look-ahead effect.

Third, somatic genotypic exploration can influence the mosaic evolution of mutation rates across the genome. Although high genome-wide mutation rates can be deleterious, individual loci can evolve higher mutation rates if selection favors their diversification (Sniegowski et al. 2000). The locus-specific rate can result from localized structural and functional properties, such as the fragility of segments of DNA strands with specific nucleotide sequences (Xie et al. 2019), how often the locus is transcribed (Chen et al. 2017), the influence of chromatin organization (Schuster-Böckler and Lehner 2012), nucleotide composition and mutation biases (Fryxell and Moon 2005; Stoltzfus and McCandlish 2017; Cano et al. 2022), or specific targeting by biomolecular mechanisms (Odegard and Schatz 2006). Selection may favor elevated mutation rates in genomic regions where adaptive phenotypes can be revealed by somatic mutation without influencing mutation rates elsewhere. The resulting mosaic of mutation

rates across loci implies that different parts of the genome could be subject to the different evolutionary regimes we uncovered.

Fourth, somatic genotypic exploration can cause developmental bias. Developmental bias exists when certain phenotypes are produced more readily than others, thus influencing evolutionary trajectories and outcomes (Maynard Smith et al. 1985; Uller et al. 2018). They can arise either from developmental constraints impeding the emergence of certain phenotypes (Zalts and Yanai 2017) or through developmental drive, which accounts for the increased likelihood of some phenotypes (Arthur 2001). Some causes of developmental drive are high mutation rates in genomic regions affecting an evolving trait (Galen et al. 2015; Xie et al. 2019), the genetic architecture of the trait (Stern and Orgogozo 2008; Besnard et al. 2020), and the number of genotypes mapping to a phenotype (Dingle et al. 2020). Somatic genotypic exploration is a form of developmental drive in the latter sense because it causes genotypes to intermittently express beneficial phenotypes that they would not otherwise express in the absence of somatic mutation, thus altering the genotype-phenotype map.

Overall, our study offers a theoretical grounding for the further analysis of somatic mutations as a source of adaptation. Future empirical studies can help evaluate the plausibility of somatic genotypic exploration, through analyses of traits affected by genomic regions with high somatic mutation rates, phenotypes that can be altered by relatively few or clonally expanding mutant cells, and phenotypic innovations derived from changes in the proliferation or mortality of cells during development. For these analyses, we need to better understand the dynamics of somatic mutant cells within the organism and how somatic genetic diversity affects phenotypes beyond cancer and senescence. By studying somatic genotypic exploration as a potential adaptive mechanism, we can elucidate whether and how the immense genetic diversity of the soma directs evolutionary trajectories toward adaptation. If that proves to be the case, the soma—and by extension the organism as a whole—is not only the instantiation of the founding genotype present in the zygote but also an important source of adaptive potential.

Methods

Baseline Model

We modeled a population of multicellular organisms with an impermeable germline-soma division navigating a fitness landscape. We used a haploid two-locus, two-allele model in which one of the four possible allele combinations represented the peak conferring a selective advantage s_{organism} over the other three genotypes (fig. 1*A*).

We used Wright-Fisher simulations with a population of N haploid individuals, where we represented each individual by the mutational distance of its germline genotype to the peak genotype. We initialized monomorphic populations at the maximum distance from the peak (i.e., genotype ab, which is two mutations from the peak). We ran each simulation for 5,000 generations, each of which consisted of a developmental phase and a reproductive phase (fig. 1*B*).

In the developmental phase, we modeled the somatic growth of each individual in the population as a branching process with D developmental cycles consisting of synchronized rounds of cell divisions starting from a single cell until the individual reached a reproductive somatic size 2^D. The starting cell contained the germline genotype and at each cell division, somatic mutations occurred at rate μ_{soma} without altering the germline genotype. To implement this, at each round of cell division we sampled the number of mutated cells from a binomial distribution $B(n, \mu_{\text{soma}})$, where n was the number of somatic cells with each genotype (ab, aB, Ab, or AB). The genotypic composition of the soma at the end of development defined organismal fitness. In the case of our baseline model, having at least one somatic cell with the peak genotype provided the full selective advantage s_{organism}, producing an organismal fitness of $1 + s_{\text{organism}}$; otherwise, the fitness was 1.

In the reproductive phase, germline genotypes were selected with replacement from the population with a probability proportional to organismal fitness at the end of development. At this step, the germline genotypes of offspring were mutated at a rate μ_{germline} per locus. These selected and possibly mutated germline genotypes produced the population of the next generation.

As a control, we also considered a version of our model where somatic mutations did not affect fitness. To do so, we included only the reproductive phase in each generation. Organismal fitness was therefore defined exclusively by germline genotype.

The default parameters for our baseline model were $D = 25$, $N = 100{,}000$, $s_{\text{organism}} = 1$, $\mu_{\text{soma}} = 5 \times 10^{-9}$, and $\mu_{\text{germline}} = 1 \times 10^{-8}$. However, we also explored the parameter space by including ranges from $D = 10$ to $D = 30$, from $N = 1{,}000$ to $N = 200{,}000$, from $s_{\text{organism}} = 0$ to $s_{\text{organism}} = 10$, from $\mu_{\text{soma}} = 1 \times 10^{-10}$ to $\mu_{\text{soma}} = 5 \times 10^{-4}$, and from $\mu_{\text{germline}} = 1 \times 10^{-10}$ to $\mu_{\text{germline}} = 5 \times 10^{-4}$.

Alterations to the Baseline Model

Fitness Functions. We ran simulations in which organismal fitness was a function of σ_{peak}, which is the fraction of the developed organism's somatic cells with the peak genotype. To do so, we defined the fitness of each individual i

as $1 + s_{\text{organism}}F_i(\sigma_{\text{peak}})$, where $F_i(\sigma_{\text{peak}})$ was a monotonic function of σ_{peak} that yielded values between 0 and 1. Thus, $F_i(\sigma_{\text{peak}})$ determined the selective advantage s_{organism} conferred to an individual, according to its fraction of somatic cells with the peak genotype. We defined $F_i(\sigma_{\text{peak}})$ as indicated in equations (1) and (2). In equation (1), f was a constant defining the shape of the function. For the seven functions used the values were $f = 5$, 10, and 100 for concave functions (fig. 4*A*, circles); $f = 1/100$, $1/10$, and $1/5$ for convex functions (fig. 4*A*, stars); and $f = 1$ for the linear function (fig. 4*A*, diamond). For the fitness function defined by equation (2), we chose six values of g in order to study a range of fitness functions that required different numbers of somatic cells with the peak genotype to confer the full selective advantage s_{organism}. These values were $g = 0$ for the linear function (fig. 4*D*, diamond) and $g = 12$, 107, 1,055, 10,538, and 10,000 for the remaining diminishing-returns functions (fig. 4*D*, circles).

The set of baseline parameters we used in combination with these fitness functions was $D = 25$; $N = 100{,}000$; a range of s_{organism} values from 0.01 to 10; $\mu_{\text{soma}} = 5 \times 10^{-9}$, 1×10^{-8}, or 5×10^{-8}; and $\mu_{\text{germline}} = 1 \times 10^{-8}$.

Cell Fitness. We ran simulations in which somatic mutations to the AB genotype conferred a selective advantage not only to the organism but also to the somatic cell. To do so, we added an extra stage to the developmental phase in which somatic cells with AB genotypes had a proliferative advantage over somatic cells with other genotypes. Specifically, they divided at a rate s_{cell} times that of somatic cells with other genotypes. Somatic mutations occurred at the same rate μ_{soma} in these cell divisions as in other cell divisions. Although under natural conditions the cellular fitness effect of mutations will depend on when in development and where in the genome the mutations occur (for a comparison of the selective effect sizes of nucleotide variants in cancerous cells, see Cannataro et al. 2018), we used a representative single fixed value of $s_{\text{cell}} = 2$, which doubles the reproductive capacity of cells with the peak genotype relative to other cells. This value approximates estimations for differential proliferative capacities among somatic variants (Morata and Ripoll 1975; Zhu et al. 2019) and populations of cells in stages of development that are comparable to each other across different species (Camacho et al. 2020).

Fitness Valleys. We ran simulations in which the intermediate germline genotypes aB and Ab conferred a fitness disadvantage to the organism relative to the genotypes ab and AB. Specifically, we modified our baseline model such that individuals with the ab germline genotype had a fitness of 1, the AB germline genotype had a fitness of $1 + s_1$, and the intermediate germline genotypes had a basal fitness of $1/1 + s_2$, which could be increased via somatic mutation to AB. In these simulations, we explored values for s_1 and s_2 ranging from 0 to 10 and values for D ranging from 10 to 30.

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Statement of Authorship

Conceptualization: P.M.; funding acquisition: J.L.P.; methods development/experimental design: P.M., E.Y.E., J.L.P.; data analysis: P.M., E.Y.E., J.L.P.; data validation: P.M.; data visualization: P.M., E.Y.E., J.L.P.; model analysis: P.M., E.Y.E., J.L.P.; coding simulation: P.M.; supervision: J.L.P.; writing—original draft: P.M.; writing—review and editing: P.M., E.Y.E., J.L.P.

Data and Code Availability

Code for this article is available from Zenodo (https://doi.org/10.5281/zenodo.6538447; Majic 2022).

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