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Review

Population genetics of non-genetic traits: Evolutionary roles of stochasticity in gene expression

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ABSTRACT

The role of stochasticity in evolutionary genetics has long been debated. To date, however, the potential roles of non-genetic traits in evolutionary processes have been largely neglected. In molecular biology, growing evidence suggests that stochasticity in gene expression (SGE) is common and that SGE has major impacts on phenotypes and fitness. Here, we provide a general overview of the potential effects of SGE on population genetic parameters, arguing that SGE can indeed have a profound effect on evolutionary processes. Our analyses suggest that SGE potentially alters the fate of mutations by influencing effective population size and fixation probability. In addition, a genetic control of SGE magnitude could evolve under certain conditions, if the fitness of the less-fit individual increases due to SGE and environmental fluctuation. Although empirical evidence for our arguments is yet to come, methodological developments for precisely measuring SGE in living organisms will further advance our understanding of SGE-driven evolution.

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1. Introduction

1.1. How stochastic is life?

Life processes are largely stochastic. Many events in life and its course are influenced by a wide variety of stochastic factors (Table 1). Stochasticity should thus be considered as one of the most basic mechanisms for generating variations among living organisms. However, stochasticity per se is non-inheritable, which makes bridging the effects of stochastic and deterministic processes in evolution difficult. While the importance of stochasticity in biological processes has been argued for many years, the roles of stochasticity in evolution might not yet be fully appreciated (Lenormand et al., 2009).

Before the 1960s, many scientists considered that evolutionary processes were predominantly regulated by natural selection (a deterministic factor). This is still the case at the macro-evolutionary scale. Contrary to this viewpoint, Kimura (1968, 1985) argued that natural selection alone could not explain the observed level of evolutionary rate at the molecular level, which led him to the neutral theory of molecular evolution. In population genetics, resampling effect between generations is called random genetic drift. This is a stochastic factor at the population level (Table 1), which plays a key role in the neutral theory. This concept has been inherited by the nearly neutral theory (Ohta 1972, 1973). The nearly neutral theory stipulates the involvement of both natural selection and genetic drift and is now largely supported by genomic surveys of a variety of species (Hughes et al., 2005; Nei et al., 2010; Akashi et al., 2012). To date, however, population genetic models rarely take interplay between stochastic factors at different levels into consideration (Ohta, 2011).

In molecular biology, on the other hand, the importance of stochastic factors and their interplay has been well recognized. Mutation and recombination are fundamentally stochastic events (Graur and Li, 2000) and stochasticity strongly affects the fates of developing cells, as in olfactory epithelium and retinal cells in rat (Vassar et al., 1993; Gomes et al., 2011). In relation to cell growth, Kiviet et al. have reported stochastic behavior of the molecules in the single cell level (Kiviet et al., 2014). In addition to those examples, bet-hedging mechanisms, stochastic switching between phenotypic states associated with phase variation and persistence, are also noted (Cohen, 1966; Seger and Brockmann, 1987). This stochasticity is thought to be beneficial to grow in dynamic environments, where the conditions can change suddenly and unpredictably from mild to harsh ones (Slatkin, 1974; Beaumont et al., 2009).

Abbreviations: SGE, stochasticity in gene expression.

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Table 1
Examples of biological processes that contain stochasticity.

Type	Level	Examples
Brownian motion	Atomic/molecular	Biophysical/biochemical properties
Mutation	Molecular	Nucleotide substitution Insertion/deletion Chromosomal rearrangements
Recombination	Molecular	Gene combination on a genome
Chromatin formation	Molecular	Histone modifications
Gene expression	Molecular	Transcription, translation
Phenotypic development	Cellular/individual	Unequal cell division Differentiated cell/tissue formation
Organismal growth	Individual	Size/number of cells
Life history	Individual/population	Survival, reproduction, migration
Gene frequency	Population	Random genetic drift
Population size	Population	Bottleneck, population expansion
Species range	Population/species	Niche occupation Species birth/death
Environment	Molecular/ecosystem	Abiotic environmental fluctuation Climate change

1.2. Stochasticity in gene expression

With recent advances in molecular technologies, precise data for gene expression has become available. It has been suggested that stochasticity in gene expression (SGE) exists in all studied species and causes large phenotypic variation even without any genetic variation (Shahrezaei and Swain, 2008). SGE is generally thought to include gene expression noise originating from extrinsic factors, such as transcription factor activity, and intrinsic factors, such as mRNA decay ratio (Elowitz et al., 2002; Raser and O'Shea, 2005). The molecular mechanisms of the SGE will not be discussed here, for which there are several existing reviews (Raj and van Oudenaarden, 2008; Shahrezaei and Swain, 2008; Eldar and Elowitz, 2010; Li and Xie, 2011; Munsky et al., 2012; Sanchez and Golding, 2013). Here we assume that SGE itself is non-genetic and not encoded in the gene or genome, but regulatory systems that enhance or reduce the magnitude of SGE could be controlled by genetic mechanisms. The evolution of such "SGE modifier genes" is discussed later.

The strong phenotypic variation by SGE can be subject to natural selection, and hence, fitness consequences are expected (Raj et al., 2010; Wang and Zhang, 2011). SGE can be either beneficial, neutral, or deleterious (Gilad et al., 2006). SGE is reportedly essential in cell-fate determination (Kaern et al., 2005; Colman-Lerner et al., 2005; Losick and Desplan, 2008; Gomes et al., 2011) and thus important in development of multicellular organisms. In unicellular organisms, stochastic switching of gene expression levels or high expression noise has been shown, both theoretically and experimentally, to be beneficial in the face of fluctuating environments or acute environmental stresses (Thattai and van Oudenaarden, 2004; Kussell and Leibler, 2005; Acar et al., 2008). In other cases, SGE can exhibit a deleterious fitness effect affecting cellular functions, preventing precise controls of cellular biological processes (Fraser et al., 2004; Lehner, 2008). In addition, several studies have provided direct and indirect evidences for lessened expression noise of genes important to cell growth (Fraser et al., 2004; Newman et al., 2006; Batada and Hurst, 2007; Lehner, 2008), and there have also been reports that increased noise in gene expression is associated with diseases (Cook et al., 1998; Kemkemer et al., 2002; Bahar et al. 2006). Regulatory network structures, confronting these deleterious effects, are found to attenuate expression noise, suggesting that gene networks might have evolved through natural selection to establish a robustness against expression noise (Becskei and Serrano, 2000; Pedraza and van Oudenaarden, 2005). Here, we have to note that not all the SGE lead to fluctuations in phenotype on which selection acts, and that many fluctuations are naturally damped by the system.

In this review, we aim to evaluate potential roles for SGE in evolutionary processes. Using simple models, we demonstrate how SGE can possibly affect key population genetic parameters, such as effective population size and fixation probability of new mutation, arguing that SGE has a potential to play an important evolutionary role. The role of SGE is largely neglected in current evolutionary biology, and understanding the significance of the role of SGE will shed new light on evolutionary mechanisms.

2. The working hypothesis: SGE changes the fate of a population

The working hypothesis is illustrated in Fig. 1. As mentioned above, SGE can have phenotypic consequences and can be subject to natural selection. Although natural selection itself is a deterministic factor, natural selection on SGE may eventually enhance the effect of random genetic drift because SGE has no genetic basis and natural selection simply places a load (through random sacrifice) on the population. Thus, the first test hypothesis is that SGE drags down effective population size (N_e) in the evolutionary process under a constant environment. On the other hand, SGE might become advantageous and increase N_e if the environment fluctuates and the fitness optimum shifts temporally. The potential interaction between environmental fluctuations and SGE produces a second test hypothesis offering that SGE can evolve if there is a genetic factor that regulates SGE magnitude (SGE modifier gene) and if SGE provides selective advantage to individuals with a larger SGE magnitude. Under such a scenario, SGE might save individuals with a maladapted gene from the brink of extinction. The evolutionary advantage of SGE, if any, would be best described by examining the fixation probability of new mutations with/without SGE and under fluctuating environments. These possibilities are discussed in more detail using theoretical methods in the following sections. Because the evolutionary consequences of SGE are discussed here, we treated SGE as a fitness parameter in the following sections for simplicity, although we acknowledge that SGE is only one of the stochastic factors that might influence the fitness of individuals (Table 1).

3. Effect of SGE on effective population size

Effective population size (N_e) is one of the core parameters in population genetics because it determines the relative power of the two major drivers of evolution, natural selection and random genetic drift (Crow and Kimura, 1970). To generally illustrate the effect of SGE on N_e, it is useful to first consider viability selection (difference in survival) against SGE. Assuming hard selection and no mutation, a case in which SGE reduced the survival rate of a diploid individual from 1 to $1 - s$ ($s > 0$) with probability p in a monoecious population is considered. The reason why we choose these assumptions is that we examined the simplest case for the first consideration. A population genetic parameter, the genetic load, represents the extent to which the average individual in a population is inferior to the best possible kind of individual. The genetic load equals the relative chance that an average individual will die before reproducing. Based on the definition of genetic load (L, equivalent of the selection load) (Crow and Kimura, 1970), $L = ps$. If a 10% chance was assumed for SGE, by which an individual had a 2% lower survival rate than a non-SGE individual ($p = 0.1$, $s = 0.02$), $L = 0.002$. This means that N_e decreased by 0.2% per generation, which appears to be a small decay. However, unique features of SGE, that SGE is non-inheritable and that natural selection cannot purge the genetic load due to SGE from the population, cause a generally unappreciated effect on N_e at the evolutionary time scale (Fig. 2A). Namely, a slight decline in N_e accumulated over time. In the above case of $L = 0.002$, the overall genetic load accumulated to 0.18 by generation 100 ($t = 100$) and 0.86 at $t = 1000$ (=1-[1 − L]^t, Fig. 2A). Thus, at the

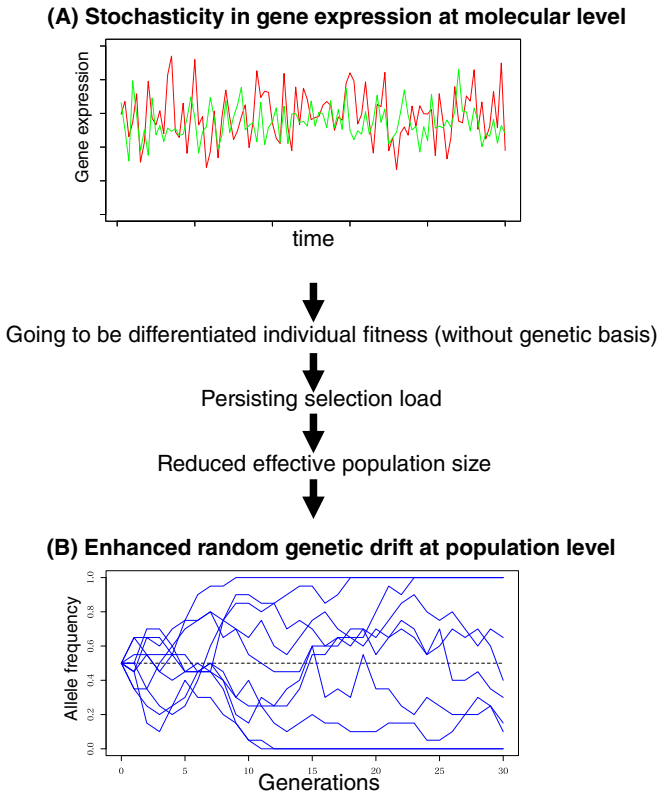

Fig. 1. Diagram of the hypothesis of SGE-driven evolution. Given that SGE (A, green and red lines) is inevitable and that it can have a phenotypic consequence, SGE can increase fitness variation. Since the phenotypic/fitness variation has no genetic basis, selection load against the maladapted individuals due to SGE persists through the evolutionary time scale. Thus, the selection load consistently reduces the effective population size, which eventually enhances the random genetic drift at the population level (B, blue line). Red and green lines represent different gene expression patterns in different individuals, whereas blue lines represent changes of the allele frequency among generations. Here, we show 10 distinct populations as an example.

evolutionary time scale, SGE can cause a drastic reduction in N_e and a population crash under hard selection. This SGE effect can be considered a consequence of genetic load, which is caused by increased variance in phenotypic traits and fitness within a population. Recombination cannot mitigate the SGE effect because there is no physical target representing SGE in the genome for natural selection.

A heterozygosity, the fraction of individuals in a population that are heterozygous for a particular locus, is a major parameter to show the genetic variations, which lead to the evolution. As heterozygosity decreases by a fraction of $1/(2N_e)$ each generation (Crow and Kimura, 1970), SGE also decreased heterozygosity through time (Fig. 2C). As expected, when selection was stronger, the rate of decay was higher. With $L = 0.2$, for example, N_e dropped to 13% within 100 generations and became virtually zero after 300 generations; heterozygosity followed similar trajectories, with a slight delay in response compared with the N_e trajectories (Fig. 2C).

In a case of fecundity selection (difference in fertility), the SGE effects on N_e and heterozygosity were slightly different. In this case, N_e of a monoecious population at generation t ($N_{e,t}$) was calculated as

$$N_{e,t} = \frac{2N_{e,t-1}}{\bar{k}-1+V_k/\bar{k}} \quad (1)$$

where $\bar{k}$ is the absolute value of the mean population fecundity and V_k is its variance (Crow and Kimura, 1970). The results were compared with those from viability selection above by replacing the selection coefficient on viability (s) with that on fecundity (s') but kept the parameter values constant ($L = ps' = 0.002$ or 0.02); fecundity selection against SGE imposed higher variance in fecundity among individuals. Decomposing V_k for the variance among individuals with SGE (V_{SGE}) and without SGE (V_{noSGE}) obtained

$$V_k = pV_{\mathrm{SGE}} + (1-p)V_{\mathrm{noSGE}} + p\left(\bar{k}_{\mathrm{SGE}}-\bar{k}\right)^2 + (1-p)\left(\bar{k}_{\mathrm{noSGE}}-\bar{k}\right)^2, \quad (2)$$

where $\bar{k}_{\mathrm{SGE}}$ and $\bar{k}_{\mathrm{noSGE}}$ are mean individual fecundities with and without SGE, respectively. An assumed constant population size ($\bar{k} = 2$) and Poisson variance in family size within each group ($V_{\mathrm{SGE}} = \bar{k}_{\mathrm{SGE}}$ and $V_{\mathrm{noSGE}} = \bar{k}_{\mathrm{noSGE}}$) for simplicity produces

$$\bar{k}_{\mathrm{SGE}} = \frac{2(1-s\prime)}{1-ps\prime}, \quad (3)$$

$$\bar{k}_{\mathrm{noSGE}} = \frac{2}{1-ps\prime}, \quad (4)$$

and

$$V_k = 2\left(1 + 2p(1-p)\left[\frac{s\prime}{1-ps\prime}\right]^2\right). \quad (5)$$

Thus, in a case of $p = 0.1$, $s' = 0.02$, and $N_{e,t=0} = 100$, V_k became 2.000145, instead of two for the neutral case. Again, the difference due to SGE was small per generation, but it accumulated over time owing to the same reason, viability selection (Fig. 2).

Although reductions in N_e and heterozygosity were smaller for fecundity selection than for viability selection in this example, we consider the former rather conservative reduction in N_e with fecundity selection was highly sensitive to family size variance and the assumption of $V_{\mathrm{SGE}} = \bar{k}_{\mathrm{SGE}}$ was rather unrealistic. If $V_{\mathrm{SGE}} = 2\bar{k}_{\mathrm{SGE}}$ and $L = 0.002$ was assumed, for instance, N_e dropped to <1 within 100 generations (data not shown).

4. SGE and fixation probability

The previous section illustrated how SGE reduces effective population size, regardless of the mode of natural selection against SGE. Thus, under the neutral or the nearly neutral theory of molecular evolution, SGE enhances the effect of random genetic drift in the evolutionary process (Fig. 1) (Kimura and Ota, 1972; Ohta, 1973). The stronger influence of random genetic drift triggered by SGE can in turn open up a space for the fixation of slightly deleterious mutations (Matsumoto et al., unpublished data). They clearly illustrated that, without SGE, the viabilities of three genotypes, *AA*, *Aa*, and *aa* were solely determined by natural selection, whereas with SGE, the viability was expected to vary among individuals due to SGE (see also Wang and Zhang, 2011). The fixation probability is a probability that a new allele is fixed in the population. This parameter shows how strong its evolutionary effect is, comparing with the neutral one. In their simulation, a relative increase in the fixation probability was observed with SGE, as opposed to without, particularly when the power natural selection was large. Their result suggests that the positive effect of SGE on the fixation probability of deleterious mutation was larger when the allele exhibited a more deleterious effect.

5. Evolution of SGE modifier gene and environmental fluctuation

As mentioned earlier, the SGE per se is not encoded in the gene or the genome. However the stochastic phenomenon of gene expression is generated by a genetic regulatory system, which is obviously inheritable (Mettetal et al., 2006). Thus, organisms with a sophisticated genetic regulatory system might possess a potential to control the magnitude of SGE. The evolutionary potential of the genetic regulation on SGE was

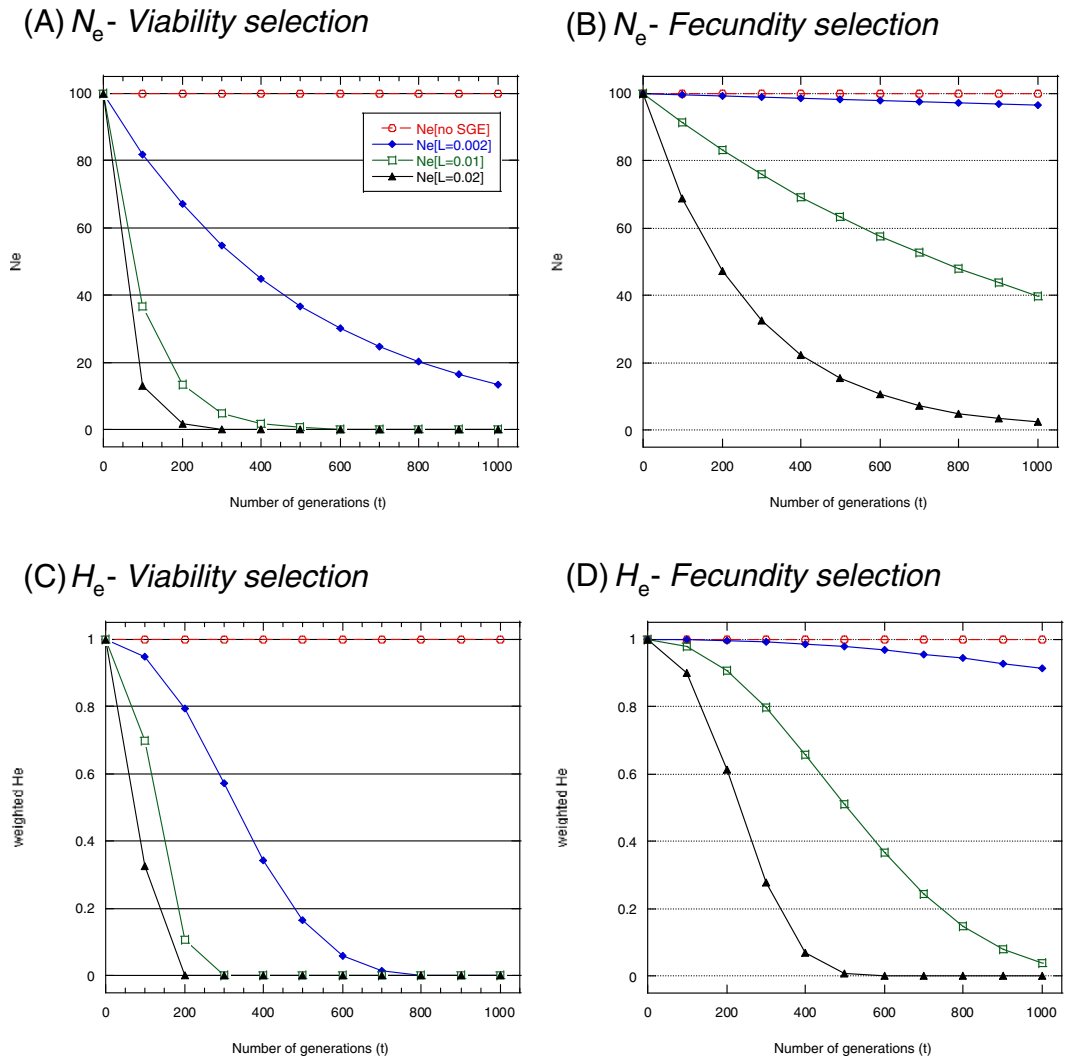

Fig. 2. Expected effective population size (N_e, A, and B) and weighted level of heterozygosity (H_e, C, and D) with natural selection on SGE. With viability selection (A and C), the influence of selection on SGE will be stronger than that with fecundity selection (B and D). In both cases, however, the selection against SGE does reduce the effective population size and the level of heterozygosity constantly as the selection load (L) increases. $N_e = 100$ and $H_e = 0.5$ were assumed at generation (t) = 0; heterozygosity level was displayed by weighting expected value by that with neutral case (H_e with no SGE, control); $p = 0.1$, $s = 0.02$, 0.1, or 0.2 were assumed for each line of $L = 0.002$, 0.01, or 0.02, respectively; no mutation assumed.

examined by conducting another simulation with an additional locus X, a SGE modifier gene. Under fluctuating environments, there are several reports (Kussell and Leibler, 2005; Acar et al., 2008; Zhang et al., 2009; Tsuru et al., 2011) on this matter. They argued and suggested that the SGE modifier gene could have been selected for under fluctuating environments and thus they had the selective advantage of stochastic switching in fluctuating environments.

Under the simple condition such as no environmental fluctuations, it is reported that the heritability of factors directly related to the fitness is low (Mousseat and Roof, 1987). Therefore, the genes suppressing SGE and thus increasing heritability to reduce the genetic load might not be important for the organisms. These genes and its SGE can indeed be selectively neutral under the stable environment. In contrast, the studies indicated the evolutionary importance of SGE under environmental fluctuations. It is possible that the selectively neutral SGE under stable environment turns into advantageous/disadvantageous under environmental fluctuations. We also note here that the studies we introduced largely neglected genomic heterogeneity and complex genetic architecture with which SGE in one gene can be indirectly associated with the phenotypic variance. Although a part of the complexities of life is discussed in the next section, these cases should be examined in future studies both theoretically and experimentally.

6. Robustness and SGE

Phenotypic robustness is one of the key concepts when considering evolutionary consequences of SGE and its regulation. Robustness is a widely used biological term, coined by Waddington (1942), that could be further classified to address robustness toward intrinsic noise, such as toward SGE, environmental fluctuation, and mutational pressure (stochastic, environmental, and mutational robustness, respectively). Waddington later developed his idea of evolutionary capacitors, in which organisms could accumulate the source of evolvability in the presence of mutational robustness (Waddington, 1957).

Organisms have to withstand a number of perturbations for survival. As described above, creating a gene network is one way to mitigate hazards and, in addition, organisms forming a cell community have developed stochastic robustness using cell–cell interaction systems. For example, a study of slime mold *Dictyostelium discoideum* has detected a pulsing of transcription during mold development although the developmental stages of individual cells were not synchronized (Chubb et al., 2006). Evolution of environmental robustness in multicellular organisms has been relatively well studied, a good example being homeostasis, in which organisms maintain a stable internal condition against environmental disturbances, such as in oxygen concentration, body temperate, and pH (Cannon, 1929).

On the other hand, there is little evidence for the evolution of mutational robustness. Although it is easy to imagine that stochastic and environmental robustness have been selected for, thereby ensuring that organisms survive short-term perturbations, mutational robustness is not necessarily driven by mutational pressure, as suggested by Waddington (1957). Lehner (2010) has argued that mutational robustness is a by-product of environmental and stochastic robustness and, based on yeast experimental data, he has demonstrated significant coupled effects of genes to mutational, stochastic, and environmental robustness.

Theoretical studies by other researchers also support the idea that mutational robustness might be a by-product of other types of robustness (Wagner, 1996; Wagner et al., 1997; Kaneko, 2007). For example, Kaneko (2007) has shown that robustness is evolvable only when intrinsic noise is larger than threshold values, with the variance among isogenic phenotypes (V_{ip}) and variance among genotypes (V_g). Using a computer simulation of gene network evolution, he found that $V_{ip} \geq V_g$ should be satisfied for both robustness types to evolve.

From the viewpoint of biological mechanisms, SGE was defined here as intrinsic and extrinsic biological noises, such that, for example, nucleosomes can decrease the accessibility of transcription factors to their target DNA sequences. Thus, it is thought that the competition between transcription factors and nucleosomes may also be a source of SGE (Tirosh and Barkai, 2008; Choi and Kim, 2009; Macneil and Walhout, 2011). On the other hand, several essential genes tend to cluster around open chromatin, which may lead to more robust expression levels (Batada and Hurst, 2007; Field et al., 2008). If robustness is established as a consequence of adaptive evolution, an evolutionary consequence might be a reduced deleterious effect by SGE on individual phenotypes. Thus, robustness is of particular importance for understanding organismal evolution in the presence of SGE as, intuitively, robustness has an opposite consequence in evolution; the relationship between evolution and robustness has been debated.

7. Concluding remarks

In this review, a non-genetic trait, SGE, is considered as a potential subject of evolution. Theoretical evaluations here suggested that SGE can possibly influence evolutionary processes in multiple ways. First, as a 'noise' in gene expression, SGE can decrease effective population size, which in turn increased the effect of random genetic drift, another stochasticity at the population level. Second, SGE can alter individual fitness and might have buffered the deterministic effect of alleles on individual fitness. The buffering effect could be beneficial when their environment fluctuated and the population was not optimal. If the effects of SGE are indeed of evolutionary significance, the long-lasting debate between neutralists and selectionists regarding the survival of the luckiest versus survival of the fittest becomes meaningless—with SGE, the fittest can be the luckiest. With recent advances in measuring gene expression at the single cell level (Bengtsson et al., 2005; Deng et al., 2014), it will be soon possible to empirically test this hypothesis. Although experimental verification is still under investigation, the importance of SGE in consideration of evolutionary processes is predicted here to increase greatly in the future research.

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