

MicroReview

A chance at survival: gene expression noise and phenotypic diversification strategies

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Summary

Phenotypic diversification plays a central role in evolution and provides species with a capacity to survive environmental adversity. The profound impact of random molecular events on the shaping of life is well accepted in the context of chance mutations and genetic drift; however, the evolution of the regulatory networks encoding microorganismal stress response and survival strategies might also have been significantly influenced by gene expression noise. This likelihood has inspired numerous investigations to characterize the sources of phenotypic diversity within isogenic populations, and to explore their direct and potential biological implications. Here, we discuss different scenarios where gene expression noise might bestow a selective advantage under stress, highlighting a potentially fundamental role of stochastic mechanisms in the evolution of microbial survival strategies.

Introduction

The term 'gene expression noise' is typically used in broad reference to observed variation in protein content among seemingly identical cells experiencing the same environment. This variation can be divided into intrinsic and extrinsic components (Elowitz *et al.*, 2002; Swain *et al.*, 2002; Raser and O'Shea, 2004; Kaern *et al.*, 2005; Raser and O'Shea, 2005; Pedraza and van Oudenaarden, 2005; Rosenfeld *et al.*, 2005; Volfson *et al.*, 2006; Maheshri and O'Shea, 2007). Extrinsic gene

expression noise arises from variations in cell-specific factors that can be physiological and global in nature, such as the metabolic state of the cell, cell-cycle phase and cell age, or specific to certain subsets of genes, such as the variability in upstream signal transduction. Intrinsic gene expression noise refers to variation that arises from 'finite-number' molecular-level fluctuations inherent to reaction kinetics in the nanomolar range during the expression of individual alleles.

While many molecular-level details remain to be uncovered, two mechanisms – transcriptional and translational bursting – are important sources of intrinsic gene expression noise that have been directly linked to DNA-encoded parameters. In the translational bursting model, variability in protein content is a direct consequence of finite-number fluctuations in mRNA abundance. When the average protein content is kept fixed, inefficient translation of highly abundant mRNA results in steady protein production while efficient translation of low-abundance mRNA results in large random bursts of protein synthesis. In the transcriptional bursting model, slow reaction kinetics cause infrequent transitions between active and inactive promoter states, which, in turn, cause multiple mRNA templates to be synthesized in rapid succession at irregular intervals. Noise generated by both of these mechanisms has been shown to depend on DNA-encoded parameters. Specifically, ribosome binding site mutations (Ozbudak *et al.*, 2002) and codon usages (Blake *et al.*, 2003) modulating translational efficiency, as well as promoter mutations modulating the stability of active promoter states (Raser, 2004; Blake *et al.*, 2006) directly impact cell–cell variability.

The direct evidence that genome sequence contributes to cell–cell variability indicates that gene expression noise, like other genome-encoded traits, is inheritable and evolvable; subject to selective pressures during the course of evolution. Indeed, the identification in yeast of quantitative trait loci influencing stochastic cell–cell variability supports the concept that gene expression noise is a heritable genetic trait (Ansel *et al.*, 2008). Moreover, the notion that gene expression noise has undergone significant evolutionary drifts is supported by differences in

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noise between groups of related genes. Genome-scale studies in yeast have shown that while dose-sensitive genes and proteins forming multicomponent complexes tend to have low gene expression noise (Fraser *et al.*, 2004; Batada and Hurst, 2007; Lehner, 2008), stress-related genes and proteins responding to changes in the environment tend to display high noise (Bar-Even *et al.*, 2006; Newman *et al.*, 2006).

Naturally, the notion of inherent uncertainty and limited precision at the very basis of life has fuelled substantial efforts to seek a deeper understanding of gene expression noise. On one hand, the inherency of noise to gene expression might necessitate counteracting noise-reduction mechanisms preserving the fidelity of regulatory signals (Becskei and Serrano, 2000; Dublanche *et al.*, 2006). On the other hand, the probabilistic features afforded by gene expression noise lead to the evident possibility that evolution has fine-tuned noise-generating mechanisms and genetic network architectures to derive beneficial population diversity (Smits *et al.*, 2006; Veening *et al.*, 2008; Lopez-Maury *et al.*, 2008). Here, we discuss recent advances demonstrating an apparently critical role of stochastic processes in a variety of microbial survival strategies. To this end, we explore the circumstances where noise in constitutively expressed stress-related genes provide a fitness advantage, the role of noise in the stochastic activation of regulatory pathways and how such phenotypic switching can be optimized to provide a better chance at survival in uncertain environments.

Stochastic expression of stress-related genes

The increased gene expression noise exhibited by stress-related genes lends support to the hypothesis that variability in protein content among cells might confer a selective advantage. By broadening the range of environmental stress resistance across a population, added gene expression noise could increase the likelihood that some cells within the population are better able to endure environmental assaults (Booth, 2002; Avery, 2006). Experimental results providing support for this hypothesis were obtained in a study by Bishop *et al.* (2007) who demonstrated a competitive advantage of stress-resistant yeast mutants under high stress due to increased phenotypic heterogeneity.

To examine how gene expression noise affects yeast cells under acute environmental stress, Blake *et al.* (2006) introduced targeted promoter mutations to modulate transcriptional bursting in the expression of ZeoR; a protein conferring resistance to the antibiotic Zeocin. The authors first demonstrated that the introduction of TATA-box mutations results in smaller transcriptional bursts and decreased gene expression noise (Fig. 1A). They then experimentally and computationally compared the fitness

of two strains with low and high ZeoR expression noise following exposure to various levels of antibiotic. Both experiments and simulations confirmed that increased gene expression noise could provide a significant selective advantage at high stress levels (Fig. 1B). This was not, however, the case at low stress levels, where the low-noise strain had higher fitness than the high-noise strain.

In a qualitative explanation, Blake *et al.* (2006) attribute the differential impact of added noise to a change in the relative fraction of surviving cells at different levels of stress. While a high-noise population will have a higher number of cells above the protein production threshold necessary for survival at high stress levels, the same will be true for a low-noise population under a low level of stress. In a quantitative model, the size of this fraction depends on the probability distribution function associated with the spread of protein content among individual cells (Fig. 1C). Consequently, if it is assumed that cells are either unaffected or killed by the stress, the mean population fitness at a certain stress level can be calculated directly from the cumulative probability distribution function. This provides a very simple quantitative framework that captures the observed impact of population heterogeneity on population fitness following acute stress (Fig. 1D).

To further explore the correlation between population fitness, environmental stress and gene expression noise, we define the differential fitness $\Delta W(\eta, s)$ as the difference in fitness at stress level s between a population with variable noise η and a reference population with fixed low noise satisfying $\eta_{\text{low}} < \eta$. The differential fitness calculated from the fitness curves in Fig. 1D clearly displays that the advantage of increased noise is only observed at stress levels above a certain critical value s_{crit} (Fig. 1E), defined by $\Delta W(\eta, s_{\text{crit}}) = 0$. Interestingly, the fitness gain at high stress ($s > s_{\text{crit}}$) is accompanied by a significant fitness loss at low stress ($s < s_{\text{crit}}$). Moreover, the magnitude of the fitness disadvantage at most subcritical stress levels exceeds the maximal fitness advantage that can be derived at high stress.

Additional interesting insights are revealed when plotting the dependence of differential fitness on both stress level and noise (Fig. 1F). First, at any given stress where a fitness benefit can be derived, the maximal advantage occurs at intermediate values of η . Second, increased noise can significantly increase the fitness disadvantage at low stress. Third, increased noise actually expands the range of stress levels where noise has a negative fitness impact. In distributions typically associated with the spread of protein across cell populations, increasing noise while maintaining a fixed mean will decrease the median population expression (as well as the expression mode). This lowers the fraction of cells in the better-fit high-

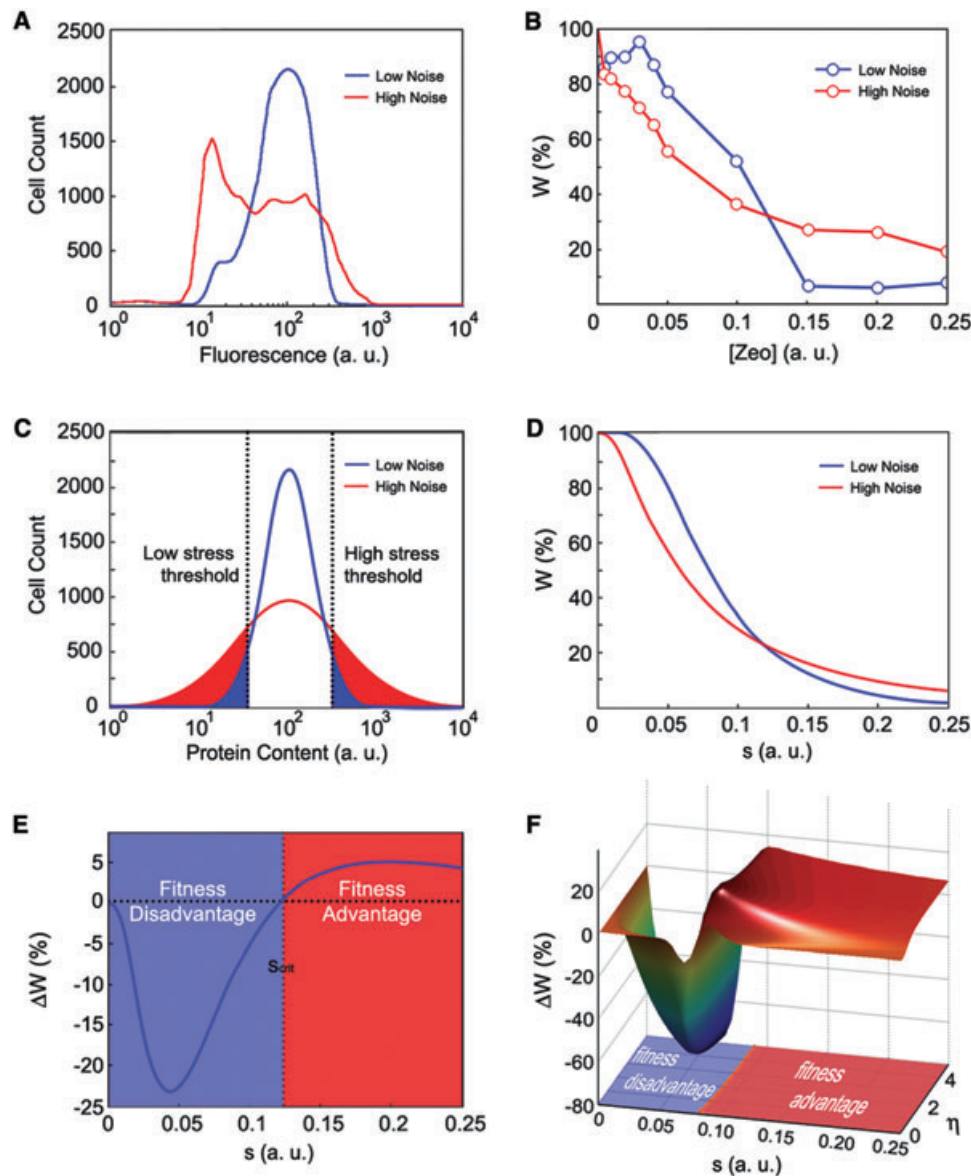


Fig. 1. Effects of heterogeneity on the fitness of populations upon exposure to stress.

A. Fluorescence histograms of the low noise ($\eta = 0.6$), and high noise ($\eta = 1.2$), yeast strains having approximately equal mean stress-protein expression (100.4 a.u. and 101.9 a.u. respectively). Adapted from Blake *et al.* (2006).

B. Mean population fitness, W , as a function of the concentration of Zeocin ([Zeo]). Here, mean fitness refers to the percentage of cells that survive the stress imposed by Zeocin ([Zeo]). Adapted from Blake *et al.* (2006).

C. Schematic illustration of lognormal distributions for a low- and high-noise population. A greater number of cells in the high-noise population express above (cell survival) and below (cell death) the high- and low-stress thresholds respectively.

D. Fitness curves portraying mean fitness as a function of imposed stress level, s . The curves are obtained from the cumulative distribution function (cdf) by calculating its complement (equal to 1-cdf) associated with low- ($\eta = 0.6$) and high-noise ($\eta = 1.2$) lognormally distributed populations of equal means (100 a.u.). Stress level is assumed proportional to the protein production threshold (P_{thres}) necessary for survival following $s = P_{\text{thres}}/1082.9$ to ensure a similar scaling as in (B).

E. Differential fitness obtained as the difference between the fitness curves in (D). High noise in stress protein expression provides a fitness advantage and disadvantage above and below a critical stress level, s_{crit} , respectively.

F. Differential fitness as a function of stress level and noise. Differential fitness is calculated as the difference between the fitness of a population with variable noise η and a reference population of fixed low noise ($\eta_{\text{low}} = 0.1 < \eta$) and equal mean protein content (300 a.u.).

expression states where protein production is sufficient for survival and therefore increases the value of s_{crit} .

Collectively, these observations suggest that high cell-cell variability in the expression of individual stress-related

genes does not unconditionally confer a selective advantage and may significantly increase the fitness disadvantage under low-stress conditions. For these reasons, selection for specific noise levels in constitutively

expressed genes for the main purpose of conferring robustness to stress might be difficult to realize. Interestingly, when Blake *et al.* (2006) induced gene expression simultaneously with the antibiotic stress, the high-noise strain demonstrated a clear initial growth advantage attributable to the presence of a subset of rapidly responding cells. In the context of promoter-mediated transcriptional bursting, it must therefore be considered that the primary function of strong TATA-box sequences might be to facilitate rapid expression in sense-and-respond gene networks. The capacity for rapidly inducing high levels of gene expression, rather than added gene expression noise, might be a more likely evolutionary basis for the prevalence of TATA-box sequences in the promoter regions of stress-response genes. This, of course, does not exclude the possibility that gene expression noise can play a critical role within the context of larger gene regulatory networks. It is also noted that these conclusions are based on the exploration of differential fitness between populations approximated by lognormal distributions and a simple threshold survival model. While the lognormal form captures the frequent experimental observation of long-tailed protein distributions, the effect of employing alternate distributions and survival models remains to be explored.

Stochastic pathway activation

Long-term exposure to environmental stress necessitates mechanisms enabling stable inheritance of better-fit phenotypic states. Intrinsic noise in a constitutively expressed stress-related gene would, in general, not be expected to provide such a mechanism due to the relative rapid nature of these fluctuations compared with cellular proliferation rates. In fact, rapid fluctuations in gene expression noise could have detrimental effects on overall population fitness under persistent stress conditions. The noise would decrease the likelihood of generating viable progeny as better-fit cells would stochastically change their expression levels and become unfit prior to cell division.

One of the simplest mechanisms to stabilize better-fit expression states is positive feedback regulation. Such control has been shown to increase the correlation time of gene expression noise by extending the lifetime of transcriptional pulses compared with those generated by purely intrinsic mechanisms (Weinberger *et al.*, 2008). This could equivalently be used to slow down fluctuation rates and improve the likelihood that beneficial expression states are stably inherited. Theoretically, the strength of the feedback loop could be modulated by the environmental stress. In this simplistic sense-and-response circuit, gene expression noise would cause above-threshold gene expression in a small subset of cells in the absence of stress. Following the onset of stress, these cells would

be able to upregulate their gene expression rapidly and stably pass this better-fit expression state to their progeny. In this case, gene expression noise essentially acts as a trigger of a feedback-based switch (Becskei *et al.*, 2001).

The above simplistic sense-and-response circuit exemplifies how gene expression noise might facilitate stochastic cell fate decisions by activating regulatory programmes that enable long-term maintenance of beneficial gene expression. All-or-none switching between phenotypic states can be driven by noise in bistable regulatory networks (Dubnau and Losick, 2006; Losick and Desplan, 2008). Such networks are commonly associated with a characteristic S-shaped curve whose turning points demarcate the region where states of high and low expression coexist (Fig. 2A). Spontaneous switching between the two states requires a perturbation that exceeds the activation threshold, which, for example, could be provided by intrinsic gene expression noise in a key regulator. The probability of such a perturbation depends on the activation threshold, that is, the distance of the current expression state to the middle branch of the S-shaped curve, and therefore on the distance to the turning point. In a cell population, spontaneous switching results in the emergence of population bimodality in which the population is statistically partitioned into distinct expression states. Biological examples include the lysis/lysogeny decision circuit in bacteriophage λ (Arkin *et al.*, 1998), the activation of the lactose utilization pathway in *Escherichia coli* (Ozbudak, 2004), the activation of the galactose utilization network in *Saccharomyces cerevisiae* (Acar, 2005), the stringent response in mycobacteria (Sureka *et al.*, 2008), sporulation in *Bacillus subtilis* (Smits, 2006; Veening, 2008) and synthetic gene circuits (Kashiwagi *et al.*, 2006).

The probability of noise-induced transitions between all-or-none expression states can be controlled by two proven mechanisms, varying the noise level or the activation threshold. These mechanisms are illustrated in Fig. 2. In Fig. 2B, a regulatory signal, for example, the activity of a transcription factor, is increased while the noise in this signal remains constant. In this case, the increased signal causes a shift towards the turning point of the S-shaped curve, which increases the probability of a spontaneous switch from the low- to the high-expression states. In Fig. 2C, the average signal is kept fixed while the noise in the signal is increased. In this case, a transition to the high-expression state becomes more likely as the probability of attaining a sufficient fluctuation is increased.

An example of stochastic pathway activation relying on threshold modulation is the development of genetic competence in *B. subtilis* (Hamoen *et al.*, 2003; Leisner *et al.*, 2007). Following entry into stationary phase, a small subpopulation enters into a transient state of competence

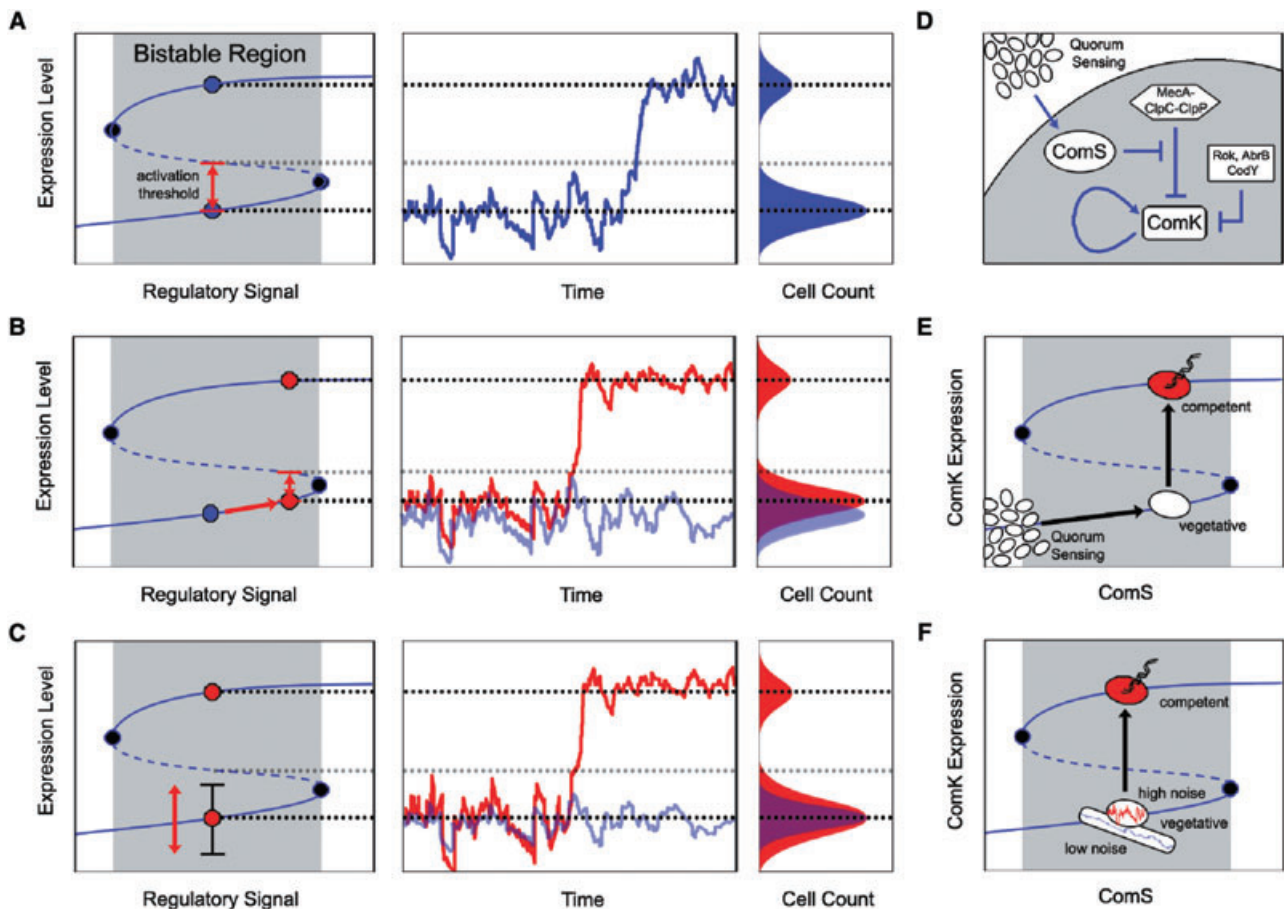


Fig. 2. Bistability, gene expression noise and competence.

A. Steady-state diagram, time-series and population distribution portraying the bistability that underlies spontaneous switching in individual cells and the resultant bimodal population distribution.

B. Increasing the regulatory signal increases the probability of a noise-induced switch from the low state by effectively lowering the perturbation necessary to cross the activation threshold.

C. Increasing the gene expression noise increases the probability of a spontaneous switch by increasing the magnitude of fluctuations towards the activation threshold.

D. Schematic representation of the competence network of *B. subtilis*.

E. Threshold modulation in the development of competence. Quorum-sensing pheromones increase ComK activity and the probability of a switch to competency by lowering the activation threshold.

F. Noise modulation in the development of competence. Cells with high ComK expression noise are more likely to switch to competence than those with low noise (mutants displaying an elongated syncytial phenotype).

characterized by the expression of specific DNA-binding and -uptake machinery, temporary growth arrest and an increased ability to absorb new genetic material. By inducing its own transcription, the master regulator of this response, ComK, generates a positive feedback loop believed sufficient to establish a bistable genetic switch (Maamar and Dubnau, 2005; Smits *et al.*, 2005). In non-competent cells, the activity of ComK is limited through transcriptional repression by Rok, AbrB and CodY, as well as MecA-mediated proteolysis (Fig. 2D). Quorum-sensing pheromones, produced in response to increased population density and nutritional stress can induce the synthesis of ComS, which, in turn, binds competitively to the MecA-complex and alleviates ComK degradation. This

contributes to a transient increase in the average basal activity of *comK* and lowers the activation threshold required for noise-induced switching to a high-ComK-expression state and competency (Fig. 2E).

The development of genetic competence has also been used to demonstrate that noise modulation can affect phenotypic switching without changing the mean signal (Fig. 2F). A study by Maamar *et al.* (2007) reduced translational bursting in ComK synthesis by lowering and raising the transcriptional and translational efficiency of the *comK* gene respectively, while maintaining constant basal ComK expression. Alternatively, Süel *et al.* (2007) lowered global variability by creating a syncytial mutant strain in which elongated filamentous cells contain mul-

multiple cell units that share cytoplasm. In this case, differences in protein concentrations among units are averaged by diffusion, resulting in reduced gene expression noise without affecting the mean concentration of cellular components. Both studies found that noise reduction substantially lowers the probability with which a switch towards competence is initiated, consistent with a role of gene expression noise as a trigger of pathway activation.

Bet-hedging

Many of the previously mentioned stochastic mechanisms are related to bet-hedging strategies in which a fraction of the cell population enters into a phenotypic state of reduced fitness in anticipation of future environmental assaults. This survival strategy is well described by evolutionary ecologists to explain why some higher organisms evolve traits that lower their fitness variance across environmental conditions to enhance long-term fitness, despite reductions in average reproduction rate (Gillespie, 1977). Bet-hedging populations might therefore increase phenotypic variance, forfeiting fitness in the average environment in favour of risk spreading (Philippi and Seger, 1989). Classical examples include the variable timing of plant seed germination and insect maturation rates (Hopper, 1999; Evans and Dennehy, 2005; Venable, 2007).

Bacterial persistence provides a prime example of bet-hedging (Balaban *et al.*, 2004; Lewis, 2007) in which a small subset of cells spontaneously enters into a dormant state without apparent environmental cues. Unlike normal cells, these non-growing persister cells can survive adverse environments and guard against population extinction by spontaneously reverting to normal growth at a slow rate. This allows the population to be reseeded when conditions improve. Although persisters reduce population fitness in the average environment, their presence provides a long-term advantage by increasing the probability of survival under prolonged exposure to adverse conditions.

The benefits of employing a pre-emptive bet-hedging strategy have been the subject of intense theoretical analysis (Thattai and van Oudenaarden, 2004; Kussell and Leibler, 2005; Kussell *et al.*, 2005; King, 2007; Donaldson-Matasci *et al.*, 2008; Malik and Smith, 2008) and inspired an experimental study by Acar *et al.* (2008) focusing on the impact of stochastic phenotypic switching on population fitness in fluctuating environments. The investigation employed a yeast strain in which the switching rates between two distinct gene expression states could be modulated (Acar *et al.*, 2005). This strain was further modified such that the high-gene-expression state conferred a fitness advantage in one environment while

the low-gene-expression state was more advantageous in another.

Following transfer from a neutral to selective conditions, fast switchers initially support faster growth than slow switchers; however, after a while, the slow switchers attain growth rates exceeding that of the fast switchers. This initial growth advantage of the fast switchers is attributed to a higher initial phenotypic variability and an increased probability of spontaneously transitioning from the unfit to the better-fit expression states. However, the growth advantage afforded by increased switching rates comes at the cost of increasing the likelihood of switching from the fit to the unfit states, which decreases the overall population fitness under prolonged selection. In other words, while fast switchers can respond rapidly to changing environments, slow switchers are better at specializing to constant environments. Therefore, while fast switchers are expected to out-compete slow switchers in rapidly changing environments, slow switchers are expected to out-compete fast switchers when the environments change less frequently. These expectations were confirmed experimentally, verifying theoretical predictions that the fitness advantage provided by bet-hedging can be further enhanced by tuning phenotypic switching rates to accommodate the frequency of environmental change (Thattai, 2004; Kussell and Leibler, 2005; Kussell *et al.*, 2005).

Discussion

It is clear that we have only begun to appreciate fully the contribution of stochastic processes to cellular responses and their influence on the evolution of the regulatory networks that underpin microbial survival strategies. While it is perhaps intuitive that many sense-and-response cellular decision-making mechanisms, such as metabolic switches, should have evolved nearly deterministic precision, mounting evidence suggests otherwise. For example, the activation of both the lactose utilization pathway in *E. coli* and the galactose utilization in yeast is highly stochastic under a broad range of environmental conditions (Ozbudak *et al.*, 2004; Acar, 2005). It is certainly possible that observed phenotypic variability, in some cases, might have limited direct impact on cell survival and simply be a consequence of cells operating in regimes where molecular-level fluctuations in regulatory networks and signalling transduction are inevitable. For example, a selective advantage of rapid protein synthesis might explain why genes responding to environmental change in yeast display noisy gene expression. Here, the formation of active promoter complexes, such as those created by strong TATA sequences, facilitate fast protein production but also cause mRNA to be synthesized in irregular bursts. It is noted, however, that a similar corre-

lation between promoter-sequence and 'bursty' mRNA synthesis has yet to be demonstrated in bacteria.

The most prominent biological examples demonstrating the benefits of stochasticity in phenotypic diversification, including persistence, sporulation and competence, represent bet-hedging strategies. In these systems, stochasticity increases phenotypic diversity in anticipation of a future adversity at the expense of reduced mean fitness. In sporulation and competence, this is accomplished by increasing the probability of noise-mediated switching between alternate phenotypes in response to environmental cues. Paradoxically, the outcome of this noise-driven switching in individual cells is a highly reproducible, almost deterministic segregation of the cell population into distinct phenotypes.

Bet-hedging, however, is not the only documented type of microbial survival strategy that involves stochastic phenotypic switching. Some microbial pathogens have been found to employ self-destructive cooperation strategies in which individual cells are sacrificed for the greater public good (Ackermann *et al.*, 2008). For example, *Streptococcus pneumoniae* and *Salmonella typhimurium* rely on the release of toxins to enhance colonization within their host. These toxins might help to secure infection by promoting inflammation of surrounding tissue or by removing competitors; however, they can only be released through cell lysis, requiring that some cells be sacrificed. Obviously, such a strategy can only persist if the self-destructive phenotype is limited to a fraction of the population, suggesting the involvement of stochastic regulatory mechanisms similar to those driving phenotypic diversification in sporulation and competence.

An element of randomness in the regulation of gene expression might also provide a primitive, or even primordial, mechanism for coping with unfamiliar environments. Stern *et al.* (2007) recently reported that yeast cells adapt to novel challenges by undergoing global transcriptional reprogramming. Interestingly, the reprogramming involves random gene activation, as the changes in expression of most genes were irreproducible in repeat experiments. Based on their findings, the authors propose a general adaptive strategy that would allow cells to overcome a broad range of stress environments. In this strategy, global mechanisms, such as chromatin remodelling, are proposed to respond by mediating stochastic gene activation. This would increase the adaptive potential of the population through phenotypic diversification by generating a library of different metabolic possibilities. While the underlying molecular-level mechanisms have yet to be identified, the results obtained by Stern *et al.* (2007) provide further strength to the hypothesis that stochastic mechanisms play a fundamental role in the evolution of a diverse range of phenotypic diversification strategies that provide an improved chance of survival.

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