Effect and evolution of gene expression noise on the fitness landscape

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Gene expression is a stochastic process that affects cellular and population fitness. Noise in gene expression can enhance fitness by increasing cell to cell variability as well as the time cells spend in favorable expression states. Using a stochastic model of gene expression together with a fitness function that incorporates the costs and benefits of gene expression in a stressful environment, we show that the fitness landscape is shaped by gene expression noise in more complex ways than previously anticipated. We find that mutations modulating the properties of expression noise enable cell populations to optimize their position on the fitness landscape. Additionally, we find that low levels of expression noise evolve under conditions where the fitness benefits of expression exceed the fitness costs, and that high levels of expression noise evolve when the expression costs exceed the fitness benefits. The results presented in this study expand our understanding of the interplay between stochastic gene expression and fitness in selective environments.

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I. INTRODUCTION

Gene expression is a process fundamental to life in which information encoded in the DNA is processed by the machinery of the cell to produce RNA and protein [1]. This process is stochastic (or noisy) and can introduce significant cell to cell variation in a population of genetically identical cells in a homogenous environment [2–4]. Gene expression noise can be characterized by the distribution of protein levels in individual cells and by the time scale or frequency of the fluctuations [2,5]. Importantly, this nongenetic variation can act as a temporary substrate for natural selection by expanding the range of phenotypes for a given genotype and can increase the fitness of a cell population [6–8].

Previously, a first-passage time framework was developed to model the effect of stress on the reproductive fitness of noisy cell populations [5]. Using this framework, it was demonstrated in the same study that long-term drug resistance could emerge independently of mutation, from fluctuations in gene expression of comparable time scales to those observed in human lung cancer cells. Although the theoretical framework proposed in Ref. [5] is general, to enable analytic solution the fitness function was assumed to be a Heaviside step function where each cell of a given population was either fit (able to divide) or unfit (no longer able to divide or change its expression level) depending on the level of expression, and did not incorporate expression-related fitness costs [9–13]. This resulted in population fitness (growth rate) being independent of gene expression noise (standard deviation divided by the mean) and monotonically increasing with nongenetic memory (relaxation time scale of the fluctuation), when the step fitness function was applied at the mean level of gene expression. The effect of expression noise on fitness when more biologically realistic fitness functions are considered remains to be investigated.

The cost of gene expression should be incorporated into cellular and population-level models of stress resistance. A recent study identified environmental conditions that defined a "sweet spot" of drug resistance that maximized the overall fitness of the cell population [10]. In these experiments, the budding yeast *Saccharomyces cerevisiae* was genetically engineered to contain an inducible positive feedback network that controlled the expression of an antibiotic resistance protein. Fitness was maximized at certain concentrations of inducer and drug. When the concentration of inducer was either too low or too high, then the cells would succumb to an insufficient level of resistance protein or to toxicity costs, respectively. Similarly, a cost-benefit relationship has been observed in *Escherichia coli*, where growth in antibiotics was optimized when the multiple antibiotic resistance promoter was moderately induced [14]. Even in the absence of drugs, microorganisms have been observed to evolve optimal expression levels that maximize growth (e.g., *E. coli* growing in different lactose environments [15]).

Natural selection may act to tune gene expression noise. The expression of genes encoding essential and complex-forming proteins [16,17], as well as proteasomal proteins [18], in budding yeast involves lower noise than most other budding yeast genes. In contrast, gene expression in budding yeast associated with stress response, heat shock, and amino acid synthesis has been found to have elevated levels of noise [17,18]. In Ref. [19], mutations introduced in a promoter driving the expression of an antibiotic resistance gene increased expression noise. The high-noise strain was found to have increased fitness under high concentrations of an acutely applied antibiotic compared to the low-noise strain with no mutations (and vice versa when antibiotic concentration was low). In light of these findings, it has been suggested that strong selective pressure selects for high noise whereas low selective pressure selects for low noise [2,20]. To develop a more comprehensive understanding of how gene expression noise may evolve to optimize fitness, investigations within a cost-benefit framework and in the context of prolonged stress are imperative.

Fitness landscapes have long been used to visualize the effect of genetic factors on fitness (introduced by Wright in 1932 [21]). Traditionally, in a three-dimensional representation, the X and Y axes represent genotypes or allele frequencies, and the Z axis population fitness. The topography of a fitness landscape is important as it contains key information on the potential

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behaviors of the cell [22]. In the present work, we employ fitness landscapes to represent the effect of gene expression noise on population fitness.

The present work investigates the evolution of both gene expression noise magnitude and relaxation time. Previously, it was shown that expression relaxation time (average time for a fluctuation in gene expression level to dissipate back to the mean) can increase the probability of acquiring a drug resistance mutation [5]. However, in that study expression noise magnitude and relaxation time were fixed in the simulations. The effect of noise properties on the fitness landscape for different gene expression cost-benefit scenarios has also not been considered in prior work. Instead, either a step-like fitness function was used and the costs associated with the expression of a stress resistance gene were ignored [5,23], or a cost-benefit fitness function was employed but the effect of noise magnitude and relaxation time on the fitness landscape was not explicitly considered [10]. Kaneko [24] simulated a simple stochastic gene expression network undergoing mutation and selection to study the conditions under which genetic and nongenetic robustness increase to maintain a high-fitness state. In contrast, here we consider how genetic and nongenetic effects shape the fitness landscape and show that noise magnitude and relaxation time can evolve to attain an optimal phenotype in different cost-benefit scenarios.

II. MODELING AND SIMULATION

A. Cellular and population fitness

The phenomenological model for microscopic or cellular fitness w was inspired by Nevozhay *et al.* [10]:

$$w(x) = \frac{\alpha_c^n}{\alpha_c^n + x^n} \frac{x^n}{\alpha_b^n + x^n}, \tag{1}$$

where the first and second terms on the right-hand side respectively describe the cost and benefit of expressing the stress resistance protein x in a stressful environment. When there is no cost to gene expression, w is modeled using only the benefit term. α_c is a constant that describes the metabolic cost or toxicity of expressing x (the lower α_c the higher the expression cost), α_b is a constant that is related to the level of stress resistance provided by x (the lower α_b the higher the expression benefit), and n is the Hill coefficient. Unless otherwise indicated, $\alpha_c = 2.3$ for no-cost expression, $\alpha_c = 1.2$ for low-cost expression, $\alpha_c = 1$ for high-cost expression, and $n = 40$ and $\alpha_b = 1$ for all three cases. The α_c and α_b values were normalized by the mean level of gene expression. The high n value was used in order to obtain sufficiently steep sigmoidal and narrow bell-shaped fitness functions such that a wide range of different fitness scenarios could be investigated and compared (alternatively, we could have used a fitness function with a lower value of n imposed on wider gene expression distributions), including scenarios from previous work that employed a Heaviside step fitness function [5]. The resulting cellular fitness function is a sigmoidal function that saturates when x is high when there is no cost associated with gene expression [Fig. 1(a)]. When there is a gene expression cost then w takes on a bell shape, with a higher maximum fitness and increased width when the expression cost is low [Fig. 1(b)] compared to when the expression cost is high [Fig. 1(c)].

Macroscopic or population-level fitness W is described by the number of cell divisions that occur during a given generation

$$W = \frac{N_{\text{div}}}{N_{\text{cell}}}, \tag{2}$$

where N_{div} is the number of division events and N_{cell} is the number of cells in the population fixed by the constant-number Monte Carlo method (see Sec. II B and Refs. [5,25,26]). All the cells in the population divide during a given generation when $W = 1$, and no cells divide when $W = 0$.

B. Gene expression, population dynamics, and mutation

We use the Ornstein-Uhlenbeck (OU) process (originally used to describe a particle in Brownian motion [27]) to model gene expression generally [5,28]. The OU process can be described by the Langevin equation

$$\frac{dx(t)}{dt} = \frac{1}{\tau}[\mu - x(t)] + c^{1/2}\xi_t, \tag{3}$$

where c and τ are the diffusion constant and the relaxation time, respectively, and ξ_t is Gaussian white noise ($\langle \xi_t \rangle = 0$, $\langle \xi_t \xi_{t'} \rangle = \delta(t - t')$) [27]. The steady-state probability density function of the OU process is a Gaussian distribution with mean μ (set to $\mu = 1000$) and variance $\sigma^2 = c\tau/2$ [thus gene expression noise is given by $\eta = \sqrt{(c\tau/2\mu^2)}$]. The OU process was simulated using an exact numerical simulation method [Figs. 1(d)–1(f)] [29].

To perform the population-level simulations at a single-cell resolution, we use a population dynamics algorithm [25]. This algorithm combines a method to simulate the gene expression in each cell [here the numerical simulation of OU process described by Eq. (3)] and a constant-number Monte Carlo approach (originally developed to model particulate processes [30]), which restores the population size to N_{cell} by randomly selecting mother and daughter cells at the end of each generation, to accurately simulate the statistical characteristics of a growing cell population. Simulations were initialized by drawing the initial values of the cell cycle clock from a uniform distribution $[0,t_D]$, where the time to next cell division, t_{div}, is given by $t_D/w(x)$, where t_D is the cell division time in absence of selection. The cell cycle clock is reset to zero and x is partitioned equally between the daughter cells at each cell division. All time scales in this study are reported with respect to t_D, which is set to unit time. All simulation results were obtained from 20 realizations of 1000 cells.

In order to model the effect of mutation on gene expression noise and fitness in Sec. III B, we assigned a probability P_m of changing parameters c or τ to the daughter cells at each cell division event. Here, P_m accounts for mutations that can occur when DNA is not copied correctly as well as other sources of mutation [31]. In these simulations, the initial values of c and τ for all the cells in the population were chosen randomly from a uniform distribution and were allowed to mutate at a rate of 5×10^{-3} per genome per division [32] over 1000 generations. We note that the basal mutation rate of stable genomes is estimated to be 10^{-10} per base pair per

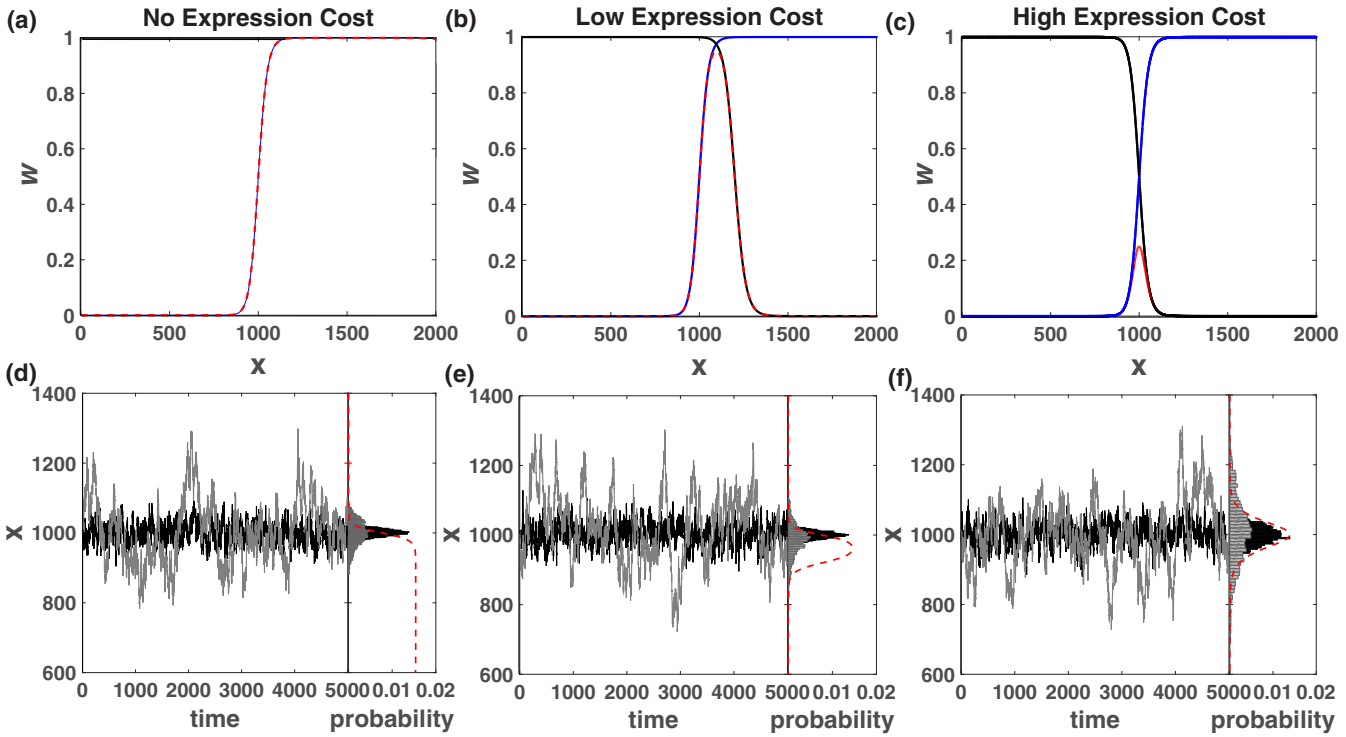

FIG. 1. (Color online) Fitness function describing the cost and benefit of expressing a stress resistance protein. Top row panels show cellular fitness (w) as a function of expression level (x) for (a) no-cost, (b) low-cost, and (c) high-cost gene expression. Black lines represent expression cost, blue (gray) lines expression benefit, and dashed red (gray) lines the resulting cellular fitness. Bottom row panels correspond to the top row panel above them (in terms of the fitness function and gene expression cost and benefit) and show expression time series for low ($\eta = 0.03$, $\tau = 10$, and $c = 200$: black lines and histograms) and high ($\eta = 0.1$, $\tau = 100$, and $c = 200$: gray lines and histograms) expression noise (η) and corresponding histograms depict the probability that a cell will have a given x.

cell generation [33]. However, in certain conditions the rate of mutation can increase significantly [34]. Hypermutation has been observed in *E. coli* [35] and murine cells [36] resulting in a mutation rate hundreds and tens of thousands of times the basal mutation rate, respectively. The high mutation rate used in our study was to render the stochastic simulations feasible by shorting transient times to steady state, and it has been assumed that mutation in multiple genes in the genome affects the expression of the drug resistance gene (increasing the effective mutation rate); no qualitative difference in the results was observed when compared to simulations performed using mutation rates of up to two orders of magnitude higher (data not shown).

III. RESULTS AND DISCUSSION

A. Gene expression noise shapes the fitness landscape

We begin by generating the fitness landscape corresponding to a model of cellular fitness w that does not consider the metabolic or toxicity cost of protein production. In this model, w is described by a step fitness function where cells cease to divide and are unable to change their protein level x if it falls below a critical threshold x_c (set to μ) [5]. The result in this case is that population fitness W is independent of gene expression noise η and increases monotonically with relaxation time τ (Fig. 2, left) [5,23]. When x_c is increased above μ, W increases monotonically with both η and τ (Fig. 2, center and right). As expected, in this scenario W decreases for all values of η and τ as x_c is increased (Fig. 2).

When w is modeled using the cost-benefit fitness function [Eq. (1)], and individual cells are allowed to recover from low levels of w by changing x, the η-τ fitness landscapes corresponding to no-cost, low-cost, and high-cost expression differ qualitatively from previous work (Fig. 2, left) and each another (Fig. 3).

Population fitness increases with η and very slightly with τ when there is no cost to expressing a resistance conferring protein (Fig. 3, left). For a low cost of resistance protein expression, there is a fitness peak similar to that found in Ref. [10] at around $\eta = 0.2$, and fitness maxima for low values of τ (Fig. 3, center). In this case, high relaxation time values are detrimental to fitness when $\eta > 0.2$. When the cost of resistance protein expression is high, the fitness landscape is flat except for a small fitness increase when the values of η and τ are low (Fig. 3, right). The fitness landscapes are largely unaffected by the relaxation time except at low values of τ (high frequency gene expression fluctuations). As expected, overall the population fitness values for a given combination of η and τ decrease as the cost of expressing the resistance protein increases (Fig. 3).

These results demonstrate that the relationship between η, τ, and W can differ significantly from a monotonically increasing fitness function when a cost-benefit fitness function is incorporated. In agreement with previous work [5], the monotonic fitness landscape is recovered in all cases when

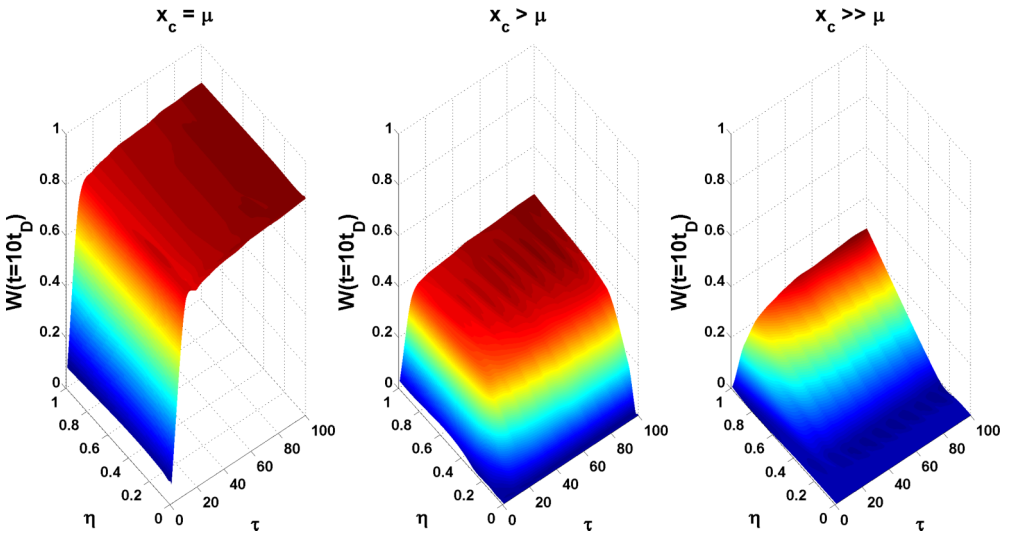

FIG. 2. (Color online) Fitness landscapes generated using a step fitness function. Left: population fitness (W) after 10 generations ($10t_D$) of exposure to a stressful environment as a function of noise magnitude (η) and relaxation time (τ) when the critical threshold step-fitness function (x_c) is set to the mean expression level ($\mu = 1000$). Similarly, center and right panels show W when x_c is set to values above μ ($x_c = 1200$ and $x_c = 2300$, respectively). Left panel was first published in Ref. [23].

fitness is modeled using a critical fitness threshold function (data not shown).

B. Evolving gene expression noise to maximize fitness

When random mutations affecting η and τ were incorporated into the simulations, the population evolved to maximize fitness (Fig. 4). When the cost of gene expression was low and the initial values of η and τ were such that fitness was not optimal, the average values of η and τ across the population continued to change until the population occupied a peak on the fitness landscape. Once the values of η and τ were such that the population occupied a region of maximum fitness on the landscape, the population remained in this region for the duration of the simulation. Similar results were found when there was no cost and a high cost associated with gene expression (data not shown). These results suggest that cell populations may evolve by mutations that tune gene expression noise magnitude and relaxation time to optimize population fitness.

In order to investigate if cell populations will evolve high levels of gene expression noise when the selection threshold is high (and vice versa when the selection threshold is low), we obtained the average η for populations with various values of expression cost (α_c) and benefit (α_b) parameters after many generations of stress exposure, both with and without mutation in parameters affecting η (Fig. 5). Without mutation, the landscape was rugged with the level of η randomly distributed for the various combinations of α_c and α_b (Fig. 5, left). The random pattern occurred in this case because the initial c and τ values for each realization of a particular combination of α_c

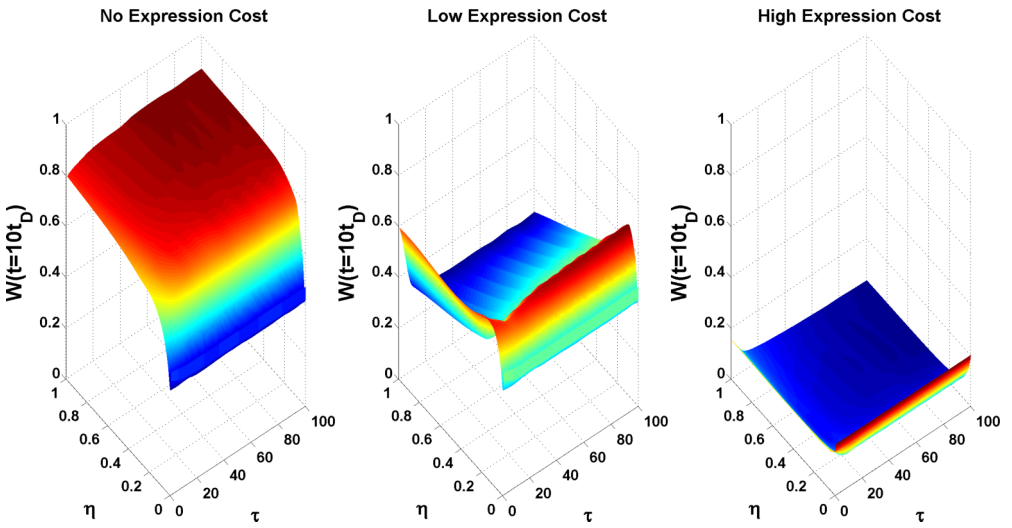

FIG. 3. (Color online) Fitness landscapes generated using a cost-benefit fitness function. Population fitness (W) after 10 generations ($10t_D$) is shown as a function of gene expression noise (η) and relaxation time (τ) for no-cost (left), low-cost (center), and high-cost (right) gene expression.

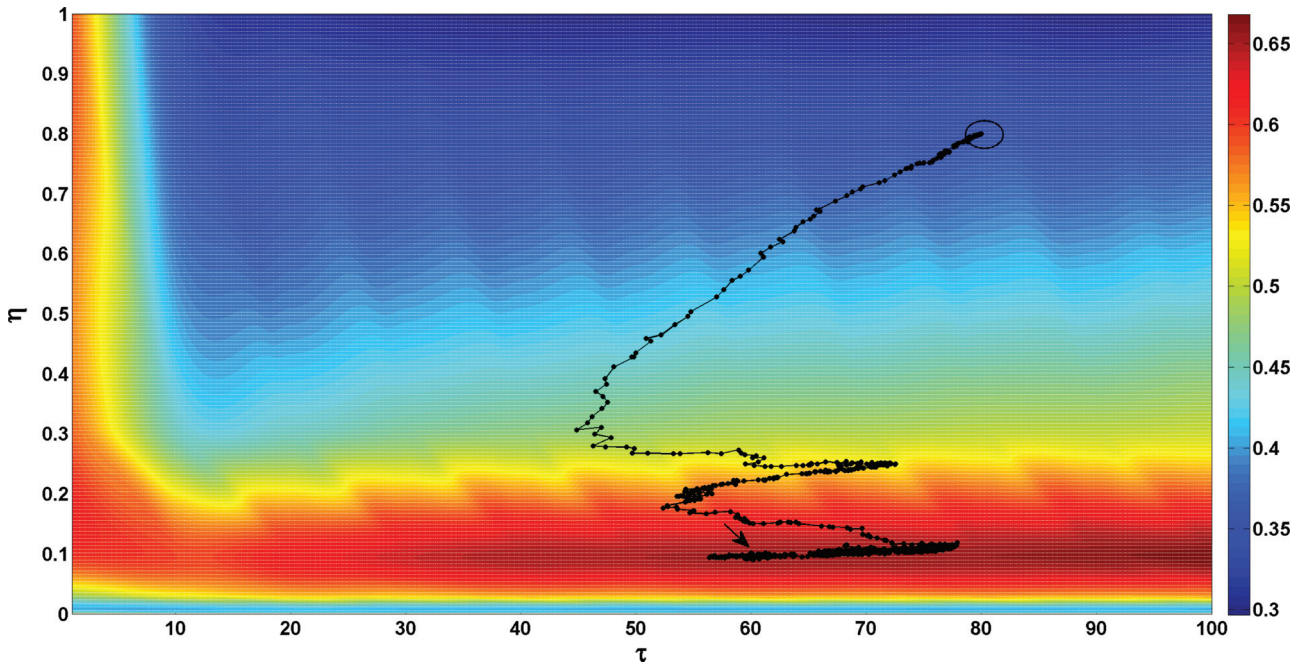

FIG. 4. (Color) Mutation of gene expression noise magnitude and relaxation time parameters optimizes stress resistance on the fitness landscape. The heat map for low-cost gene expression shows how population fitness (W) (value indicated by the color bar) depends on gene expression noise (η) and relaxation time (τ). The open circle and arrow respectively represent the initial position (80.0,0.800) and final position (60.1,0.0963) of the trajectory of a representative population that evolved over 1000 generations on the fitness landscape.

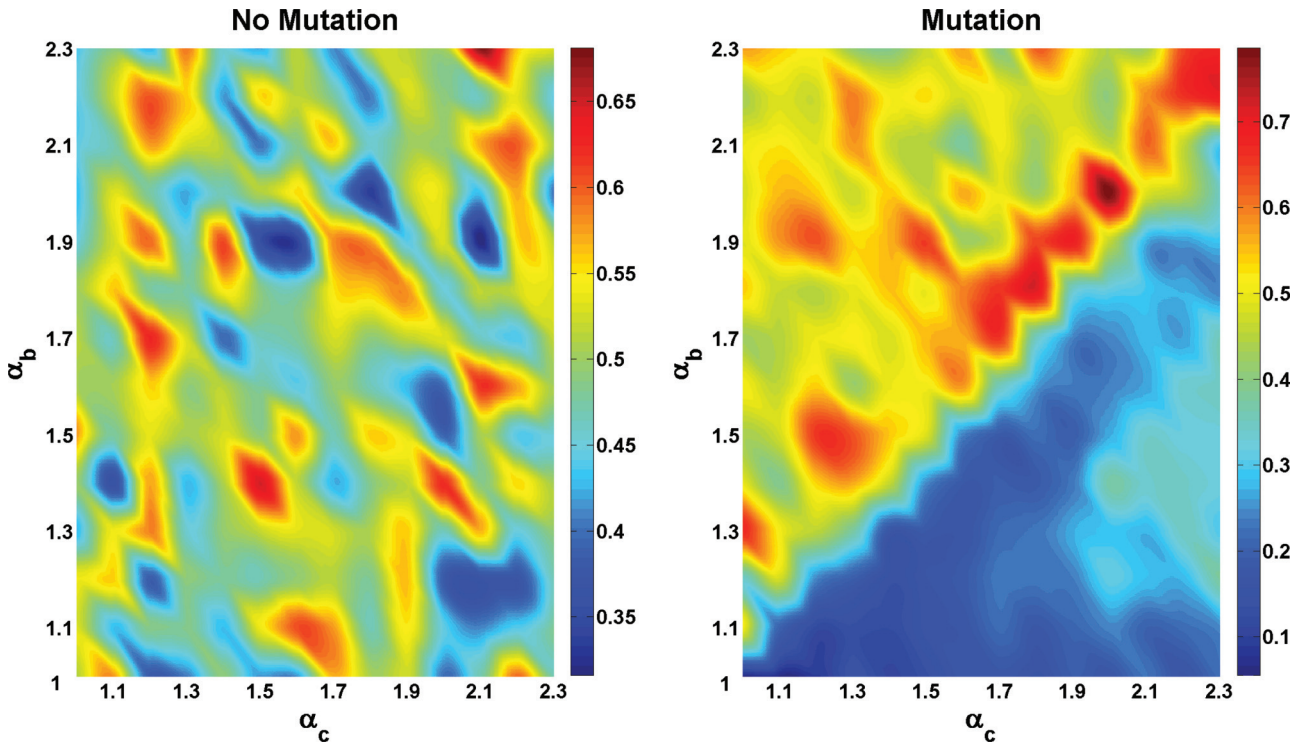

FIG. 5. (Color) Evolution of gene expression noise when fitness costs and benefits are considered. The heat map shows the final level of gene expression noise (η) after 1000 generations of stress exposure without mutation (left) and with mutation (right) for various values of cost (α_c) and benefit (α_b) parameters (higher values of α_c and α_b respectively represent lower fitness costs and benefits of expressing a stress resistance gene). The color bars indicate the level of η.

and α_b were drawn from a random distribution and not allowed to mutate. Interestingly, when mutation was permitted, lower levels of η evolved when α_c exceeded α_b (Fig. 5, right). Recall that in the present model higher α_b (or lower α_c) values are indicative of higher levels of selection, as cellular fitness is decreased if α_b is increased (or α_c is decreased) for the same level of gene expression. Therefore, these simulation results confirm that lower expression noise will evolve under a low selection threshold and that higher expression noise will evolve under a high selection threshold (Fig. 5, right) [2,20], when the costs and benefits as well as the relaxation time of gene expression are considered.

IV. CONCLUSION

In this study, we relaxed the assumptions made previously [5] by using a fitness function that accounts for the costs and benefits of expressing a resistance protein to study how population fitness depends on both gene expression noise magnitude and relaxation time. To investigate the evolution of gene expression noise in the context of a stressful environment, we allowed the expression noise properties of the cell to mutate under selective pressure for different cost-benefit scenarios.

The relationship between gene expression noise and population fitness turned out to be more complex than previously described [5,23]. The use of a more biologically realistic cost-benefit fitness function resulted in fitness landscapes where the topology depended on both noise magnitude and the fluctuation time scale, as well as the expression-related fitness cost. The fitness landscape was shaped by the properties of gene expression noise such that, depending on the cost of gene expression, fitness peaks as well as plateaus defined the fitness landscape.

Natural selection may act on random mutations to tune noise frequency as well as noise magnitude to maximize population fitness. The *in silico* cell populations in our study evolved to occupy the plateaus and peaks of the fitness landscapes under random mutation that modulated noise properties. The topology of a gene regulatory network may in fact be subject to selection in this context, as network topology has been shown to modulate gene expression noise and relaxation time [26,37–39].

We found that lower gene expression noise evolved when the fitness benefits of gene expression exceeded the fitness costs. The explanation for this phenomenon in our model is that when expression benefits exceeded expression costs, population fitness was maximized when the constituent cells minimized expression noise by expressing around a narrow optimum level of gene expression. There are many scenarios where low levels of gene expression noise are beneficial, including bacterial persistence against antibiotics [9,40], bacterial competence under nutrient limitation [41,42], and the coordination of multiple downstream stress response mechanisms [43]. Conversely, when the expression costs exceeded the benefits there was no longer a level of expression that significantly enhanced fitness, and as a result there was no selective pressure to minimize gene expression noise. The latter scenario, though possible in certain cases (e.g., phenotype switching in fluctuating environments [44,45]), will be selected against in a constant environment of sufficient duration.

Due to the general nature of the model of gene expression and the fitness function, we anticipate that our findings will apply to other cases of cell populations under stress. It would be interesting to investigate, for example, how the costs and benefits of noisy heat-shock protein expression [17] in selective high temperature environments impact cellular fitness, or the specific genetic and nongenetic contributions to the evolution of phenotypic variance [24] when both gene expression noise magnitude and frequency are explicitly considered.

The hypotheses advanced in this study as well as in previous work [5,26] are under experimental investigation. Presently, we are evolving synthetic gene regulatory networks that control inducible drug resistance genes in budding yeast to better understand how mutation affects gene regulatory network dynamics and the development of drug resistance.

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[1] F. Crick, Central dogma of molecular biology, Nature (London) **227**, 561 (1970).
[2] A. Eldar and M. B. Elowitz, Functional roles for noise in genetic circuits, Nature (London) **467**, 167 (2010).
[3] M. Kaern, T. C. Elston, W. J. Blake, and J. J. Collins, Stochasticity in gene expression: From theories to phenotypes, Nat. Rev. Genet. **6**, 451 (2005).
[4] M. S. Samoilov, G. Price, and A. P. Arkin, From fluctuations to phenotypes: The physiology of noise, Sci. STKE **366**, re17 (2006).
[5] D. A. Charlebois, N. Abdennur, and M. Kaern, Gene Expression Noise Facilitates Adaptation and Drug Resistance Independently of Mutation, Phys. Rev. Lett. **107**, 218101 (2011).
[6] A. Brock, H. Chang, and S. Huang, Non-genetic heterogeneity—a mutation-independent driving force for the somatic evolution of tumours, Nat. Rev. Genet. **10**, 336 (2009).
[7] C. J. Davidson and M. G. Surette, Individuality in bacteria, Annu. Rev. Genet. **42**, 253 (2008).
[8] D. Fraser and M. Kaern, A chance at survival: Gene expression noise and phenotypic diversification strategies, Mol. Microbiol. **71**, 1333 (2009).
[9] N. Q. Balaban, J. Merrin, R. Chait, L. Kowalik, and S. Leibler, Bacterial persistence as a phenotypic switch, Science **305**, 1622 (2004).
[10] D. Nevozhay, R. M. Adams, E. V. Itallie, M. R. Bennett, and G. Balázsi, Mapping the environmental fitness landscape

of a synthetic gene circuit, PLoS Comput. Biol. **8**, e1002480 (2012).
[11] T. N. Nguyen, Q. G. Phan, L. P. Duong, K. P. Bertrand, and R. E. Lenski, Effects of carriage and expression of the Tn10 tetracycline-resistance operon on the fitness of *Escherichia coli* K12, Mol. Biol. Evol. **6**, 213 (1989).
[12] E. Rotem, A. Loinger, I. Ronin, I. Levin-Reisman, C. Gabay, N. Shoresh, O. Biham, and N. Q. Balaban, Regulation of phenotypic variability by a threshold-based mechanism underlies bacterial persistence, Proc. Natl. Acad. Sci. USA. **107**, 12541 (2010).
[13] L. Van Melderen and M. Saavedra De Bast, Bacterial toxin-antitoxin systems: More than selfish entities?, PLoS. Genet. **5**, e1000437 (2009).
[14] K. B. Wood and P. Cluzel, Trade-offs between drug toxicity and benefit in the multi-antibiotic resistance system underlie optimal growth of E. coli, BMC Syst. Biol. **6**, 48 (2012).
[15] E. Dekel and U. Alon, Optimality and evolutionary tuning of the expression level of a protein, Nature (London) **436**, 588 (2005).
[16] H. B. Fraser, A. E. Hirsh, G. Giaever, J. Kumm, and M. B. Eisen, Noise minimization in eukaryotic gene expression, PLoS Biol. **2**, e137 (2004).
[17] J. R. S. Newman, S. Ghaemmaghami, J. Ihmels, D. K. Breslow, M. Noble, J. L. DeRisi, and J. S. Weissman, Single-cell proteomic analysis of *S. cerevisiae* reveals the architecture of biological noise, Nature (London) **441**, 840 (2006).
[18] A. Bar-Even, J. Paulsson, N. Maheshri, M. Carmi, E. O'Shea, Y. Pilpel, and N. Barkai, Noise in protein expression scales with natural protein abundance, Nat. Genet. **38**, 636 (2006).
[19] W. J. Blake *et al.*, Phenotypic consequences of promoter-mediated transcriptional noise, Mol. Cell **24**, 853 (2006).
[20] Y. Ito, H. Toyota, K. Kaneko, and T. Yomo, How selection affects phenotypic fluctuation, Mol. Syst. Biol. **5**, 264 (2009).
[21] S. Wright, The roles of mutation, inbreeding, crossbreeding and selection in evolution, Proc. 6th Int. Cong. Genet. **1**, 356 (1932).
[22] S. Huang, Non-genetic heterogeneity of cells in development: More than just noise, Development **136**, 3853 (2009).
[23] D. A. Charlebois and M. Kaern, An accelerated method for simulating population dynamics, Commun. Comput. Phys. **14**, 461 (2013).
[24] K. Kaneko, Evolution of robustness to noise and mutation in gene expression dynamics, PLoS One **2**, e434 (2007).
[25] D. A. Charlebois, J. Intosalmi, D. Fraser, and M. Kaern, An algorithm for the stochastic simulation of gene expression and heterogeneous population dynamics, Commun. Comput. Phys. **9**, 89 (2011).
[26] D. A. Charlebois, G. Balazsi, and M. Kaern, Coherent feedforward transcriptional regulatory motifs enhance drug resistance, Phys. Rev. E **89**, 052708 (2014).
[27] G. E. Uhlenbeck and L. S. Ornstein, On the theory of the Brownian motion, Phys. Rev. **36**, 823 (1930).
[28] V. Shahrezaei and P. S. Swain, Analytical distributions for stochastic gene expression, Proc. Natl. Acad. Sci. USA. **105**, 17256 (2008).
[29] D. T. Gillespie, Exact numerical simulation of the Ornstein-Uhlenbeck process and its integral, Phys. Rev. E **54**, 2084 (1996).
[30] M. Smith and T. Matsoukas, Constant-number Monte Carlo simulation of population balances, Chem. Eng. Sci. **53**, 1777 (1998).
[31] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter, *Molecular Biology of the Cell* (Garland Science, New York, 2007).
[32] G. I. Lang and A. W. Murray, Estimating the per-base-pair mutation rate in the yeast *Saccharomyces cerevisiae*, Genetics **178**, 67 (2008).
[33] C. F. Baer, M. M. Miyamoto, and D. R. Denver, Mutation rate variation in multicellular eukaryotes: Causes and consequences, Nat. Rev. Genet. **8**, 619 (2007).
[34] S. Rosenberg, Evolving responsively: Adaptive mutation, Nat. Rev. Genet. **2**, 504 (2001).
[35] H. Lee, E. Popodi, H. Tang, and P. L. Foster, Rate and molecular spectrum of spontaneous mutations in the bacterium *Escherichia coli* as determined by whole-genome sequencing, Proc. Natl. Acad. Sci. USA **109**, E2774 (2012).
[36] M. Wabl, P. D. Burrows, A. von Gabain, and C. Steinberg, Hypermutation at the immunoglobulin heavy chain locus in a pre-B-cell line, Proc. Natl. Acad. Sci. USA. **82**, 479 (1985).
[37] M. Acar, A. Becskei, and A. van Oudenaarden, Enhancement of cellular memory by reducing stochastic transitions, Nature (London) **435**, 228 (2005).
[38] D. Orrell and H. Bolouri, Control of internal and external noise in genetic regulatory networks, J. Theor. Biol. **230**, 301 (2004).
[39] V. Shahrezaei, J. F. Ollivier, and P. Swain, Colored extrinsic fluctuations and stochastic gene expression, Mol. Syst. Biol. **4**, 196 (2008).
[40] K. Lewis, Persister cells, Annu. Rev. Microbiol. **64**, 357 (2010).
[41] G. M. Suel, J. Garcia-Ojalvo, L. M. Liberman, and M. B. Elowitz, An excitable gene regulatory circuit induces transient cellular differentiation, Nature (London) **440**, 545 (2006).
[42] G. M. Süel, R. P. Kulkarni, J. Dworkin, J. Garcia-Ojalvo, and M. B. Elowitz, Tunability and noise dependence in differentiation dynamics, Science **315**, 1716 (2007).
[43] J. Garcia-Bernardo and M. Dunlop, Noise and low-level dynamics can coordinate multicomponent bet hedging mechanisms, Biophys. J. **108**, 184 (2015).
[44] M. Acar, J. T. Mettetal, and A. van Oudenaarden, Stochastic switching as a survival strategy in fluctuating environments, Nat. Genet. **40**, 471 (2008).
[45] E. Kussell and S. Leibler, Phenotypic diversity, population growth, and information in fluctuating environments, Science **309**, 2075 (2005).