Stochastic Gene Expression and the Processing and Propagation of Noisy Signals in Genetic Networks

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Abstract. Over the past few years, it has been increasingly recognized that stochastic mechanisms play a key role in the dynamics of biological systems. Genetic networks are one example where molecular-level fluctuations are of particular importance. Here stochasticity in the expression of gene products can result in genetically identical cells displaying significant variation in biochemical or physical attributes. This variation can influence individual and population-level fitness.

Cells also receive noisy signals from their environments, perform detection and transduction with stochastic biochemistry. Several mechanisms, including cascades and feedback loops, allow the cell to manipulate noisy signals and maintain signal fidelity. Furthermore through a biochemical implementation of Bayes's rule, it has been shown that genetic networks can act as inference modules, inferring from intracellular conditions the likely state of the extracellular environment.

Keywords: stochastic gene expression, fitness, genetic networks, signal processing and propagation, Bayesian inference.

1 Introduction

Genetic networks, defined as ensembles of molecules and interactions that control gene expression, produce and regulate cellular dynamics. At a fundamental level, a gene is information encoded in a sequence of nucleotides. This information is processed by the machinery of the cell to execute the instructions it contains. Understanding the process by which this information is produced, processed, and propagated is vital for understanding cellular behaviour.

Advancements in experimental techniques for empirically measuring gene expression in single cells, as well as in corresponding theoretical methods, have

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enabled the rigorous design and interpretation of experiments that provide incontrovertible proof that there are important endogenous sources of stochasticity (randomness) that drive biological processes [51]. For example, heterogeneity within a population of a single cell type can be measured experimentally using flow-cytometry analysis, a technique commonly employed for counting and examining the chemical and physical properties of cells. Specifically, one can obtain within a few seconds a histogram of a given protein in individual cells across a large cell population. Within the histogram, the abundance of the protein in the cells with the lowest and highest expression level typically differs by orders of magnitude; this spread far exceeds signal measurement noise [15].

The stochastic expression of gene products (mRNA and protein) is important for human health and disease. Take for example the development of drug resistance during chemotherapy. When the drug Imatinib is used to treat chronic myeloid leukemia, the disease recurs with a frequency of 20-30 % [14]. Even though numerous genetic mutations have been shown to render the drug ineffective [27,23,63], in two-thirds of cases no mutations have been found [14]. Instead, elevated levels of survival pathway proteins in Imatinib-resistant leukaemia cell lines were detected [37]. The rapid rate of resistance development, its dose dependence and high frequency of upregulation of the correct pathways are consistent with non-genetic heterogeneity, that is, variation in gene expression across a population of genetically identical cells. This mechanism generates enduring outlier cells with distinct phenotypes (i.e. any observable biochemical or physical attributes), some of which may be subject to selection.

Cells sense and process information using biochemical networks of interacting genes and proteins [29]. At a specific point of the network (input) a signal is detected and then is propagated to modulate the activity or abundance of other network components (output). In order to process information reliably, the cell requires a high degree of sensitivity to the input signal but a low sensitivity to random fluctuations in the transmitted signal. However, the signals that a cell receives from its environment and propagates through its genetic network are noisy [29,43]. Understanding how this noise is processed and propagated in gene networks is crucial for understanding signal fidelity in natural networks and designing noise-tolerant gene circuits [42]. For example, several network motifs allow for amplification or attenuation of noisy signals [4,8,18,28,38,42,44,49,52,57]. Additionally, it has been shown that genetic networks can be used by cells to infer the likely state of their stochastic external environment from noisy intercellular conditions [32,43].

The chapter is organized as follows: Section 2 presents the process of gene expression, the inherent stochasticity in this process, and common measures of noise. Some background for the deterministic and stochastic modelling and simulation of gene expression, as well as a comparison between these two methods, is provided in Section 3. Section 4 introduces mechanisms, namely genetic cascades and feedback loops, that enable the cell to process and propagate noisy intracellular and extracellular signals. In Section 5, the relationship between noise and fitness is explored. Specifically, the stochastic expression of stress-related genes

and bet-hedging cell populations are discussed, and corresponding models and simulations are presented. The final section (Section 6), illustrates how genetic networks can infer the likely state of their extracellular environment through a biochemical implementation of Bayes' rule.

2 Gene Expression and Stochasticity

A gene is a specific sequence of nucleotides encoded in the DNA. Gene expression is the process by which a gene is transcribed and translated to produce messenger RNA (mRNA) and protein, respectively. To initiate transcription, an RNA polymerase (RNAp) must recognize and bind to the promoter region of the gene. Promoters have regulatory sites to which transcription factors can bind to either activate or repress gene transcription. The promoter is followed by the coding sequence, which is transcribed by the RNAp into an mRNA molecule. Transcription stops when the RNAp reaches a termination sequence and unbinds from the DNA. Next, translation ensues wherein ribosomes read the mRNA sequence, and for each codon, a corresponding amino acid is added to a polypeptide chain (a.k.a. a protein). After post-translational processing, the protein becomes capable of performing its specific tasks.

A model of the process of expressing a single gene is shown in Figure 1. Although this depiction is simple compared to the true complexity of gene expression, it captures the essential features including the synthesis of mRNA (M) from a single gene promoter (A) (at a rate s_A), the synthesis of protein (P) from mRNA templates (rate s_P), and the decay of mRNA and protein molecules (rates δ_M and δ_P respectively). Although more complex models of gene expression have been developed (e.g. [34,47,50,56]), the simple model depicted in Figure 1 is sufficient for the purpose of this chapter.

Fig. 1. A simple model for the expression of a single gene (each step represents several biochemical reactions). All steps are modelled as first-order reactions with the indicated rate constants (units of inverse time) associated with these steps.

The expression of gene products is a noisy process [51,30,31,35,41]. The term 'noise' when used in the context of gene expression is a broad reference to the observed variation in protein content among apparently identical cells exposed to the same environment [21]. This noise can be divided up into extrinsic and intrinsic components. Extrinsic noise can be generally defined as fluctuations and

variability that arise in a system due to disturbances originating from its environment, and therefore depends on how the system of interest is defined [53]. Extrinsic gene expression noise arises from several sources including: the metabolic state of the cell, cell-cycle phase, cell age, variability in upstream signal transduction, and the external cellular environment [19,21,30,32,35,42,45,46,56,62]. Intrinsic expression noise refers to the multistep processes that lead to the synthesis and degradation of mRNA and protein molecules which are inherently stochastic due to the underlying binding events which occur as a result of the random collisions between small numbers of molecules (e.g. the binding of transcription factors to one or two copies of a gene) [30].

Several noise measures are used to quantify the degree of heterogeneity in gene expression. The most common is the relative deviation from the average, which is determined by the ratio of the standard deviation σ to the mean μ. In this chapter, noise η refers to this ratio. Another measure of noise, known as the 'fano factor' ($\phi = \sigma^2/\mu$), can be used to uncover trends that might otherwise be obscured by the characteristic $1/\sqrt{\mu}$ scaling of the noise [30,57].

3 Modelling Gene Expression

Biological systems can be modelled at multiple scales, from detailed physical descriptions of molecular interactions to phenomenological representations of populations of organisms. Here we present the approximate ordinary differential equation (ODE) approach and the exact stochastic method to simulate the phenomenological model of gene expression shown in Figure 1.

3.1 Deterministic Modelling

Traditionally, the time evolution of a chemical system is modelled as a deterministic process using a set of ODEs. This approach is based on the empirical law of mass action, which provides a relation between reaction rates and molecular concentrations [60]. Generally, the instantaneous rate of a reaction is directly proportional to the concentration (which is in turn proportional to mass). In the deterministic description of the model shown in Figure 1, the cellular mRNA and protein concentrations ($[M]$ and $[P]$, respectively) are governed by the macroscopic rate equations

$$\frac{d[M]}{dt} = s_A - \delta_M[M], \tag{1}$$

$$\frac{d[P]}{dt} = s_P[M] - \delta_P[P], \tag{2}$$

where the terms $\delta_M[M]$ and $\delta_P[P]$ are the degradation rates for mRNA and protein, respectively; the term $s_p[M]$ is the rate of protein synthesis, and mRNA production occurs at a constant rate (s_A) due to the presence of a single promoter. The steady-state concentrations are given by

$$[M^s] = \frac{s_A}{\delta_M}, \tag{3}$$

$$[P^s] = \frac{[M]s_P}{\delta_P} = \frac{s_A s_P}{\delta_M \delta_P}, \tag{4}$$

and are related to the average steady-state number of M and P (M^s and P^s, respectively) by the cell volume V.

Note that the deterministic mathematical model (Eqs. (1) and (2)) was obtained by treating each step as a first-order chemical reaction and applying the law of mass action. The law of mass action was developed to describe chemical reactions under conditions where the number of each chemical species is so large that concentrations can be approximated as continuous variables without introducing significant error [53].

In order for the deterministic approach to provide a valid approximation of the exact stochastic description, the system size must be large in terms of the numbers of each species and the system volume (e.g., here large s_A and V so that the number of expressed mRNA and protein molecules is high with the ratio s_A/V remaining constant) [30]. When this condition is not satisfied, the effects of molecular noise can be significant. The high molecular number condition is not satisfied for gene expression, due to low copy number of genes, mRNAs, and transcription factors within the cell [64].

When the deterministic ODEs presented in Eqs. (1) and (2) are numerically simulated (e.g. via a variable step Runge-Kutta method), the resulting trajectory can in certain parameter regimes capture the mean behavior of the cells. They cannot, however, capture the fluctuations about the mean and therefore the resulting probability distributions (Fig. 2). Futhermore, when reaction rates

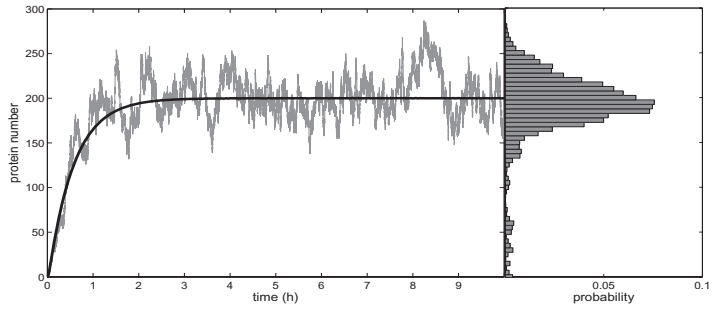

Fig. 2. Time series of protein number generated by deterministic and stochastic simulations (black and gray curves, respectively). The histogram in the right-hand panel corresponds to the stochastic simulation and shows the probability that a cell will have a given intracellular protein level. Parameters were set to (units s^{-1}): $s_A = 0.02$, $s_P = 0.05$, $\delta_M = 0.0005$, and $\delta_P = 0.01$.

depend nonlinearly on randomly fluctuating components, macroscopic rate equations may be far off the mark even in their estimates of averages [40].

3.2 Stochastic Modelling

Due to the importance of noise in many biological systems, models involving stochastic formulations of chemical kinetics are increasingly being used to simulate and analyze cellular control systems [26]. In many cases, obtaining analytical solutions for these models is not feasible due to the intractability of the corresponding system of nonlinear equations. Thus, Monte Carlo (MC) simulation procedures for the number of each molecular species are commonly employed. Among these procedures, the Gillespie stochastic simulation algorithm (SSA) is the *de-facto* standard for simulating biochemical systems in situations where a deterministic formulation may be inadequate [24,25].

In the *direct method* Gillespie SSA, M chemical reactions $\{R_1, \ldots, R_M\}$ characterised by numerical reaction parameters $c_1, ..., c_M$ among N chemical species $X_1, ..., X_N$, are simulated one reaction event at a time. The fundamental hypothesis of the stochastic formulation of chemical kinetics is that the average probability of a given reaction i, occurring in the next infinitesimal time interval, dt, is given by $a_i dt$. Here, a_i is the reaction propensity obtained by multiplying c_i by the number of reactants (for first order reactions) or reactant combinations (for second order and higher reactions) h_i available for reaction R_i. The next reaction to occur (index μ) and its timing τ are determined by calculating the M reaction propensities $a_1, ..., a_M$ to obtain an appropriately weighted probability for each reaction. The SSA determines when ($\tau = \ln(1/r_1)/a_0$) and which ($\min\{\ \mu \mid \sum_{i=1}^{\mu} a_i \geq r_2 a_0\}$) reaction will occur next, using uniformly distributed random numbers r_1 and r_2, and the sum of the reaction propensities a_0.

The direct method Gillespie SSA can be implemented via the following pseudocode [24,25]:

if $t < t_{end}$ and $a_0 = \sum_{i=1}^{M} a_i \neq 0$ **then**
  for $i = 1, M$ **do**
    Calculate a_i and $a_0 = \sum_{v=1}^{i} a_v$
  end for
  Generate r_1 and r_2
  Determine τ and μ
  Set $t = t + \tau$
  Update $\{X_i\}$
end if

The following reaction equations are required to stochastically simulate the model of gene expression under consideration (Fig. 1)

$$A \xrightarrow{s_A} A + M \tag{5}$$

$$M \xrightarrow{s_P} M + P \tag{6}$$

$$M \xrightarrow{\delta_M} \oslash \tag{7}$$

$$P \xrightarrow{\delta_P} \oslash \tag{8}$$

Eqs. (5) and (6) respectively describe the transcription and translation processes. The degradation of M and P are accounted for by Eqs. 7 and 8, respectively.

The advantage of using a stochastic framework to simulate the present model of gene expression can be seen in Figure 2. Specifically, the stochastic method captures not only the mean protein concentration, but also the fluctuations in protein abundance. These fluctuations provide the information necessary for the histograms that describe the probability that a cell will have a given level of a particular molecular species, and can play a significant role in cellular dynamics.

4 Processing and Propagation of Noisy Signals

The genetic program within a living cell is encoded by a complex web of biochemical interactions between gene products. The proper execution of this program depends on the propagation of signals from one gene to the next. This process may be hindered by stochastic fluctuations arising from gene expression. Furthermore it has been found that gene expression noise not only arises from intrinsic fluctuations, but also from noise transmitted from the expression of upstream genes [42]. We now consider how noise can be processed and propagated in genetic networks.

4.1 Cascades

A common regulatory motif, especially in development, is a transcriptional cascade where each gene (A_i) influences the expression of a subsequent gene (A_{i+1}) to form a cascade (Fig. 3 Inset) [44]. Experimental studies have shown that variability can be transmitted from an upstream gene to a downstream gene, adding substantially to the noise inherent in the downstream gene's expression [42,49].

Using a reduced version of the model of gene expression presented in Figure 1, where transcription and translation are combined into a single step, we model a generic linearised genetic cascade as follows. The input signal for the cascade is provided by A_0, which itself is constitutively expressed to produce a protein P_0 and described by the following reactions

$$A_0 \xrightarrow{s_{P_0}} A_0 + P_0 \tag{9}$$

$$P_0 \xrightarrow{\delta_{P_0}} \oslash \tag{10}$$

The protein expression dynamics P_i of the subsequent genes A_i (where i $\in \{1, \ldots, N\}$, and N is the total number of genes) in the cascade are modelled as follows

$$A_i + P_{i-1} \xrightarrow{s_{P_i}} A_i + P_i + P_{i-1} \tag{11}$$

$$P_i \xrightarrow{\delta_{P_i}} \oslash \tag{12}$$

The protein expression of the genes $A_1 - A_N$ in the cascade are each subject to the stochastic fluctuations in the previous gene's expression. Therefore the noise in protein number, for the same mean expression, increases with each subsequent step in the cascade (Fig. 3 - includes parameters).

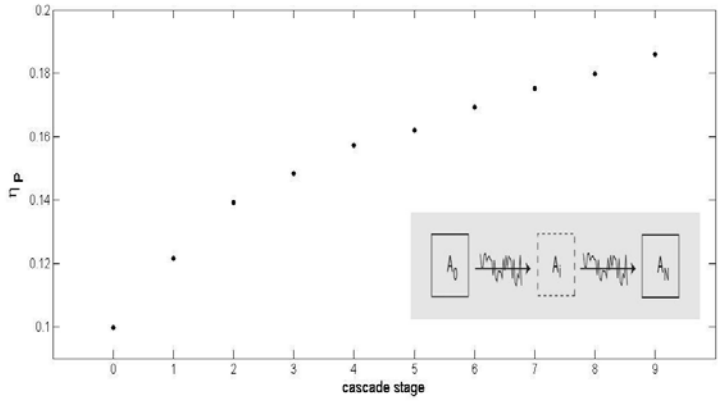

Fig. 3. Propagation of noise in a genetic cascade. The noise in protein number (η_P) is plotted against the cascade stage. Parameters were set as follows (units s^{-1}): $k_{P_0} = k_{P_i} = 100$ and $d_{P_0} = d_{P_i} = 1$ and the simulation was run for 100000 s in order to obtain accurate statistics. Inset shows a schematic of a generic linearised stochastic cascade where each gene (A_i) influences the expression of the subsequent gene in the cascade.

Genetic cascades can produce a wide range of dynamics in addition to those presented in this section. For example, it has been shown that genetic cascades can be either 'fluctuation-unbounded' (as in Fig. 3) or 'fluctuation-bounded' (i.e. expression noise moves towards some asymptotic limit as the size of the cascade is increased) [59]. Furthermore, longer genetic cascades can actually function to filter out rapid fluctuations at the expense of amplifying noise in the timing of propagated signals [59]. To perform this function, the cascade must not only be fluctuation-bounded, but must also be intrinsically less noisy than the input signal.

4.2 Feedback Loops

Feedback loops, in which a protein regulates its own transcription, play an important regulatory role in many genetic networks [38,44]. Positive feedback loops (e.g. where a protein activates its own expression) can act as noise amplifiers [38], whereas negative feedback loops (e.g. where a protein represses its own expression) can act to suppress noise [8,18,54]. Specifically, negative feedback can reduce the effects of noise because fluctuations above and below the mean are pushed back towards the mean [4,8,18,52,57]. Here we provide a simple example of relative noise amplification and attenuation in genetic feedback loops.

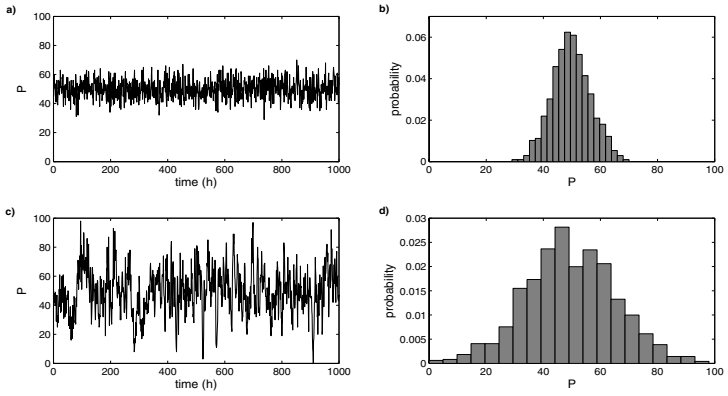

Fig. 4. Stochastic simulations of negative and positive feedback networks. Protein (P) time series and corresponding probability histograms of negative (a,b) and positive (c,d) auto-regulatory systems (Eqs. (13)-(16) and Eqs. (17)-(21), respectively). Note the increase in variability about the same mean when positive auto-regulation is compared to negative auto-regulation. Parameters are given in the text.

Again using the reduced version of the model of gene expression presented in Section 4.1, but where the protein P represses its own formation, we obtain a simple example of a network with negative auto-regulation [38]. The reactions are as follows

$$A + P \xrightarrow{k_1} AP \tag{13}$$

$$AP \xrightarrow{k_2} A + P \tag{14}$$

$$A \xrightarrow{s_P} A + P \tag{15}$$

$$P \xrightarrow{\delta_P} \oslash \tag{16}$$

Here, Eqs. (13) and (14) respectively describe the binding and unbinding of P with a promoter A, Eq. (15) the production of P which occurs only when the promoter is not bound to P, and Eq. (16) the degradation of P. The reaction parameters were set as follows: $k_1 = 4\ mol^{-1}h^{-1}$, $k_2 = 100\ h^{-1}$, $s_P = 150\ mol^{-1}h^{-1}$, and $\delta_P = 1\ h^{-1}$. The protein time series and corresponding probability histogram are shown respectively in Figure 4a and 4b.

The corresponding positive auto-regulation system, where protein production occurs at a higher rate (than basal) when P is bound to A, can be described by the following reactions

$$A + P \xrightarrow{k_1} AP \tag{17}$$

$$AP \xrightarrow{k_2} A + P \tag{18}$$

$$A \xrightarrow{b_P} A + P \tag{19}$$

$$AP \xrightarrow{s_P} AP + P \tag{20}$$

$$P \xrightarrow{\delta_P} \oslash \tag{21}$$

These equations are similar to those describing negative auto-regulation (Eqs. (13)-(16)) except that Eq. (19) describes basal protein production (which is required for activation) and Eq. (20) the promoter bound production of P. Here the parameters were set to: $k_1 = 1\ mol^{-1}h^{-1}$, $k_2 = 100\ h^{-1}$, $b_P = 3\ mol^{-1}h^{-1}$ $s_P = 147\ mol^{-1}h^{-1}$, and $\delta_P = 1\ h^{-1}$. Note the increase in noise in the protein time series and histogram (Fig. 4c and 4d, respectively) relative to the negative feedback case (Fig. 4a and 4b).

It is important to note that many dynamics not discussed in the present section can result from the manner in which a genetic network propagates and processes signals. For example, in the presence of noise, positive feedbacks can behave as a switch, eventually flipping the gene from an 'off' to an 'on' state [20,44]. Furthermore, negative feedback loops can control speed of response to intra or extra-cellular events [48] and lead to oscillations in the expression of a gene product [7]. Feedback loops have also been shown capable of shifting the frequency of gene expression noise such that the effect on noise behaviour of downstream gene circuits within a cascade may be negligible, thus acting as noise filters [54].

5 Noise and Fitness

Heterogeneity in a cell population resulting from the variation in molecular content [30,58] is probably the most apparent manifestation of stochastic gene expression. In the simplest case, the concentration of some expressed protein could display some variability from cell to cell [19,39]. A more complex scenario involves populations of identical cells splitting into two or more groups, each of which is characterized by a distinct state of gene expression and growth rate [58]. Here, fluctuations in gene expression can provide the cell with a mechanism for 'sampling' physiologically distinct states, which may increase the probability of survival during times of stress without the need for genetic mutation [30,58].

5.1 Stochastic Expression of Stress-Related Genes

The probabilistic features arising from gene expression noise led to the hypothesis that evolution has fine-tuned noise-generating mechanisms and genetic architectures to derive beneficial population diversity [55,61,33]. Direct evidence that genome sequence contributes to cell-cell variability indicates that gene expression noise, like other genome-encoded traits, is inheritable and subject to selective pressures, and therefore evolvable. Specifically, large-scale proteomic studies in yeast have shown that genes associated with stress response pathways have elevated levels of intrinsic noise [6,22,36]. Stress-response genes have thus experienced positive pressure toward high population variability, presumably because this providing a selective advantage during periods of stress.

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 [5,12]. Experimental results providing support for this hypothesis were obtained in a study by Bishop *et al.* [9], which demonstrated a competitive advantage of stress-resistant yeast mutants under high stress due to increased phenotypic heterogeneity.

Investigations on the effect of gene expression noise have been carried out in yeast cells under acute environmental stress [10]. Both experiments and simulations confirmed that increased gene expression noise can provide a significant selective advantage at high stress levels. 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.* [10] attribute the differential impact of added noise to a change in the relative fraction of surviving cells at different levels of stress. While a low-noise population will have a higher number of cells above the protein production threshold necessary for survival at low stress levels (Fig. 5a), the same will be true for a high-noise population under a high level of stress (Fig. 5b). 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. Consequently, if it is assumed that cells are either unaffected or killed by the stress, the population fitness (reproductive rate) and differential fitness (difference in reproductive rates between two populations, e.g. a low and a high noise cell population) for a certain stress level can be calculated (Fig. 5c and 5d, respectively) [21]. This provides a very simple quantitative framework that captures the observed impact of population heterogeneity on population fitness following acute stress.

Theoretical Models and Simulations

The impact of acute stress on the fitness W of a cell population can be calculated theoretically by evaluating the integral

$$W = \int_0^\infty w(x) f(x) dx, \tag{22}$$

where $w(x)$ is the relative reproductive rate of cells expressing a stress-related gene at a level given by x, and $f(x)$ describes the population distribution of gene expression when cells are exposed to stress [65]. In a study by Fraser *et al.* [21], this distribution was approximated by the lognormal distribution

$$f(x) = \frac{1}{x\beta\sqrt{2x}} \exp\left[\frac{(\ln(x) - \alpha)^2}{2\beta^2}\right], \tag{23}$$

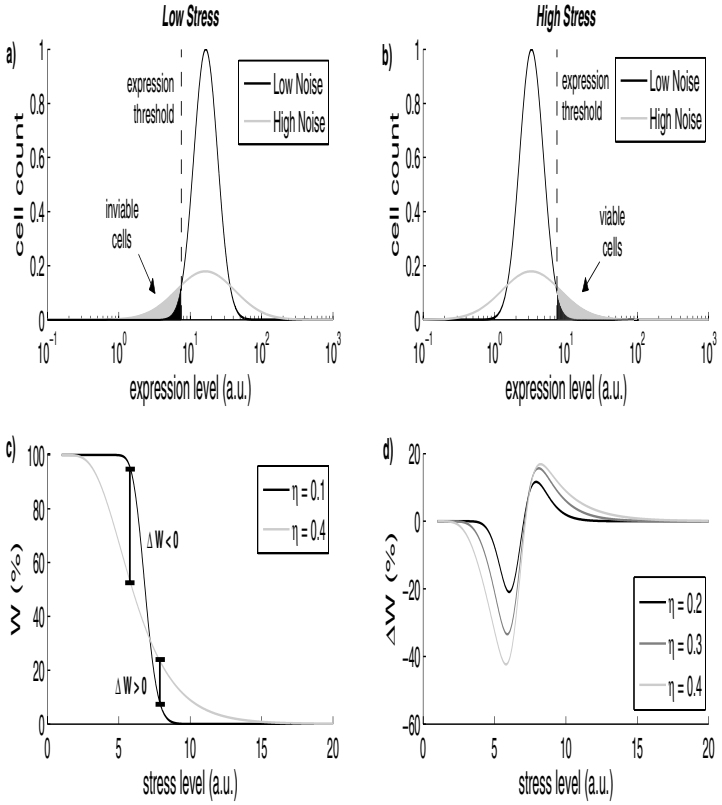

Fig. 5. Modelling the effects of noise in the expression of a stress-resistant gene. (a) Low noise is beneficial when most cells express the stress-inducing gene at levels above a certain threshold. (b) High noise is beneficial when most cells express the stress-inducing gene at levels below the threshold. (c) The effect of varying the stress level on fitness for low and high noise cell populations. Stress levels where noise is beneficial and disadvantageous are defined by positive and negative values of the differential fitness ΔW, respectively. (d) Differential fitness at varying stress levels for three populations with elevated noise relative to a low noise ($\eta_0 = 0.1$) reference population.

where α and β are defined by the average gene expression level μ and gene expression noise η through the relationships $\beta^2 = \ln(1 + \eta^2)$ and $\alpha = \ln(\mu) - 0.5\beta$. The distributions in Figure 5a and 5b were obtained for $\eta = 0.4$ and $\eta = 1.2$, respectively. Moreover, the impact of acute stress was approximated by a step function such that cells expressing a stress-resistance gene below a certain threshold would have a reproductive rate of zero, i.e., fitness $w(x) = 0$ for $x < s_{thr}$ and are otherwise unaffected, i.e., $w(x) = 1$ for $x \geq s_{thr}$.

Continuing with a positive selection scheme, where cells with high expression of a stress-resistant gene have high fitness, and cells with low expression have

low fitness, we now compute W. Specifically, if it is assumed that the level of stress s experienced by the population is related to the most likely level of gene expression (i.e. the mode of the distribution in Eq. (23)), then the noise-dependency of population fitness in Eq. (22) for a threshold model is given by the error function (erf) describing the cumulative lognormal distribution

$$W(\eta, s) = \int_0^\infty w(x) f(x) dx = \int_{s_{thr}}^\infty f(x) dx$$
$$= \frac{1}{2} + \frac{1}{2} erf \left[\sqrt{\frac{\ln(1+\eta^2)}{2}} \left(\frac{\ln(s_{thr}/s)}{\ln(1+\eta^2)} - 1 \right) \right]. \quad (24)$$

This equation was used to calculate the fitness curves displayed in Figure 5c using $s_{thr} = 6.91$ and $\eta = 0.1$ or $\eta = 0.4$, for the low and high noise populations respectively. Correspondingly, the differential fitness curves displayed in Figure 5d were obtained by evaluating the quantity $\Delta W(\eta, s) = W(\eta, s) - W(\eta_0, s)$, where $W(\eta, s)$ is the fitness of the population with variable high noise ($\eta = 0.2$ 0.3, or 0.4) and $W(\eta_0, s)$ is a reference population with low noise ($\eta_0 = 0.1$).

5.2 Bet-Hedging Cell Populations

Another interesting example of how noise can influence fitness involves cells that can switch between phenotypes in a changing environment [1,58]. Under fixed environmental conditions, the net growth rate (and therefore fitness) of the population is maximized when all cells are of the fastest growing phenotype. However, in a changing environment, it is thought that a statically heterogeneous population (i.e. a population where transitions between states are not influenced by environmental conditions) can deal with an uncertain future by hedging its bets. Specifically, a broad distribution of phenotypes is generated in the 'hope' that some of these phenotypes will remain viable after an environmental change. In contrast, a dynamically heterogeneous population has a more reliable strategy: individuals in such populations can sense and respond to external changes by actively switching to the fit state. If the response rate is sufficiently rapid compared to the rate of environmental fluctuations, as is the case for many real systems, then transitions from the fit state to the unfit state are actually detrimental. Thus, bet-hedging is only beneficial if response rates are sufficiently low.

Acar *et al.* [1] experimentally investigated how stochastic switching between phenotypes in changing environments affected growth rates in fast and slow-switching *Saccharomyces cerevisiae* (budding yeast) populations. Specifically, a strain was engineered to randomly transition between two phenotypes, ON and OFF, characterized respectively by high or low expression of a gene encoding the Ura3 enzyme, necessary for uracil biosynthesis. Each phenotype was designed to have a growth advantage over the other in one of two environments. In the first environment (E_1) uracil was lacking and cells with the ON phenotype had an advantage. In the second environment (E_2), cells with the OFF phenotype had an advantage due to the presence of a drug (5-FOA), which is converted into a

toxin by the Ura3 enzyme. In this environment, which also contains uracil, cells expressing Ura3 will have low viability while cells not expressing Ura3 will grow normally.

Simulating Complex Population Dynamics

In order to simulate the scenario described above, we used a population dynamics algorithm [16] and a model of gene expression described by the following biochemical reaction scheme [30]

$$A_{act} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A_{rep} \tag{25}$$

$$A_{act} \xrightarrow{s_{A,act}} A_{act} + M \tag{26}$$

$$A_{rep} \xrightarrow{s_{A,rep}} A_{rep} + M \tag{27}$$

$$M \xrightarrow{s_P} M + P \tag{28}$$

$$M \xrightarrow{\delta_M} \oslash \tag{29}$$

$$P \xrightarrow{\delta_P} \oslash \tag{30}$$

Eq. (25) describes the transitions to the active (upregulated level of gene expression) A_{act} and repressed (basal level of gene expression) A_{rep} promoter states with rates k_1 and k_2 respectively, Eqs. (26) and (27) the mRNA production from the A_{act} (at a rate $s_{A,act}$) and A_{rep} (at a rate $s_{A,rep}$) states respectively, Eq. (29) the protein production from mRNA at a rate s_P, and Eqs. (28) and (30) respectively the mRNA (at a rate δ_M) and protein (at a rate δ_P) degradation. The fitness w_k of each cell k, which is here defined as a function of the environment and cellular protein concentration $[P]$, was described by a Hill function

$$w_k(E,[P]) = \begin{cases} \frac{[P]^n}{[P]^n+K^n}, \ if\ E = E1, \\ \frac{K^n}{K^n+[P]^n}, \ if\ E = E2. \end{cases} \tag{31}$$

This equation describes partitioning of cells into fit ($w_k(E,P) \geq 0.5$) and unfit ($w_k(E,P) < 0.5$) phenotypes corresponding to whether or not their $[P]$ in a particular environment is above or below a particular value given by the Hill coefficient K. The volume of each cell was modelled using an exponential growth law

$$V_k(t_{div}) = V_0 \exp\left[\ln(2)\left(\frac{t_{div}}{\tau_0}\right)\right]. \tag{32}$$

Here, V_0 is the cell volume at the time of its birth, and $\tau_0 = \tau_\phi / w$, where τ_ϕ is the cell division time in absence of any selective pressure. To incorporate the effect of fitness on gene expression, the value of transcription rate parameter s_A depended on whether or not a cell was fit in either $E1$ or $E2$ (see Fig. 6 and [1]

for parameters). Note that in this model the cells divided symmetrically when their volume reached $2V_0$.

The population distributions obtained for this model are shown in Figure 6. Specifically, we first obtained the steady-state protein concentration distributions for cells in $E1$ and $E2$ (Fig. 6a and 6b, respectively). Here, the majority of cells either fell within a distribution centered at higher value of P, characterizing the ON cells, or a distribution centered at a lower value, characterizing the OFF cells, in $E1$ or $E2$ respectively. The rest of the cells fell within the distribution capturing the unfit subpopulation in both environments. These results were found experimentally in [1] and are expected, as higher levels of the Ura3 enzyme are either favorable or unfavorable with respect to the fitness of

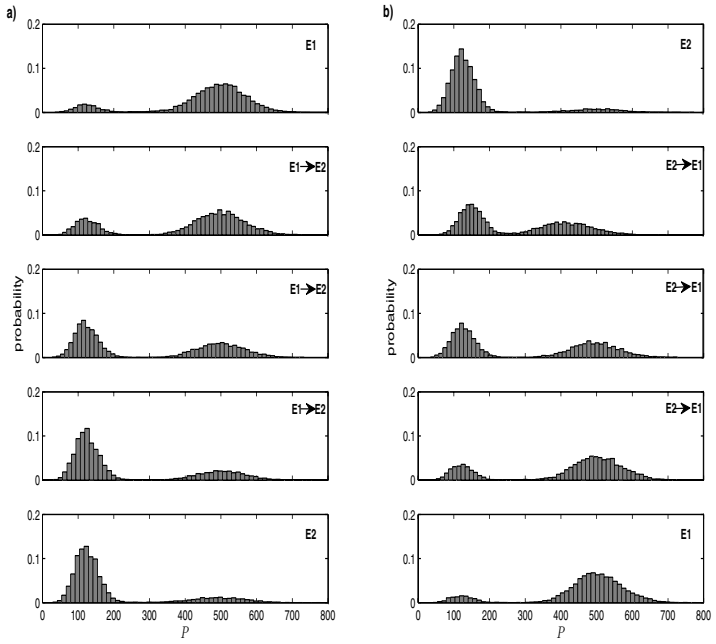

Fig. 6. Simulations of environmental effects on phenotypic distribution. (a) Steady-state (top and bottom figures) and time-dependent (middle figures) protein distributions of cells transfered from an environment lacking uracil (E1) to an environment containing uracil and 5-FOA (E2). (b) Steady-state (top and bottom figures) and time-dependent (middle figures) protein distributions of cells transfered from E1 to E2. Note that when a sufficient amount of time has elapsed after the environmental transition from either E1 to E2 or vice versa, cells with either the OFF or ON phenotype proliferate, respectively, in agreement with experimental results found in [1]. The following parameters were used (units s^{-1}): $\delta_M = 0.005$, $s_P = 0.1$, $\delta_P = 0.008$, $K = 200$, $n = 10$. For fit cells in E1 $s_{A,act} = 0.2$ and for unfit cells $s_{A,rep} = 0.05$ - vice versa in E2. Additionally τ_ϕ was set to the mean doubling time (MDT) of 1.5 hours for *Saccharomyces cerevisiae* [13].

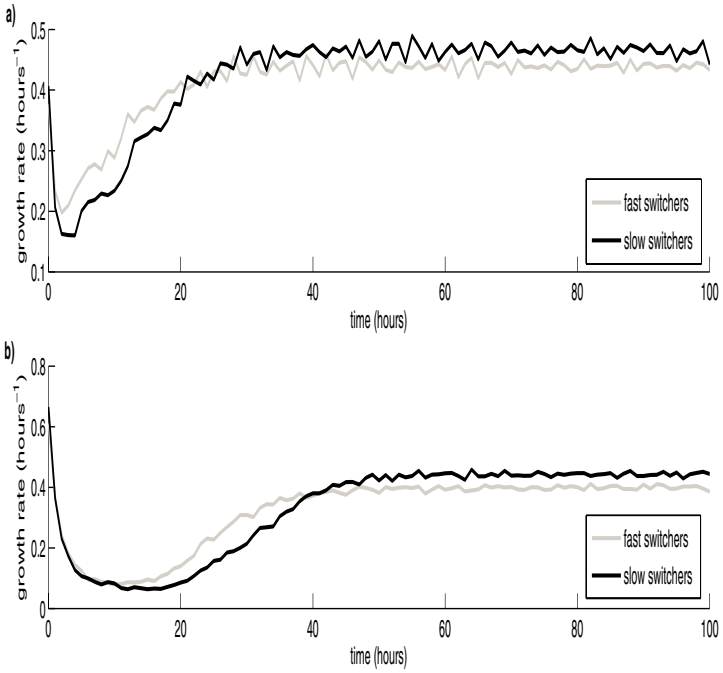

Fig. 7. Simulations of populations of slow and fast-switching cells. (a) Growth rates of cells after an environmental change from E2 to E1 at $t = 0$. (b) Growth rates of cells after environmental change from E1 to E2 at $t = 0$. Note that the transient before the steady-state region is shorter in (a) than in (b), and that fast-switching cells recover faster from the environment change but slow-switching cells have a higher steady-state growth, in agreement with experimental results found in [1].

the cells depending on the environment. Additionally, the time-dependent population distributions after the transition to $E1$ from $E2$, and vice versa, were obtained (Fig. 6a and 6b, respectively). Here, the dynamics of the two distinct subpopulations of cells in transition between the steady-states are visible. As time progresses after the environmental transition, fewer and fewer of the cells are in the unfit state (ON in Fig. 6a and OFF in Fig. 6b), as the cells in the more fit state (OFF in Fig. 6a and ON in Fig. 6b) grow and divide at a faster rate and therefore come to dominate the population in terms of absolute numbers. Figure 7 shows the growth rates obtained from simulations of slow and fast-switching cell populations, where cells were transfered from E2 to E1, and vice versa, at $t = 0$. Growth rates show a transition period and a steady-state region. In agreement with experiments (see Acar *et al.* [1]), fast-switching cells were found to recover from the effect of environment change faster than slow-switching cells but have a lower steady-state growth rate.

6 Cellular Decision-Making in a Noisy Environment

Previous sections have described sources of noise in gene regulatory networks, how noise can impact fitness, and how different regulatory mechanisms can either attenuate or amplify noise. While noise is an inherent part of the stochastic chemistry of cells, it is also an inherent part of their sensing apparatus as well as of the signals they sense. For example, cells can respond to the concentrations of numerous kinds of chemicals, including nutrients, toxins, signaling molecules, as well as physical properties of the environment such as pressure and temperature. A recent line of research has investigated models of how cells should process such noisy signals, and in particular, whether human theories of optimal signal processing might be embodied in cells–implemented chemically, as it were [17,2,3,32]. We present a simplified version of the analysis of Libby *et al.* [32]. We show that it is possible, in principle, for the chemistry of gene regulation to approximate probability-theoretic computations related to the analysis of noisy signals. This general viewpoint provides one possible interpretation, a detailed quantitative interpretation, for the function of real regulatory networks.

6.1 Two-Class Bayesian Discrimination Problems

The work of Libby *et al.* [32] used the framework of two-class Bayesian discrimination problems to interpret gene regulatory mechanisms, and the lac operon of *E. coli* in particular. In these problems, we imagine that there is an unobserved binary random variable X, whose value one wants to estimate. For example, it may be important to an *E. coli* whether its immediate environment has a low or high concentration of a particular sugar (Figure 8), in order for it to make the right choices about expressing genes useful for the import and metabolism of that sugar. In other cases, the relevant variable may be the presence or absence

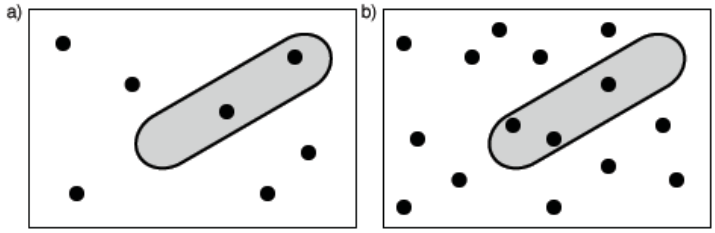

Fig. 8. Conceptualization of an inference problem solved by a cell. (a) An *E. coli* cell (oblong) in an environment low in a particular sugar (black circles). (b) The same cell in a higher sugar environment. The amount of intracellular sugar is related, albeit imperfectly and stochastically, to the extracellular sugar concentration. While intracellular sugar directly drives the regulation of genes related to its metabolism, it is the extracellular sugar that is of true importance to the regulatory decisions made by the cell.

of a toxin, a mating partner, a competitor organism, etc. Although X is not directly observed, we assume there is another variable S which is observed, and the value of which depends stochastically on the value of X. For example, in the situation depicted in Figure 8, S may be the intracellular sugar concentration. This S can be viewed as "observed by" or "known to" the cell, because this sugar can interact directly, chemically, with the regulatory machinery of the cell and bring about changes in cellular behavior (e.g., changing the expression of certain genes). The exact value of S may depend on many factors—the size of the cell, the number of permeases, and so on, but it clearly depends as well on the extracellular environment state, X. We can imagine that there are different probability distributions for S depending on the state X, $P(S = s|X = low)$ an $P(S = s|X = high)$. The problem the cell faces, then, is to estimate the probabilities of $X = low$ and $X = high$ based on the signal value $S = s$. This can be done via Bayes's rule

$$P(X = high|S = s) = \frac{P(S = s|X = high)P(X = high)}{P(S = s)}$$

$$= \frac{P(S = s|X = high)P(X = high)}{P(S = s|X = high)P(X = high) + P(S = s|X = low)P(X = low)}.$$

From this formula, it is clear that the probability of X being high or low depends not just on the value of S, via the probability distribution for S as a function of X, but also on the terms $P(X = high)$ and $P(X = low) = 1 - P(X = high)$. The are called the prior probabilities, which are one's beliefs about X before the signal S has been accounted for, while $P(X = high|S = s)$ and $P(X = low|S = s) = 1 - P(X = high|S = s)$ are called the posterior probabilities, representing one's beliefs about X after the signal S has been accounted for.

6.2 A Model of Genetic Response to Intracellular Sugar

We present a simplified chemical model of gene activation that is broadly similar to the function of the lac operon of *E. coli*, as well as a number of other sugar metabolic systems. It is not intended as a description of the lac operon per se, but rather as a generic model of negatively regulated control. We model intracellular sugar, S, a repressor molecule R, and the promoter A of a gene whose protein P is expressed in a correlated fashion to sugar S. In a real system, P might actually represent a set of proteins involved in the metabolism or import of the sugar S, but we do not model these aspects. We merely think of P as being the response of the cell that is turned on by the presence of S.

$$\oslash \xrightarrow{r_S(X)} S \tag{33}$$

$$S \xrightarrow{\gamma_S} \oslash \tag{34}$$

$$S + R \underset{r_{SR}}{\overset{r_{RS}}{\rightleftharpoons}} SR \tag{35}$$

$$SR \xrightarrow{\gamma_S} R \tag{36}$$

$$A + R \underset{r_{RA}}{\overset{r_{AR}}{\rightleftharpoons}} AR \tag{37}$$

$$A \xrightarrow{s_P} A + P \tag{38}$$

$$P \xrightarrow{\delta_P} \oslash \tag{39}$$

Eq. (33) describes the process of intracellular sugar entering the system at rate $r_S(X)$, which, because X is binary, can be one of two values—r_{low} when $X = low$ and r_{high} when $X = high$. Sugar "decays", whether bound to the repressor (Eq. (36)) or not (Eq. (34)), which would realistically represent the sugar being metabolized, or concentration decreasing via dilution. The repressor can bind to the promoter and make it transcriptionally inactive (Eq. (37)). However, a repressor molecule bound by sugar (Eq. 35) cannot bind the promoter. In this way, increasing S leads to decreasing free R, and thus increasing transcriptional activation and increasing level of P. At this qualitative level, the model behaves as would be expected by a system that responds to the sugar S. Is a more quantitative interpretation of the system possible? Is it possible for the system to implement, or approximate, the Bayesian two-class computation described above, so that the "output" of the system, the expression of the protein P, is proportional to the posterior probability that the external environment being in state $X = high$?

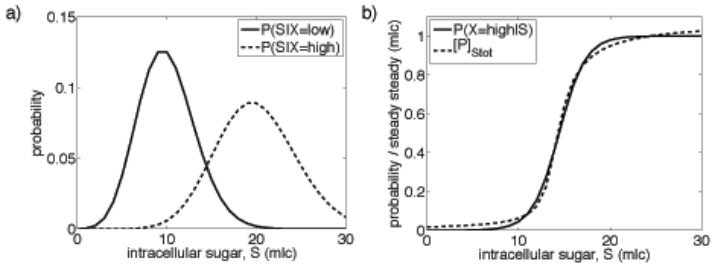

Fig. 9. Conditional and posterior probabilities for a problem of inferring environment state X (low or high in sugar) based on the noisy intracellular sugar level, S. (a) The probability distributions for S in the two environment states. (b) The posterior probability of $X = high$ given an intracellular sugar level S, and the output of the chemical model of gene regulation, with parameters tuned to match the posterior probability.

6.3 Chemically Approximating Bayesian Two-Class Discrimination

Libby *et al.* [32] showed that a variety of different chemical regulatory models of sugar metabolism are indeed capable of approximating the Bayesian two-class computation. To demonstrate this using the model above, suppose that $r_{low} = 10$ molecules per second, $r_{high} = 20$ molecules per second, and $\gamma_S = 1\ s^{-1}$. When $X = low$, the steady-state probability distribution for S is Poisson with parameter $\lambda = 10$, and when $X = high$, it is Poisson with parameter $\lambda = 20$ (Figure 9a). Assuming that $X = low$ and $X = high$ are equally likely *a priori*, so that $P(X = low) = P(X = high) = \frac{1}{2}$, then Equation 6.1 can be used to compute the posterior probability that the environment is in a high sugar state. The result of this computation is shown in Figure 9b.

Returning to the chemical model, let $[P]_{Stot}$ denote the steady-state number of molecules of P when the total intracellular sugar $S_{tot} = S + RS$ is fixed at a certain level. That is, we remove reactions 33, 34 and 36 from the model, and compute the (deterministic) steady-state of the system. We implemented this steady-state computation in `Matlab` and used the `fminsearch` utility to find reaction rate parameters for the system that minimize the squared error function

$$\sum_{S_{tot}=0}^{30} \left(P(X = high|S_{tot}) - [P]_{Stot}\right)^2. \tag{40}$$

As shown in Figure 9b, the parameters of the chemical model can be chosen so that the average number of molecules of P, given intracellular sugar level S_{tot}, closely matches the Bayesian computation of the probability that the environment is in the high sugar state. This demonstrates that even the simplest gene regulatory mechanisms are capable, in principle, of approximately reproducing fairly sophisticated probability-theoretic computations, and thus are capable of implementing inferential procedures to help the cell reason about its environment.

Whether or not this is an appropriate interpretation of the behavior of real gene regulatory systems remains to be seen. Libby *et al.* [32] showed that the experimentally measured response of the lac operon to two signals, lactose concentration and cAMP concentration (a starvation signal), is consistent with a solution to a two-class discrimination problem. Relatedly, Dekel *et al.* [17] showed that expression of the lac operon seems to balance the metabolic benefit from the sugar against the metabolic cost of expression. Andrews *et al.* [2,3] have shown that chemotactic behavior can be interpreted through the lens of filtering and information theory. Thus, there is growing evidence that human theories of noisy signal processing and decision making may indeed be implemented biochemically in the cell, and that these theories provide explanations for the detailed quantitative behaviors of cellular networks.

7 Conclusion

Our understanding of the origins and consequences of stochasticity in gene expression has advanced significantly in recent years. This advancement has been

fueled by theoretical developments enabling biological hypothesis formulation using stochastic process and dynamical systems theory, as well as experimental breakthroughs in measurements of gene expression at the single cell level [53].

Noise in gene expression was originally viewed as being detrimental in terms of cellular function due to the corruption of intracellular signals negatively affecting cellular regulation with possible implications for disease. However, noisy gene expression can also be advantageous, providing the flexibility needed by cells to adapt to stress such as a changing environment [1,21,58]. Stochasticity in gene expression provides a mechanism for the occurrence of heterogeneous populations of genetically identical cells, in terms of phenotypic and cell-type diversity, which can be established during cellular growth and division [14,30,51]. Furthermore, studies have suggested that intrinsic stochasticity in gene expression is an evolvable trait [22,39].

Gene expression noise not only arises from intrinsic fluctuations, but also from noise propagated through the network from upstream genes [42]. Several genetic network motifs including cascades and feedback loops can act to modulate this noise, resulting in a range of behaviour including amplification, bounded fluctuations, and noise filtration [42,49,59].

Cells depend on the information they obtain from their environment to remain viable. Yet this information, received at the cell surface, is conveyed through gene and protein networks and is transferred via biochemical reactions that are inherently stochastic [11,19,39,45]. Stochastic fluctuations can undermine both signal detection and transduction. As a result, cells are confronted with the task of predicting the state of the extracellular environment from noisy and potentially unreliable intracellular signals. In addition to employing noise reduction mechanisms, cells may statistically infer the state of the extracellular environment from intracellular inputs [32,43].

The study of noise in genetic networks has provided novel insights into how cells survive, propagate and ultimately perish in stochastic environments. This line of research is likely to continue to prove fundamental for developments in the fields of molecular and synthetic biology and in furthering our understanding and treatment of human disease.

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