# Control, exploitation and tolerance of intracellular noise

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**Noise has many roles in biological function, including generation of errors in DNA replication leading to mutation and evolution, noise-driven divergence of cell fates, noise-induced amplification of signals, and maintenance of the quantitative individuality of cells. Yet there is order to the behaviour and development of cells. They operate within strict parameters and in many cases this behaviour seems robust, implying that noise is largely filtered by the system. How can we explain the use, rejection and sensitivity to noise that is found in biological systems? An exploration of the sources and consequences of noise calls for the use of stochastic models.**

*"For it is simply a fact of observation that the guiding principle in every cell is embodied in a single atomic association existing only in one copy (or sometimes two) — and a fact of observation that it results in producing events which are paragons of orderliness [...] the situation is unprecedented, it is unknown anywhere else except in living matter."*

Erwin Schrödinger *What is Life?*
(Cambridge University Press, 1944)

When Erwin Schrödinger wrote *What is Life?*, he was interested in whether new physical laws were necessary to describe biological systems. He was acutely concerned with how "a single group of atoms existing in one copy produces orderly events". Although the molecular basis of genetics did not require new physical laws, how cells function and process information when the underlying molecular events are random still remains an open question. Gene expression, for example, involves a series of single-molecule events and belies a deterministic description. As each of these molecular events is subject to significant thermal fluctuations, gene expression is best viewed as a stochastic process. Even in cases where population measurements are regular and reproducible, single-cell measurements often display significant heterogeneity[1]. Overall, these observations suggest that the molecular events underlying cellular physiology are subject to fluctuations and have led to the proposal of a stochastic model[2–4] for gene expression and biochemistry in general. Other cellular processes influenced by noise include ion-channel gating[5], neural firing[6], cytoskeleton dynamics[7] and motors[8], although here we focus primarily on the role of noise in intracellular networks.

How do we explain the complex, highly orchestrated and robust physiology of the cell when the underlying molecular events are basically random? Despite the stochastic function of the foundations of regulatory circuits within cells, most cellular events are ordered and precisely regulated. Development in *Caenorhabditis elegans* is so regular that we can trace the differentiated state of nearly every cell[9]. One example where the transition from disorder to order has been measured is in *Drosophila melanogaster* embryos[10]. Although the anterior-to-posterior gradient of the maternal morphogen Bicoid in *D. melanogaster* embryos displays significant variability, the profile of the *hunchback* gap gene, regulated by Bicoid, is precise. The need for order has led to the proposal that robustness is an intrinsic property of intracellular networks[11,12].

Although most cellular processes are ordered, not all noise is rejected. Cell fate and population heterogeneity is viewed increasingly as a noise-driven process. In the phage lambda infection process, which is governed by the lysis–lysogeny decision circuit, only a fraction of infecting phage chooses to lyse the cell. The remainder become dormant lysogens awaiting bacterial stress signals to enter the production phase of their life cycle[13]. Another example of population heterogeneity can be found in the soil-growing bacterium *Bacillus subtilis*, which responds to environmental stress with an arsenal of probabilistically invoked survival strategies. *B. subtilis* can become motile and swim towards new food sources, secrete degradative enzymes to scavenge resources, secrete antibiotics to eliminate competitors, produce stress-resistant spores, or become competent for genetic transformation[14]. The particular fate of each cell seems random, although biased by environmental and intercellular signals. Still more examples of population heterogeneity include differentiation of progenitor haematopoietic stem cells[15], non-genetic individuality in bacterial chemotaxis[16], and epigenetic inheritance and incomplete penetrance of transgenes in mice[17]. However, even heterogeneity is ordered; once a particular fate is chosen, the resulting process is tightly controlled.

Does the noise manifested as random cell fate and population heterogeneity help or hurt the organism, or does it have an indifferent effect? In at least some cases, randomness and heterogeneity seem to be a boon to survival. Phase variation in pathogenic bacteria, where cells alternate randomly between expressing certain genes and silencing others, is thought to be a form of cultivated noise[18]. Type 1 pili expression in uropathic *Escherichia coli*[18–21], pili expression in *Neisseria gonorrheae*[22], polysaccharide intercellular adhesin synthesis in *Staphylococcus epidermidis*[23], lipopolysaccharide epitope expression in *Haemophilus influenzae*[24], and capsular polysaccharide expression in *Vibrio vulnificus*[25] are just a few examples of this common mode of control[26]. Even though the molecular events leading to phase variation seem random in the individual, regulatory factors tune the variation to ensure mean levels of

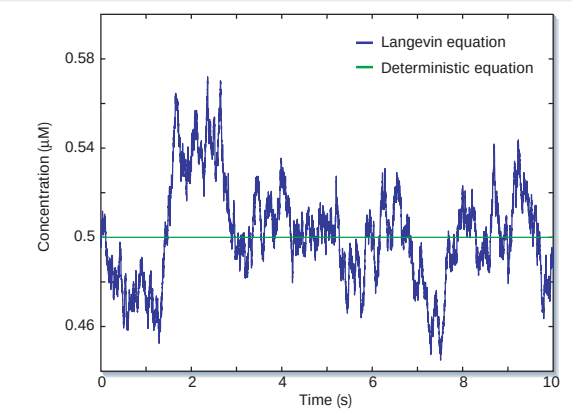


**Figure 1** Comparison of the deterministic and stochastic solution for an isomerization reaction with dissociation constant $K_d = 1$. The deterministic solution predicts a constant equilibrium (green line). The stochastic solution obtained by solving a Langevin equation includes fluctuations about the equilibrium concentration. The Langevin equation was solving using a first-order Euler method.

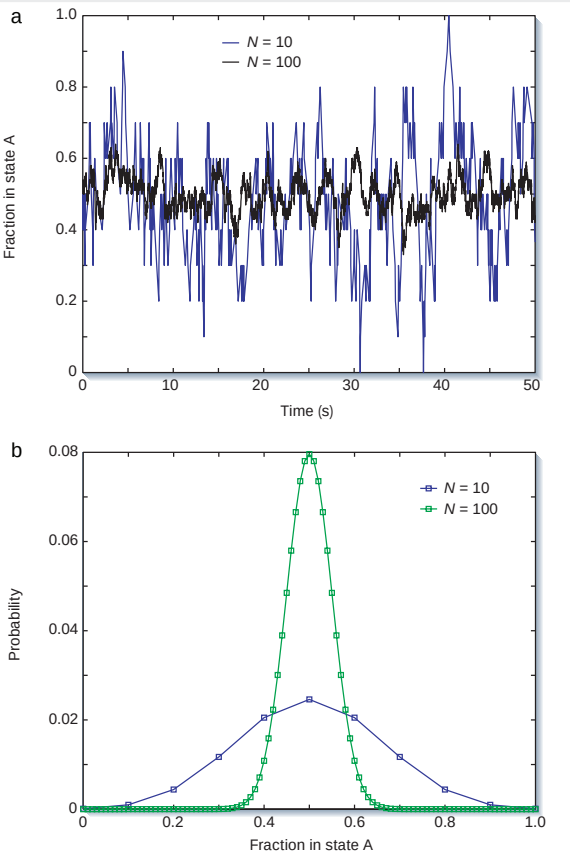


**Figure 2** A comparison of the isomerization reaction with 10 and 100 molecules using a discrete stochastic model with $k_1 = 1\ s^{-1}$ and $k_2 = 1\ s^{-1}$. **a**, The sizes of fluctuations decrease as the number of molecules increases. Simulations were performed using the Gillespie algorithm. **b**, The steady-state probability density function. As the number of molecules increases, the density becomes sharper. The figure shows a plot of the analytic solution for the steady-state master equation. The distribution is given by the expression

$$p(j) = \binom{n}{j} \frac{k_1^j k_2^{n-j}}{(k_1 + k_2)^n}$$

This discussion is adapted from ref. 62.

heterogeneity for the population. Environmental factors can shape population diversity, presumably allowing for an adaptive response to the conflicting demands of offence (infection of the host) and defence (immune system recognition and destruction of the pathogen)[13,26].

Although examples of tightly ordered or potentially noise-exploiting cellular processes abound, how cells are able to reign in biochemical noise remains unknown. Where does noise arise in the cell? By what means do regulatory networks attenuate this noise? And how and why do networks exploit noise? These questions present one of the most challenging and fascinating problems for systems (if not all) biologists, as they open questions in physiology, development and evolutionary biology. The answer likely resides in the complex networks that underlie cellular physiology. Computational models are the ideal tool for such investigations, because they allow us to express formally the current state of knowledge about network composition and structure, and to explore network dynamics. These tools allow us to test and generate hypotheses about the fundamental operating principles of a network and the sources and consequences of intracellular noise, something not possible with qualitative arguments.

## Modelling tools

Biochemical reactions are described traditionally in terms of kinetic rates that describe how the concentrations of the various species (for example, proteins or metabolites) in a cell (or test tube) change with time. The reaction rates are embodied by rate laws such as mass action or Michaelis–Menten kinetics, and the biochemical dynamics are described with differential equations. A typical form of the equation is

$$\frac{dC(t)}{dt} = vr(C)$$

where the variables $C(t)$, $t$, $v$ and $r(C)$ represent the concentrations, time, stoichiometric matrix and the rate law, respectively. Implicit in the above formulation is the assumption that the cell is well mixed and homogenous. This assumption is not limiting as the model can be formulated with a spatial component that describes phenomena such as cytoplasmic heterogeneity, compartmentalization, diffusion and wave phenomena. Literally hundreds of software packages (both commercial and freeware) are available to construct and solve, either analytically or numerically, equations of these forms[27,28].

These models are deterministic; if the starting conditions are fixed, then the future evolution is also fixed precisely. Despite this, it is possible to study the effects of noise to a first approximation using bifurcation and spectral analysis. These approaches assume noise arises from an exogenous source and tacitly ignore intrinsic fluctuations in pathway (for example, a noisy ligand signal is assumed and fluctuations arising in the signal-transduction cascade are ignored).

Molecular fluctuations can be incorporated explicitly by including random variables (or rather stochastic processes) in the model. The easiest approach is to append a noise term to the end of the differential equation

$$\frac{dC(t)}{dt} = vr(C) + x(t)$$

where $x(t)$ is the additive (white) noise term. The equation above is often referred to as the Langevin equation or a stochastic differential equation[29]. The appeal of the Langevin approach is that it builds on the deterministic formulation (Fig. 1).

While many algorithms exist for simulating the Langevin equation[30], often one calculates the probability density function instead.

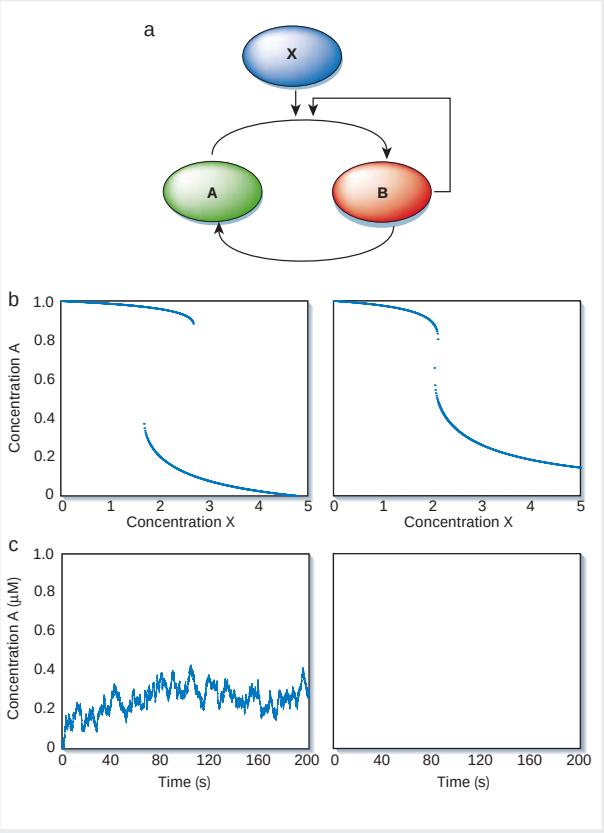


**Figure 3** Switches and chattering. **a**, A simple reaction network with positive feedback produces a switch. **b**, The steady-state behaviours of two switches as a function of the signal X. The left curve is a hysteresis whereas the right curve is ultrasensitive. Differences between the two curves result from the use of different kinetic parameters in the model. **c**, The dynamic behaviour of the two switches subject to similar noisy X signals was simulated using the Gillespie algorithm. The hysteresis of the first switch provides a buffer so that the switch is robust to noise. The second switch, which is ultra-sensitive and lacks such a buffer, is sensitive to noise and subject to accidental switching (indicated by arrow). Hysteretic switches provide one mechanism to reduce switching chatter.

The Fokker–Planck (or Kolmogorov's forward equation) describes the evolution of the probability density function

$$\frac{\partial p(C,t)}{\partial t} = -\nabla\cdot[vr(C)p(C,t)] + \frac{1}{2}\sum_{i,j}\frac{\partial^2\sigma_{ij}p(C,t)}{\partial C_i\partial C_j}$$

where $p(C,t)$ is the probability density function and the matrix $\sigma_{ij}$ is the covariance of the noise process $x(t)$. The quantity $p(C,t)\partial C$ is the probability of finding a cell with a concentration of a certain chemical between $C$ and $C+\partial C$ at time $t$. One advantage of working with the Fokker–Planck equation is that it is possible to analyse the model. Tools such as sensitivity analysis and bifurcation theory are applicable. However, for systems involving more than a few species, it is impossible to solve the Fokker–Planck equation, even numerically. Most researchers analyse these models using Monte-Carlo methods, where one solves the Langevin equation many times and then uses statistics to estimate the probability density function. Compared to deterministic equations, Monte-Carlo methods are time consuming when simulating many molecules and reactions, although they currently are the only option for complex (that is, realistic) models.

Implicit, however, in either differential or Langevin equations is a continuous description of molecular species, where the dynamics are cast in terms of infinitesimal changes in concentration. This description is limiting when modelling processes involve a few molecules, discrete structures or single-reaction events such as the binding of a transcription factor to its cognate promoter.

Recent research in biological noise has been directed towards modelling molecular species (such as proteins, messenger RNA and ribosomes) as discrete entities using elements of probability theory. In this framework, reaction events replace reaction rates, and each distinct reaction event is explicitly modelled. The likelihood of a reaction event (for example, a protein undergoing a transition) is analogous to a reaction rate. Rather than referring to a differential rate, we assign a probability that the protein will undergo a transition in an infinitesimal amount of time. Consider a protein existing in two states A or B. We can now write a differential equation of the form

$$\begin{aligned}\frac{dP(n_a,n_b;t)}{dt} = &-(k_1n_a + k_2n_b)P(n_a,n_b;t) + \\ &k_1(n_a+1)P(n_a+1,n_b-1;t) + \\ &k_2(n_b+1)P(n_a-1,n_b+1;t)\end{aligned}$$

which describes how the probability $P(n_a, n_b;t)$ that $n_a$ proteins exist in state A and $n_b$ proteins exist in state B changes as a function of time. The parameters $k_1$ and $k_2$ denote the likelihood of an A-to-B and B-to-A transition, respectively. This equation is called a master equation and describes what statisticians call a birth–death process. It also defines a homogenous Markov chain, and is actually no different mathematically than the equations used commonly in sequence analysis, population biology and theoretical genetics. The master equation is linear and, from a mathematical perspective, it is about as simple an equation as one can hope for. The caveat is that the equation is large, so large you never want to write it down. Because the problem above is simple, we can calculate an analytic solution for the steady-state probability distribution (Fig. 2).

As with the Fokker–Planck equation, the master equation is deterministic in the sense that if the starting probabilities are fixed, then the future probabilities are fixed. The main difference between the two formulations is how the species are represented: the description is continuous in the Fokker–Planck equation, but discrete in the master equation. When modelling only a few reacting molecules, the discrete representation is believed to be more accurate than the continuous representation. However, as the number of molecules increases this difference becomes less significant. In fact, the master equation is asymptotically equivalent to the Langevin equation

$$\frac{dC(t)}{dt} = vr(C) + v\sqrt{r(C)}x(t)$$

where $x(t)$ is a unit white-noise process[31–33]. This equation predicts that the relative magnitude of the molecular fluctuations scales roughly as the inverse square root of the number of reacting molecules.

Rarely do we work directly with the master equation, as many equations are necessary to model systems involving more than few reactions or species. For example, the master equation requires ten thousand equations to describe a three-step linear pathway involving one hundred molecules, as an equation is necessary to account for each possible combination of molecules. Rather than enumerate every state (the tumour suppressor p53 has at least 11 phosphorylation and acetylation sites, implying $2^{11}$ distinct states for the monomer and potentially $2^{44}$ states for the tetramer[34]), it is easier to simulate the random evolution of the system and use Monte-Carlo approaches. This solution was formulated by Gillespie[35], who proposed a simple, elegant algorithm for simulating stochastic kinetics. This task is then repeated many times to estimate the relevant probabilities and statistics. Although this procedure may be time consuming, it is far easier than forming and then solving the master equation. In Gillespie's algorithm, the time for the next reaction event is calculated and the system is updated accordingly in an iterative manner.

An alternative approach to the Gillespie algorithm for stochastic simulation is the StochSim algorithm[36,37]. In StochSim, the master equation is discretized to facilitate numerical approximations of the transition probabilities describing the evolution of the biochemical dynamics. The approach is reminiscent of an explicit forward Euler method for solving differential equations. It is not 'exact'; the error is proportional to the size of the time increments. If, however, we choose small time increments, the error is negligible and StochSim is asymptotically equivalent to the Gillespie algorithm. An alternate approach to the master equation, tailored for diffusion processes in complex geometries such ion transport in synapses, is MCELL (http://www.mcell.cnl.salk.edu/). MCELL uses a ray-tracing algorithm for tracking molecular motion and interactions. For systems in thermodynamic equilibrium, the problem can often be recast in terms of the Boltzmann equation, and Monte-Carlo solutions can be obtained using the Metropolis algorithm and variants thereof.

There are still many unresolved issues regarding stochastic simulation, computational efficiency being the most pressing. Although a few strategies have been proposed to increase the efficiency of the Gillespie algorithm[38,39], there are currently no satisfactory approaches for simulating processes concurrently across multiple scales of time, space or concentration. An alternative approach is to separate timescales explicitly and reduce the model by singular perturbations[40]. Yet other approach is to construct hybrid models involving continuous and discrete representations[41]. Both these approaches require direct intervention by the modeller — a cumbersome and sometimes impossible task. The long-term goal is to develop algorithms that do this both automatically and adaptively. But the challenge to multiscale simulation is rare events. How do we simulate the rare events of interest without wasting computational resources simulating frequent events that are irrelevant to the question being asked? One can envision algorithms analogous to adaptive methods used to solve stiff differential equations, whose realization will likely involve a time discretization similar to the StochSim algorithm.

How is a modeller to choose between modelling approaches — an implicit or explicit treatment of noise, a continuous or discrete representation of molecules? When simulating processes that involve only a few molecules, discrete stochastic models are superior to continuous models. However, in many processes, there are many copies of some species and few of others. In these circumstances, it is not always clear which approach is better. Detailed mechanisms are easier to include using discrete representations. For example, we can explicitly model the structure of the chromosome, transcription, translation, ribosome and polymerase queues on mRNA and DNA respectively, and events such as convergent transcription[42]. The disadvantage of discrete models is that they are more difficult to formulate, test and solve computationally. As multiscale approaches for simulating stochastic processes are desperately lacking, personal proclivities currently dictate the choice of approach, as modelling and simulation are, at this stage, more art than science.

## Noise analysis

The modelling tools described above allow us to address questions concerning intracellular noise. A few of these questions include where noise arises in cells, how pathways function robustly in spite of noise, how molecular noise can selectively generate population heterogeneity, and how cells potentially exploit noise.

### Origin of noise

To study the origins of noise in gene expression, McAdams and Arkin[4] proposed a stochastic model for gene expression in prokaryotes. Their model suggests that proteins are produced in random bursts. As a single mRNA transcript can produce multiple copies of a protein, protein translation amplifies transcriptional noise. Numerous other models have further validated and extended this hypothesis by analysing the mechanisms contributing to noise in gene expression[43–45]. As an experimental verification, van Oudenaarden and colleagues studied how the frequencies of transcription and translation contribute to variability in gene expression by measuring expression of a green fluorescent protein (GFP) marker[46]. Their results provided explicit evidence that most noise arises during translation.

What fraction of noise is attributable to fluctuations in gene expression and what fraction to external (or extrinsic) fluctuations arising from other cellular components? To discriminate between the two sources, Elowitz and colleagues[47] measured differential expression of distinguishable cyan and yellow fluorescent protein markers under the control of identical promoters. The degree of correlation in a single cell provides a measure of discrimination; as fluctuations in gene expression increase, the degree of correlation decreases. By varying levels of gene expression using a lac promoter, they showed that fluctuations in gene expression decrease as the expression increases. Likewise, extrinsic noise decreases with increased levels of gene expression, although remarkably it first passes through a maximum at intermediate levels of expression. In other words, at low levels of expression both forms of noise are present, whereas extrinsic noise dominates at intermediate levels, and both forms are absent at high levels. It was also shown that noise has a genetic component; *recA* mutants are twice as noisy as their wild-type counterparts.

### Noise control mechanisms

Many researchers have found it useful to invoke analogies from signal processing when investigating noise[48,49]. From this perspective, a pathway is viewed as an analog filter and is classified in terms of its frequency response. Cascades and relays such as two-component systems and the mitogen-activated protein kinase pathway have inherent noise-rejecting properties[50]. In terms of signal processing, these pathways function as low-pass filters, as they transduce low-frequency signals whereas high-frequency signals are attenuated. In fact, most physical systems attenuate high-frequency noise on input signals because of inherent time lags and delays. But noise also arises in the pathway as a result of internal molecular fluctuations, and we cannot simply ignore this noise or separate noise in the signal from that in the pathway. Where this type of separation has been attempted, it has been observed that in certain network topologies, such as cascades, there seems to be a trade-off between noise attenuation of an input signal and inherent noise generated at each step of the pathway. van Oudenaarden and colleagues examined this trade-off for cascade structures, and suggested that there is an optimal cascade length for attenuating noise[51]. This analysis illustrates how conclusions regarding noise may be derived from deterministic models through indirect analysis.

Perhaps the simplest and most common noise-attenuating regulatory mechanism is negative feedback. The principle of negative feedback is to measure whether the behaviour is acceptable, and to make corrections based on the 'error' between the desired and measured behaviours. In the fields of engineering and economics, it is well known that negative feedback is necessary to operate robustly in an uncertain environment. Not surprisingly, feedback is ubiquitous in biology as it provides a simple mechanism to attenuate the effects of noise[52–54]. In terms of its signal-processing capabilities, a simple negative feedback loop functions as a low-pass filter. Becksei and colleagues[55] demonstrated this effect by constructing a negative feedback module in *E. coli*. Their experiments showed that constitutive expression of the GFP is highly variable, in terms of the measured fluorescence intensity, whereas the addition of the negative feedback using the tetracycline repressor significantly reduces the measured variability, as expected.

Whereas simple negative feedback results in a low-pass filter, another type of feedback — integral feedback — shapes a band-pass filter. Integral feedback is a form of negative feedback that uses an internal memory state to amplify intermediate frequencies and attenuate low and high frequencies. Bacterial chemotaxis is an example of a system using integral feedback[56]. Here, integral feedback

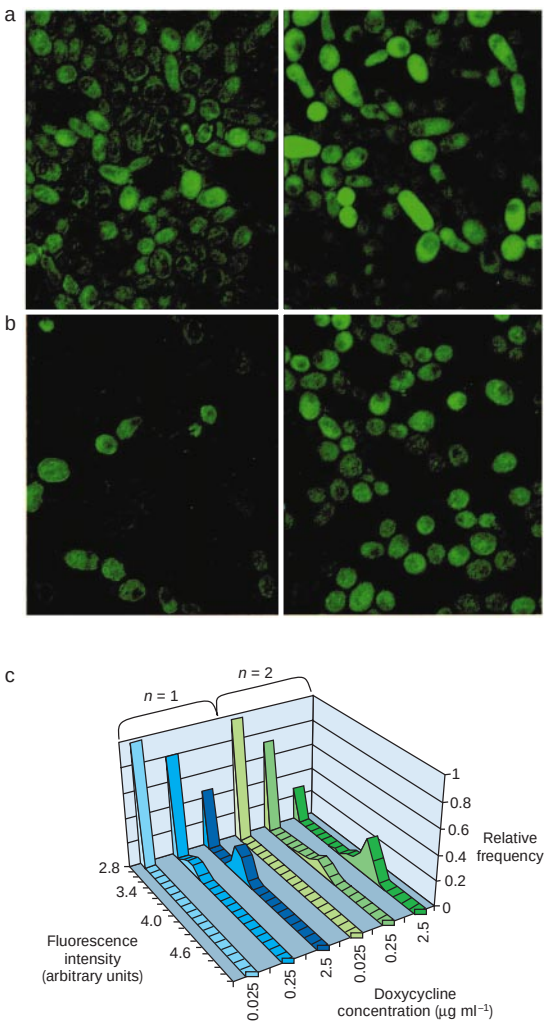


**Figure 4** Construction of the synthetic positive feedback loop of Becksei and colleagues[66]. **a**, Constitutive expression of the tetracycline-responsive transactivator (rtTA). The degree of activation, measured by expression of the green fluorescent protein (GFP), is proportional to the amount of inducer, doxycycline, added. Cells were induced with 0.25 μg ml$^{-1}$ (left) and 2.5 μg ml$^{-1}$ (right) doxycycline. **b**, rtTA under the control of a positive feedback loop. In this set up, rtTA regulates the expression of GFP and itself. Cells were induced with 0.25 μg ml$^{-1}$ (left) and 2.5 μg ml$^{-1}$ (right) doxycycline. At low concentrations of inducer, the response is heterogeneous. **c**, Distribution of fluorescence level in the positive feedback loop construction as a function of inducer concentration and gene copy number (*n*). The heterogeneous response is indicated by the bimodal distribution. (Images courtesy of A. Becskai and *EMBO Journal*[66]).

measures temporal changes in chemical concentrations, rather than steady-state changes, and results in biased motion towards attractants and robust adaptation.

In addition to intrinsic chemical damping, negative feedback and integral feedback, many other simple mechanisms attenuate noise in systems. One example is redundancy mechanisms such as gene dosage and parallel cascades[57,58]. These mechanisms attenuate the effects of noise by increasing the likelihood of gene expression or establishing a consensus from multiple signals. Another example is regulatory checkpoints[59]. Best characterized in the cell cycle and flagellar biosynthesis, checkpoints ensure that each step in a pathway is successfully completed before proceeding with the next step. Yet another example is kinetic proofreading in protein translation, where mechanisms are in place to correct possible errors[60].

### Noise amplification and exploitation

Complementary work has focused attention on cellular processes that amplify or exploit noise in some sense, rather than just controlling or eliminating it. These processes fall into two classes — mechanisms that give rise to population heterogeneity (and thus diversity), and mechanisms that use noise to attenuate noise. Isogenic heterogeneity seems to arise from a noisy step in the commitment portion of an otherwise ordered process. One example is the genetic circuit governing development in phage lambda, where it was proposed[42] that molecular fluctuations cause an initially homogenous population to partition into a heterogeneous lytic and lysogenic population. The basic mechanism governing the decision circuit involves two antagonistic feedback loops — crossed repressive feedback loops generate a switch, and molecular fluctuations partition the population statistically so that individuals may (by chance) follow one path or the other. These results illustrate how intrinsic molecular noise is used to generate diversity.

The *fim* network regulates phase variation of type 1 pili in uropathic *E. coli*. Type 1 pili, which are adhesive organelles expressed on the surface of the cell, are virulence factors in urinary tract infections[18,20]. A mechanism was proposed[61] where the system components (invertible DNA element and the global regulators and invertases that act stochastically upon it) realize a number of devices that together transduce environmental signals into inversion probabilities and thus the heterogeneity level of the population, presumably creating piliated populations in the bladder and unpiliated populations outside the host. This network includes a switch based on the ratio of regulatory proteins, a temperature tuning device capable of reading the temperature and increasing piliation at mammalian body temperature, and a delay line using feedback as memory to prevent rapid cycling between ON and OFF switching states (discussed below). This system provides an example of how integrated regulatory modules in a network can function to both shape and filter noise, thereby creating environmentally tuned heterogeneity in a cell population.

The *fim* network seems to include a delay that decreases the sensitivity of the switch to noise. Switches may be sensitive to both noise and 'chatter' (Fig. 3). Chattering arises commonly in engineering, where noisy signals may cause switches to rapidly turn off and on, and it was proposed that the flagellar motor in bacterial chemotaxis possesses a mechanism to prevent chatter[62]. The expected fluctuations in the response regulator CheY were shown not correlate with the switching behaviour, suggesting that the flagellar motor has a mechanism that decreases sensitivity to noise in CheY. Latter experiments showed that the flagellar switch may possess a hysteresis[63], one mechanism known to reduce chatter.

Feedback can also amplify the effects of noise by autocatalytic mechanisms[64,65] (that is, positive feedback). In an experimental study by Becksei and colleagues[66], a synthetic positive feedback loop in yeast was constructed using the tetracycline transactivator and a GFP marker (Fig. 4). In this system, activation of the feedback loop is variable and randomness at the single-cell level leads to a mixed colony of cells.

In addition to generating heterogeneous populations, cells also use noise to filter noise. Whereas in most systems noise degrades a signal, noise actually enhances a signal when certain nonlinear effects are present. One example is stochastic resonance[67]; numerous examples of this exist in biology, such as electroreceptors in paddlefish[68], mechanoreceptors in the tail fins of crayfish[69] and hair cells in crickets[70]. It has also been suggested that noise can potentially increase sensitivity in certain signalling cascades[71].

### Complex interactions and multiple feedback loops

Some of the elementary mechanisms for noise attenuation, amplification and exploitation enumerated above present the illusion of

tractability (that is, they appear simple and readily identifiable). However, elementary mechanisms typically do not function in isolation, but rather interact in complex networks involving multiple feedback loops. These regulatory networks can produce diverse phenomena ranging from switches to memory to oscillators[72,73]. Although it is straightforward to understand how a single feedback loop shapes noise, it is far more difficult to understand the composite behaviour of multiple mechanisms interconnected in complex architectures.

It is for these interactions that computational models are most useful. For example, the network that controls circadian rhythms consists of multiple, complex, interlocking feedback loops. Many researchers have investigated the mechanisms for noise resistance in circadian rhythms, using both deterministic and stochastic models[74–77]. General models of chemical oscillators are sensitive to kinetic parameters. However, the proposed mechanisms for circadian rhythms produce regular oscillations in the presence of noise. Remarkably, the stochastic model is able to produce regular oscillations when the deterministic models do not[76], suggesting that the regulatory networks may utilize molecular fluctuations to their advantage.

Other examples of complex networks functioning in the presence of noise are early expression of *hox* genes[78] and bacterial chemotaxis[79,80]. As with the previous example, noise attenuation arises from the systematic properties of the network rather than from a single mechanism. What specific mechanisms confer robust functionality in the presence of noise? Apparently, noise attenuation arises from complex mechanisms involving multiple feedback loops. Although theoretical and computational tools exist for analysing the properties of a given network, no good theory exists (and perhaps never will) for identifying all possible mechanisms that generate robust networks.

It is clear that large, complex networks are able to function reliably despite inherent noise attributable to molecular fluctuations. Although simple, specific mechanisms to explain this phenomenon can be elusive, robustness has been hypothesized as an intrinsic property of intracellular networks. In two landmark papers, Leibler and colleagues showed that the chemotaxis pathway in *E. coli* is robust[11,81]; the pathway is functional for a wide range of enzymatic activities and protein concentrations. Other examples of robustness include developmental processes[12,82] and phage lambda regulation[83]. Although robustness is often studied independently of noise, the two problems are not distinct. When studying robustness, the typical question is how sensitive the behaviour of a network is to the parameters in the model. As these parameters are subject to fluctuations, a noise-resistant network is likely to be robust. But a network that is insensitive to the kinetic parameters may still be sensitive to molecular noise, as internal and external noise are rarely parameterized explicitly in these models. A comprehensive investigation of robustness needs to account explicitly for noise.

## Beneath the noise

The studies described above highlight the need for understanding the role of noise in biology. We are still far from answering the question "How does order arise from disorder?", but we are beginning to get a glimpse of some of the mechanisms by which cells control and exploit noise.

Considerations of noise and robustness offer insight into the design and function of intracellular networks[84–86]. In particular, what design features or constraints are necessary for pathways to function robustly in the presence of noise? Design and function often imply teleological arguments. Rather than teleology, the hypothesis is that the function of a network and the need for robustness impose constraints on its design and canalize evolution. For example, protein function often implies a specified chemistry, such as a membrane protein having a hydrophobic region, a soluble globular protein having a hydrophobic core, and the active site of serine protease containing a Ser-His-Asp catalytic triad. We expect similar constraints on networks; in particular, function imposes a specific regulatory and information structure. We do not suggest that networks are designed optimally for fitness, but rather that certain design features are necessary for a stable phenotype. These design constraints allude to a theoretical biology distinct from physics and chemistry, more akin to engineering than the new physical laws that Schrödinger originally envisioned. □

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## erratum

# Control, exploitation and tolerance of intracellular noise

**Christopher V. Rao, Denise M. Wolf & Adam P. Arkin**

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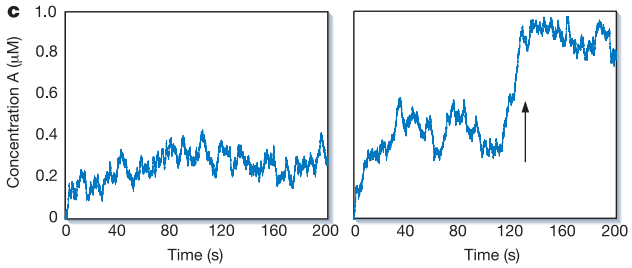
In this Insight Review Article, the right panel of Fig. 3c incorrectly appeared blank. Figure 3c should have appeared as shown:




## corrigendum

# Altered performance of forest pests under atmospheres enriched by $CO_2$ and $O_3$

**Kevin E. Percy, Caroline S. Awmack, Richard L. Lindroth, Mark E. Kubiske, Brian J. Kopper, J. G. Isebrands, Kurt S. Pregitzer, George R. Hendrey, Richard E. Dickson, Donald R. Zak, Elina Oksanen, Jaak Sober, Richard Harrington & David F. Karnosky**

*Nature* **420**, 403–407 (2002).

In this Letter, the conversion to SI units led to several errors. On page 404, left column, lines 16 and 17, the values should read 10–15 and 30–40 nanolitres per litre. On page 405, right column, lines 3 and 4, the values should read 360 microlitres per litre and 36.0–38.8 nanolitres per litre. On page 407, left column, lines 3 and 4, the values should read 560 microlitres per litre, and 46.4 to 55.5 nanolitres per litre. The conclusions of the paper are not affected. □