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It's a noisy business!

Genetic regulation at the nanomolar scale

Many molecules that control genetic regulatory circuits act at extremely low intracellular concentrations. Resultant fluctuations (noise) in reaction rates cause large random variation in rates of development, morphology and the instantaneous concentration of each molecular species in each cell. To achieve regulatory reliability in spite of this noise, cells use redundancy in genes as well as redundancy and extensive feedback in regulatory pathways. However, some regulatory mechanisms exploit this noise to randomize outcomes where variability is advantageous.

Even in clonal cell populations and under the most uniform experimental conditions, considerable variation is observed in the rates of development, morphology and the concentration of each molecular species in each cell. The molecular-level phenomena that produce these differences are deeply rooted in the statistical mechanical behavior of so-called 'small' (or nanoscale) chemical systems, where concentrations of reacting species are extremely low and, consequently, fluctuations (noise) in reaction rates are large. Many genetic regulatory reactions occur at just such low concentrations. Genetic regulatory circuit designs use redundancy, feedback loops and other features to produce the needed determinism in outcome for circuits constructed from such inherently noisy elements. Operational reliability in regulation is particularly crucial to the development of complex metazoan organisms (see below). On the other hand, cells can also exploit noise in some developmental switch circuits to deliberately introduce indeterminism into the switching and randomize phenotypic outcomes. Diversity introduced in this manner is commonly found in bacterial and yeast responses to environmental stress and in bacterial virulence mechanisms that vary surface features to avoid host cell responses (Table 1). Random variations in eukaryotic cell developmental lineages[1] can be produced by similar mechanisms.

In this review, we focus on the cell to cell variations in the concentration of regulatory molecules that arise from internal cellular processes rather than from differing environments. These variations are commonly observed as irreducible cell to cell concentration differences in well-stirred cultures of single-cell organisms. (In tissue cultures, uniform extracellular environments are virtually impossible to achieve.) There are several internal sources of regulatory noise. For example, there is inevitable statistical variation in the random partitioning of small numbers of regulatory molecules between daughter cells when cells divide. Many regulatory molecules are present in bacterial cells at extremely low concentrations – anywhere from a few tens to a few hundred molecules per cell[2]. Thus, in random partitioning of, say, 50 molecules between equal-sized daughters, 6% of the daughters will

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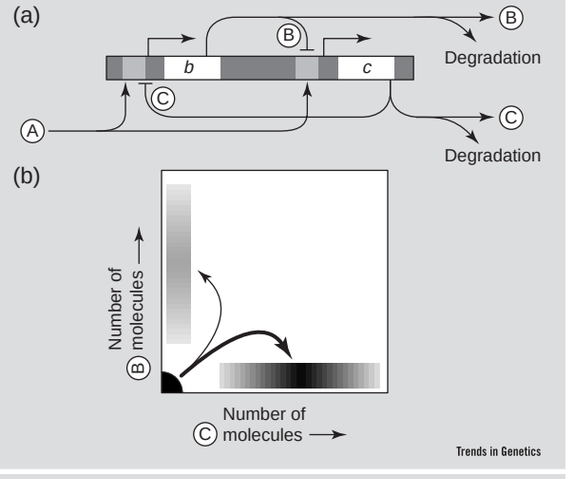
TABLE 1. Competitive reactions controlling the expression of alternative genes

Organism	Mechanism	Function	Ref.
Escherichia coli Pap system	Differential methylation of alternative Lrp (leucine-responsive protein) binding sites	Phase variation in pili expression, affecting virulence	36
E. coli Fim system	Invertible DNA segments	Phase variation in type I pili, affecting virulence	37
Phage Mu	Invertible DNA segments	Phase variation in type I pili, affecting virulence	38
Salmonella typhimurium Hin system	Invertible DNA segments	Phase variation in flagellin alters antigen response	38
Moraxella bovis	Invertible DNA segments	Phase variation in pilin alters antigen response	39

receive fewer than 19 molecules and 6% will receive more than 30 – a sufficient difference to have regulatory consequences for some regulatory reactions.

A less obvious but more important cause of cellular variations is the distinctive statistical properties of regulatory chemical reactions that involve a small number of reaction centers and slow reaction rates. Regulation of bacterial gene transcription, for example, predominantly involves reactions of small intracellular populations of one to three regulatory species. These bind to the promoter region of a given gene, and there are generally two or less copies of the gene in a growing bacterial cell. Even at fully activated bacterial promoters, the average time between transcript initiations at each promoter can be many seconds and the distribution of intertranscript times is highly skewed around the average. Detailed consideration of the statistical properties of transcript initiation and translation suggests that proteins are ultimately produced from an activated promoter in short bursts of variable numbers of proteins, and that the bursts occur at random time intervals, both in bacterial[3] and eukaryotic[4] cells. Stochastic gene expression has been observed directly in eukaryotic cells[5–8]. Protein production from eukaryotic genes is erratic and bursty as in prokaryotes, but with longer average intervals between bursts[4].

FIGURE 1. Bistable regulatory circuit



(a) Two promoters, coordinately controlled by protein A, produce mutually repressive proteins B and C. The system is bistable, so that either B or C, but not both, can accumulate to activate any downstream pathways they respectively control. (b) The number of cells (indicated by depth of shading) with various numbers of molecules B and C. Prior to activation of transcription of genes *b* and *c* all cells are at the {no A, no B} position. After A initiates transcription, short term, independent bursts of B and C are produced. By chance, in some cells B will rise rapidly and repress further C production; in others, C will 'win'. In the case illustrated, circuit parameters favor C so that only a minority of cells end up with a high level of protein B. Wide dispersion of the concentration of the 'winning' protein results from the erratic nature of gene expression.

Stochastic outcomes at regulatory switch points

A particularly interesting case occurs when two independently produced regulatory proteins are involved in the competitive control of a developmental switch that selects between alternative pathways. Because the independent, stochastic temporal patterns of production of each regulatory protein can vary widely from cell to cell, the pathway selection by the competitively regulated switch can be random. The probabilities of selecting each pathway will depend on the stochastic properties of the gene expression mechanisms and the design of the switch circuit[9]. Cells can take advantage of stochastic expression of the regulatory proteins to randomize the regulatory outcome – the pathway choice – using appropriately designed regulatory circuits. The simple cross-repressive configuration in Fig. 1 illustrates how this phenomenon can produce subpopulations expressing alternative phenotypes, even in genetically homogeneous populations in identical environments. In the example shown, competitive autoregulating feedback loops can lock the cell into one or another pathway with some fraction of the cells, by chance, taking each path. In such systems, environmental signals can act on the parameters of the regulatory circuit to bias the probabilities of path choice under different conditions. Organisms exploit this mechanism to achieve diversity and increase the likelihood of species survival over a wide range of environments. Two examples of such a mechanism are the phage λ lysis–lysogeny decision circuit[9] (see below) and the networks controlling *Bacillus subtilis* commitment to competence and sporulation[10].

Another stochastic bistable genetic regulatory mechanism is the random inversion of DNA segments used in many organisms to produce subpopulations of distinct phenotypes[11]. Table 1 shows a small sample of well-known cases of bistable regulatory mechanisms used in genetic circuits that produce stochastic phenotype outcomes. These stochastic bistable switching mechanisms are common virulence mechanisms in pathogenic organisms. For example, random alteration of proteins on the bacterial surface or in external features such as flagella can aid in avoidance of the host's immune response.

Common features of the dynamics of these stochastic regulatory switches that randomly select among several alternative pathways include: (1) transient, low-level expression of key regulatory proteins; (2) stochastic progress toward pathway commitment as concentrations of the controlling proteins in each cell change from moment to moment, so that there is a transient period of partial (i.e. reversible) commitment before a definitive choice eventually emerges[9]; and (3) multiple feedback loops that reinforce the activation of the selected path and repression of rejected alternative(s).

Kinetics of stochastic regulatory circuits

Conventional kinetics does not model statistics of regulatory systems that produce probabilistic outcomes, such as the

stochastic switching mechanisms discussed above, and might not even describe the average behavior of such systems correctly[12,13]. For these cases, a stochastic kinetic analysis[14] can be used to predict the behavior of systems that are probabilistically regulated and might permit improved exploitation of information in the statistics of phenotypic outcomes. Analytical resolution of the resulting systems of stochastic reaction equations is only practical for simple reaction systems. The so-called 'Langevin approach' for approximation of the effect of fluctuations has been used to model the microscopic kinetics of stochastic regulatory systems, but this practice is theoretically unsound[15] and can yield invalid predictions for bistable systems[16]. However, the Monte Carlo simulation algorithm described by Gillespie[14] does provide valid numerical solutions for complex systems of coupled stochastic reactions. Stochastic switching in the phage λ lysis–lysogeny decision circuit (Fig. 2) has been analyzed using stochastic kinetics and the Gillespie algorithm[9] to show in detail how initially homogeneous cell populations can partition randomly into distinct phenotypic subpopulations[9]. Host-cell hunger and higher numbers of phage particles infecting the cell bias the decision circuit to produce a higher percentage of lysogens.

How do cells achieve regulatory determinism?

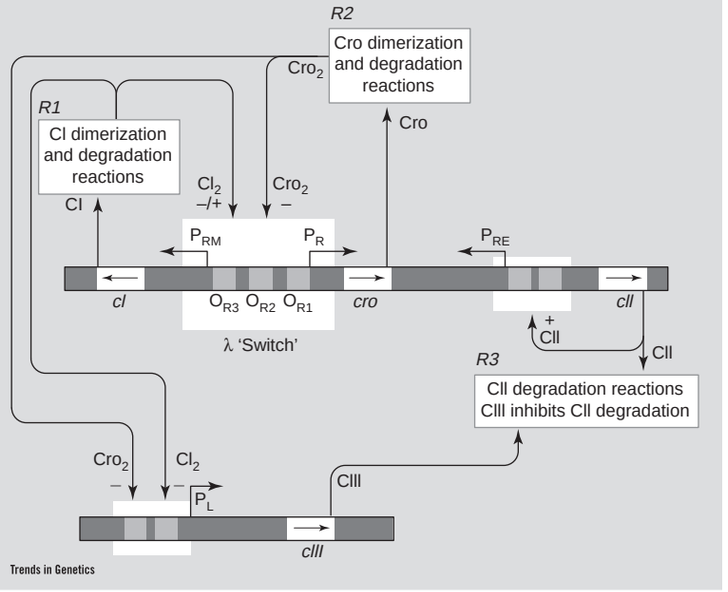
In spite of the randomness in basic regulatory mechanisms discussed above, many regulatory pathways in cells have highly predictable outcomes. The strategies that cells use to ensure that critical proteins are expressed when needed, in spite of infrequent and stochastic gene expression, include: (1) population transcriptional cooperation (i.e. it is not necessary for every cell in a population to make all the gene products)[4]; (2) checkpoints to assure that cascaded events are adequately synchronized[17–19]; and (3) widespread redundancy in genes[20–22] and in regulatory pathways[23,24].

Even in uniform conditions, normal fluctuations in protein production can be large, relative to the regulatory thresholds that control the expression of downstream genes. One consequence is wide variations from cell to cell in the 'switching time' for the controlling protein to activate the genes it controls[3]. Without a coordinating mechanism, these timing variations will cause errors in synchronization of cellular functions when complex networked signal paths control the sequencing of cellular functions. One mechanism to provide coordination is provided by regulatory checkpoints that halt regulatory cascades until conditions for further progress (e.g. availability of essential nutrients, external environmental signals or completion of precursor cellular events) are satisfied[17–19]. Checkpoints assure the orderly execution of cellular activities, but the time required to execute cascaded functions can still vary widely between cells. Thus, check points yield certainty in outcome, but not certainty in the timing of regulatory events. A common example is the random distribution of generation times of cells in growing cell cultures that causes progressive desynchronization of initially synchronized cell populations[25,26].

Development of large metazoans from egg to adult requires the highly reliable execution of very large numbers of developmental processes, with correct timing, sequencing and spatial positioning. The regulatory processes controlling this development must act predictably, in spite of large fluctuations in the function of elemental regulatory mechanisms and fluctuations in environmental conditions. The reliability requirement for individual somatic developmental processes depends on the function's criticality for production of a successful adult. For example, regulatory processes early in embryonic development that are prerequisites for extensive downstream cell lineages, and processes whose failure might allow dangerously uncontrolled cellular proliferation, have to be particularly reliable[21]. Thus, regulatory circuit designs and the molecular details that determine kinetic parameters must be under selective pressure for reliable and robust operation (including robustness to large variations in the organism's normal external environment).

Several complementary strategies can be combined to construct a reliable regulatory system from noisy biochemical elements and inherently mutable genes. Dynamic stability in the regulatory circuit designs results principally from the exploitation of redundancy and feedback[23,27]. Redundancy is applied both at the level of individual components (i.e. genes[21]) and through parallelism and interlinking in the control pathways, so that regulatory networks are more reliable than their parts[27,28]. A common genetic criterion for functional redundancy between two genes is that single gene mutations have little phenotypic effect while mutation of all paralogues produces a strong effect[21,29]. This test does not imply that redundant genes are necessarily genetic duplicates. Indeed, genes with redundant or overlapping function but unrelated sequences are well known[30].

FIGURE 2. Phage λ lysis–lysogeny decision circuit



Simplified version of the phage λ decision circuit that determines whether infected *Escherichia coli* cells follow the lytic or lysogenic pathway. Bold horizontal lines indicate stretches of double-stranded DNA. Arrows in genes indicate the direction of transcription. The boxes R1–R3 indicate non-genetic protein reaction subsystems. The three operator sites, $O_{R1–R3}$, of the 'λ switch' implement a concentration-dependent 'logic', controlling promoters P_{RM} and P_R. Cro and CI dimers bind to the three sites with different affinities and in opposite order to control the activation level of the P_{RM} and P_R promoters[40,41]. The CI dimer acts as either a repressor or activator of promoter P_{RM}, depending on its concentration. The result is a mutually exclusive locking mechanism, so that either P_{RM} or P_R ends up being activated with the other promoter locked off. Strong production of CI relatively soon after infection is necessary for locking on the P_{RM} loop to select the lysogenic pathway. This occurs only when the strong promoter P_{RE} is activated by CII to 'jump start' CI production. Degradation of CII is inhibited by CIII, so production of CIII increases the probability of CI 'winning' the race. Environmental signals influence the outcome by affecting the rate of CII degradation. Due to the stochastic character of protein production and the other reactions involved, both the lytic and the lysogenic outcome can occur with some probability, so that two alternative phenotypes result.

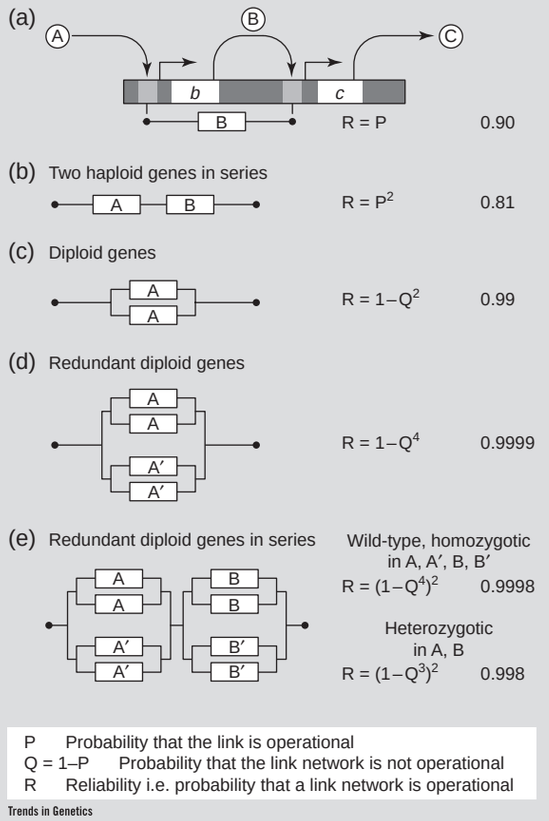
Reliability through redundancy

In the 1940s and 1950s, the notion that there are genetically specified, self-stabilizing capabilities in developing organisms was recognized and characterized as 'canalization'[29]. In the 1950s, redundant genes were suggested as a possible mechanism for this genetic capacity to buffer development pathways against mutational or environmental perturbations[31]. Recently, analysis of the connection between genetic redundancy and reliability has focussed largely on conditions for the evolutionary stability of redundant genes[21,22], with general agreement that the redundancy provides some sort of 'back up' for somatic development functions[30]. The dramatic increases in chromosome size at the prokaryotic– eukaryotic and the invertebrate–vertebrate evolutionary boundaries are attributed to chromosome duplications that provided the opportunity to create the redundant genetic network designs necessary for reliable regulatory operations[20,32]. After a gene is duplicated, several things can occur that lead to maintenance of the duplication: (1) The duplication can provide a fitness advantage owing to increased regulatory reliability and, hence, be preserved. (2) Mutations in the duplicate gene can change its function and the fitness benefit of this new, or added, function causes the gene to be preserved. (3) Duplication is initially retained owing to reliability benefits, and then further opportunistic optimization occurs as beneficial mutations add functions to both of the duplicate genes. Extension of the range of response is an example. One of the duplicates could become slightly better for growth at higher temperatures, the other slightly better for lower temperatures, so that the range of temperature coverage is extended with net increase in fitness.

Interestingly, the extensive redundancy in networked genes and the extensively interlinked and redundant genetic control pathways, in fact, resemble standard engineering approaches for design of high-reliability systems using unreliable or noisy components[33]. This suggests that we should evaluate genetic regulatory networks using engineering methods routinely applied to reliability analysis of complex physical systems[33]. This approach to reliability analysis requires the consideration of the potential failure patterns of the regulatory network and not simply of individual genes or sets of redundant genes. The stochastic characteristics of nanoscale regulatory chemistry cause random variations in regulatory effectiveness for genetic links that are functioning perfectly normally[3]. Regulatory signal failures will always occur in individual links with some probability. However, the reliability of signal transmission in genetic networks will increase predictably with redundancy[3]. Addition of other independent and parallel regulatory pathways involving different gene products can further increase the reliability of a regulatory network's performance. Figure 3 illustrates the dramatic increases in overall link reliability from parallel redundancy. Although the simple examples in Fig. 3 demonstrate the benefits of redundancy, quantitative analysis of particular genetic networks is complex because the statistical characteristics of gene expression are determined by the stochastic properties of the molecular mechanisms controlling the expression of each gene[3]. Regardless of the statistical details, however, networks with redundant elements will perform more predictably and with less variance in outcome than non-redundant networks of the same elements owing to the statistical independence of variations in the different chemical reactions. In the small number of regulatory networks where molecular mechanisms are relatively well known, the statistics of operation of each mechanism can be estimated and the effects of redundant components on the robustness of genetic network performance can be analyzed. Given the complexity of even small genetic networks, the use of simulation techniques[3,34] is necessary for such an analysis.

Redundancy affords resilience in genetic network performance both to gene mutations and to the short-term, transient regulatory failures caused by erratic protein production. Figure 3(e) illustrates how mutations in one or more of the genes in a redundant regulatory network can increase the probability of failure of the network. This phenomenon results from the statistical character of the robustness afforded by redundancy against 'outages' in a regulatory link: $(n-1)$-fold redundancy will always provide less reliability than n-fold redundancy. For low levels of redundancy, mutations can increase the probability of failure of the regulatory network significantly during development, so that a fraction of the population exhibits a mutant phenotype; that is, there is partial penetrance of the mutant phenotype.

FIGURE 3. Reliability analysis



A highly simplified reliability analysis shows that even simple redundant configurations provide high payoff in regulatory link reliability. (a) A single, genetically coupled link3 where effector B (controlled by A) controls the downstream gene *c*. Assume the statistics of operation of the link are such that a single gene is capable of producing an effective signal (i.e. the link is operational) with probability $P = 0.90$. (b) A link of two genes *b* and *c* in series is only operational if both genes are operational, so the reliability is 0.81. (c) A parallel configuration will only fail if both genes fail and so has reliability 0.99. (d) With the same assumptions, two redundant, homozygous diploid genes are operational if one out of the four genes is operational, so the reliability is 0.9999. (e) The redundant configuration also decreases sensitivity to individual mutations. Here, two mutations producing a configuration AaA′A′ in series with configuration BbB′B′ still has a reliability of 0.998.

The dynamic stability of genetic networks arises in part from redundancy but, importantly, is dependent on the extensive interlocking feedback loops incorporated within network designs[23,28]. The stochastic lineage of the *Caenorhabditis elegans* anchor cell (AC) is a particularly relevant example. The development pattern varies randomly in different animals between two distinct lineages. In half the animals, by chance, the AC is derived from the Z1 gonadal precursor cell; in the other half, it is derived from the Z4 gonadal precursor. The final regulatory outcome, however, is not affected because regulatory feedback via intercellular signaling involving the receptor *lin-12* and its ligand LAG-2 causes the alternative cell to become a ventral uterus cell[1,35]. Thus, in this case, random developmental lineage variation caused by molecular-level noise in the regulatory circuit is dynamically compensated by cellular level feedback.

Conclusions

In summary, the consequences of molecular-level statistical mechanics of nanoscale chemistry in cellular regulatory mechanisms have pervasive effects. Random variations in the performance of genetically coupled regulatory links can be exploited beneficially to produce variability with fitness advantages. However, more commonly, regulatory determinism is necessary, particularly for complex metazoans. For these organisms, pervasive redundancy in regulatory networks, as well as extensive feedback and other network design features, are used to produce determinism. This requirement for redundancy is thought to be a major factor contributing to the large size of metazoan chromosomes. Because of the network robustness resulting from redundancy, feedback and other design features, mutations of genes within the network might have no phenotype, but might also have a probabilistic phenotype exhibiting partial penetrance. Analysis and prediction of effects of mutations within redundant genetic regulatory networks requires reliability analysis of the regulatory network design as a whole.

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